PAIN PERCEPTION, BRAIN ACTIVITY, AND MANAGEMENT IN INDIVIDUALS WITH CHRONIC PAIN AND INSOMNIA

CHANG RUI

PhD

The Hong Kong Polytechnic University

2025

The Hong Kong Polytechnic University

Department of Rehabilitation Sciences

Pain Perception, Brain Activity, and Management in Individuals with Chronic Pain and Insomnia

Chang Rui

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

July 2025

CERTIFICATE OF ORIGINALITY

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

_____ (Signed)

Chang Rui

Abstract

Sleep disturbance is commonly complaint among individuals with chronic pain, may exacerbate pain intensity, and cause functional impairment and poor prognosis. Although the interaction between disrupted sleep and pain is well documented, the underlying mechanisms for this relationship remain insufficiently understood. Growing attention has been directed toward changes in both peripheral and central mechanisms of pain regulation, yet the neurophysiological mechanisms linking sleep and pain in clinical populations are still not fully understood. Furthermore, the prospective relationship between these two conditions remains uncertain, particularly whether changes in sleep are correlated with corresponding changes in pain-related outcomes. More importantly, there is limited evidence identifying the most effective non-pharmacological treatments for enhancing sleep in people with chronic pain and how existing treatment protocols could be optimized for those with comorbid chronic pain and insomnia. This project used three systematic reviews, a cross-sectional study, and a pilot randomized controlled trial to address these research gaps.

The first systematic review and meta-analysis revealed that sleep loss led to heightened pain perception. However, different sleep deprivation paradigms had varying effects on subjective pain intensity and the exacerbation of peripheral or central pain sensitization in healthy individuals. Our cross-sectional study using quantitative sensory testing and resting-state electroencephalography to investigate pain perception and neural oscillatory patterns among females with chronic low back pain (CLBP), insomnia, comorbid conditions, or neither. The results found that individuals with comorbid CLBP and insomnia showed significantly reduced pressure pain thresholds at the back, greater impairment in descending pain modulation, altered

fucntional connectivity across multiple brain networks compared to tother groups. More importantly, insomnia remained to be independently linked to lower mechanical pain threshold and aberrant functional connectivity in the comorbid group, after adjusting for pain-related factors and psychological variables. The second systematic review showed better self-reported sleep quality and longer total sleep time were significantly linked to reductions in pain severity and improvements in disability among individuals with CLBP. The third systematic review and network meta-analysis found that among 14 identified non-pharmacological interventions, eight showed significantly greater improvements in sleep quality immediately after treatment compared to passive control in individuals with chronic musculoskeletal pain. Our a pilot randomized controlled trial showed that repetitive transcranial magnetic stimulation (rTMS) was a feasible and acceptable treatment for comorbid conditions. Both active stimulation protocols significantly reduced pain intensity and enhanced descending pain inhibitory function compared to sham stimulation. Importantly, only rTMS targeting the left dorsolateral prefrontal cortex significantly improved insomnia severity and reduced objective wake after sleep onset.

In summary, this project has advanced our understanding of the complex interplay between sleep disturbance and chronic pain. These results emphasize the critical importance of integrating sleep assessment and treatment into pain management strategies. Future research should aim to elucidate the underlying mechanisms further and evaluate the effectiveness of personalized, biomarker-informed treatment approaches. Such efforts may significantly advance our understanding of the interactions between these two conditions and improve the sleep and pain management in these complex populations.

List of Research Output during the Course of Study

Journal Publications Arising from this Thesis

1. **Chang JR**, Cheung KW, Sharma S, Li SX, Tao RR, Lee, JL, Sun ER, Pinto SM, Zhou Z, Chan WW, Zheng DK, Samartzis D, Fu SN, Wong AY. Comparative effectiveness of non-pharmacological interventions on sleep in individuals with chronic musculoskeletal pain: A systematic review with network meta-analysis. *Sleep Medicine Reviews*. 2024 73: 101867.

2. **Chang JR**, Fu SN, Li X, Li SX, Wang X, Zhou Z, Pinto SM, Samartzis D, Karppinen J, Wong AY. The differential effects of sleep deprivation on pain perception in individuals with or without chronic pain: A systematic review and meta-analysis. *Sleep Medicine Reviews*. 2022 Sep 27:101695.

3. **Chang JR**, Kwan LC, Sun ER, Li SX, Liang P, Liu QJ, Zheng DK, Zhou Z, Huang FF, Samartzis D, Fu SN, Wong AY. Differential pain perception among females with or without non-specific chronic low back pain and comorbid insomnia: a quantitative sensory testing analysis. *PAIN*. 2025, 10-1097.

4. **Chang JR**, Li SX, Mei XL, Kwan LC, Traeger AC, Tao R, Liang P, Zheng DK, Liu QJ, Zhou Z, Huang FF, Samartzis D, Fu SN, Sun ER, Wong AY. Neural oscillations and brain connectivity in females with chronic low back pain and comorbid insomnia. *Journal of Pain*. 2025, in press.

5. **Chang JR**, Wang X, Lin G, Samartzis D, Pinto SM, Wong AY. Are changes in sleep quality/quantity or baseline sleep parameters related to changes in clinical outcomes in patients with nonspecific chronic low back pain? A systematic review. *The Clinical Journal of Pain*. 2022 Apr 1;38(4):292-307.

Conference Resentations Arising from this Thesis

1. **Chang JR**, Cheung KW, Sharma S, Li SX, Tao RR, Lee, JL, Sun ER, Pinto SM, Zhou Z, Chan WW, Zheng DK, Samartzis D, Fu SN, Wong AY. Comparative effectiveness of

non-pharmacological interventions on sleep in individuals with chronic musculoskeletal pain: A systematic review with network meta-analysis. *The Hong Kong Physiotherapy Association 60th Anniversary Conference* on 23rd-25th June 2023. Hong Kong, China [Oral Presentation] (**Won the best oral presentation**).

2. **Chang JR**, Cheung KW, Sharma S, Li SX, Tao RR, Lee, JL, Sun ER, Pinto SM, Zhou Z, Chan WW, Zheng DK, Samartzis D, Fu SN, Wong AY. Comparative effectiveness of non-pharmacological interventions on sleep in individuals with chronic musculoskeletal pain: a network meta-analysis. *The 13th Pan-Pacific Conference on Rehabilitation* on 23rd-24th November 2023. Chiang Mai, Thailand [Oral Presentation].

3. **Chang JR**, Kwan LC, Sun ER, Li SX, Liang P, Liu QJ, Zheng DK, Zhou Z, Huang FF, Samartzis D, Fu SN, Wong AY. Distinct quantitative sensory testing profiles in female chronic low back pain individuals with and without insomnia. *The 50th International Society for the Study of the Lumbar Spine Annual Meeting* on 26th-31st May 2024. Milan, Italy [Poster Presentation].

4. **Chang JR**, Kwan LC, Sun ER, Li SX, Liang P, Liu QJ, Zheng DK, Zhou Z, Huang FF, Samartzis D, Fu SN, Wong AY. Distinct quantitative sensory testing profiles in female with or without chronic low back pain and concurrent insomnia. *The World Physiotherapy Congress 2025* on 29th-31st May 2025. Tokyo, Japan [Poster Presentation].

5. **Chang JR**, Sun ER, Li SX, Kwan LC, Liang P, Liu QJ, Zheng DK, Zhou Z, Huang FF, Samartzis D, Fu SN, Wong AY. Distinct brain activity in females with or without chronic low back pain and comorbid insomnia. *The World Physiotherapy Congress 2025* on 29th-31st May 2025. Tokyo, Japan [Oral Presentation].

6. **Chang JR**, Wang X, Lin G, Samartzis D, Pinto SM, Wong AY. A systematic review on the relationships between sleep quality or quantity and clinical outcomes in patients with chronic low back pain. *The 17th International Forum for Back and Neck Pain*

Research in Primary Care on 11th-13th November 2021. Melbourne, Australia [Oral Presentation].

7. **Chang JR**, Wang X, Lin G, Samartzis D, Pinto SM, Wong AY. The relationships between sleep quality or quantity and clinical outcomes in patients with chronic low back pain-A systematic review. *The 48th International Society for the Study of the Lumbar Spine Annual Meeting* on 9th-13th May 2022. Boston, MA, USA [Poster Presentation].

Journal Publications not Arising from this Thesis

1. Altinger G, Jones C, Ferreira G, Soon J, Hoffmann T, Maher C, **Chang JR**, Linder JA, Traeger AC. Effectiveness of clinician-directed default nudges on reducing overuse of tests and treatments in healthcare: A systematic review of randomised controlled trials. *BMJ Quality & Safety*. 2025

2. Che Y, Qian Z, Chen Q, **Chang JR**, Xie X, Hao Y. Effects of rehabilitation therapy based on exercise prescription on motor function and complications after hip fracture surgery in elderly patients. *BMC Musculoskeletal Disorders*, 2023, 24(1):817.

3. Heikkala E, Rissanen I, Tanguay-Sabourin C, Vachon-Presseau E, **Chang JR**, Wong AYL, Karppinen J, Oura P. Antenatal socioeconomic status of childhood family and the risk of pain spreading (ROPS) in early and mid-adulthood - a descriptive study from the northern Finland birth cohort 1966. *Journal of Psychosomatic Research.* 2024, 189:112014.

4. Heikkala E, **Chang JR**, Nieminen SS, Vehkaperä K, Kajantie E, Karppinen J, Miettunen J, Wong AYL. Does birth weight or preterm birth predict worse pain prognosis in adulthood? A Northern Finland Birth Cohort study followed up to 46 years of age. *Journal of Pain*. 2024, 27:104773.

5. Huang FF, Liang J, Lin CY, Samartzis D, Karppinen J, Zheng Y, Zhou Z, Zheng

DKY, **Chang JR**, de Luca K, Wong AYL. Measurement properties of self-reported outcome measures for older adults with nonspecific low back pain: a systematic review. *Age and Ageing*. 2025, 54(3):afaf045.

6. Lee TKW, **Chang JR**, Hao D, Fu SN, Wong AYL. The Effectiveness of Auricular Acupressure on Chronic Musculoskeletal Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Journal of Integrative and Complementary Medicine*. 2024, 31(1):25-35.

7. Liu JQJ, Hui K, Al Z, Zhou Z, Samartzis D, Yu C, **Chang JR**, Wong AY. The great detectives : humans versus AI detectors in catching large language model-generated medical writing. *International Journal for Educational Integrity*, 2024, 20(1), 8.

8. Longtin C, **Chang JR**, Hersch J, Sharma S, Ferraro M, Rizzo R, McBride J, Wong AYL, Maher C, Guppy M, McAuley J, Traeger AC. One-page patient fact sheets for low back pain in primary care: A randomized clinical trial. *JAMA Network Open*. 2025.23352

9. Qi L, **Chang JR**, Zhang E. Cross-cultural adaptation, reliability and validity tests of the Chinese version of the Profile Fitness Mapping neck questionnaire. *BMC Musculoskeletal Disorders*, 2023, 24(1), 26–26.

10. Tao R, Yang Y, Wilson M, **Chang JR**, Liu C, Sit CHP. Comparative effectiveness of physical activity interventions on cognitive functions in children and adolescents with Neurodevelopmental Disorders: a systematic review and network meta-analysis of randomized controlled trials. *International Journal of Behavioral Nutrition and Physical Activity*. 2025, 22(1):6.

11. Zheng DKY, Liu JQJ, **Chang JR**, Ng JCY, Zhou Z, Wu J, Cheung CKC, Huang FF, Pinto SM, Samartzis D, Ferreira ML, Ekanayake K, Lord S, Wang X, Wong AYL. Are

changes in pain intensity related to changes in balance control in individuals with chronic non-specific low back pain? A systematic review and meta-analysis. *Journal of Sport and Health Science*. 2024, 14:100989.

12. Zheng DKY, Sun Z, **Chang JR**, Huang FF, Liu Y, Yu S, Wu J, Wang Z, Wong AYL, Wang X. Poor Sleep Quality Worsens Static and Dynamic Balance Control in Individuals With Chronic Low Back Pain: A Cross-Sectional Study. *Pain Research and Management.* 2025, 5224748.

13. Zhou Z, Hui ES, Kranz GS, **Chang JR**, de Luca K, Pinto SM, Chan WW, Yau S, Chau KH, Samartzis D, Jensen MP, Wong AY. Potential mechanisms underlying the accelerated cognitive decline in people with chronic low back pain: A scoping review. *Ageing Research Reviews*, 2022, 82, 101767–101767.

14. Wang C, Lu EY, Sun W, **Chang JR**, Tsang HWH. Effectiveness of interventions on sedentary behaviors in office workers: a systematic review and meta-analysis. *Public Health*. 2024, 230:45-51.

15. Xu Z, An N, **Chang JR**, Yang Y. Modulation of pain perceptions following treadmill running with different intensities in females. *Physiological Reports*, 2023, 11(18):e15831.

Other Awards

1. 1st Runner-up at the *GBA Health Tech Future Forum 2022*.

2. The People's Choice Award at the *Three Minute Thesis Competition of RS 2024*.

3. HKSAR Government Scholarship Fund-Reaching Out Award 2023/24.

4. The PolyU International Collaborative Research Fellowship 2023/24.

Acknowledgements

I am deeply thankful to my chief supervisor, Dr. Arnold Wong, whose unwavering support and expert guidance have been instrumental throughout my PhD journey. His mentorship has not only shaped the direction of my research but also greatly enriched my academic development.

I am also sincerely grateful to my co-supervisors Prof. Amy Fu, Dr. Eliza Sun, Dr. Shirley Li, Dr. Rachel Kwan, Dr. Xiaolin Mei, Dr. Ran Tao, and Dr. Dino Samartzis for their invaluable expertise in the areas of sleep, pain, and neuroimaging. Their insightful feedback and thoughtful discussions have inspired and refined many aspects of my work.

Special thanks go to the members of Dr. Wong's research team: Dr. Sabina Margaret Pinto, Dr. Zhixing Zhou, Mr. Daniel Zheng, Mr. Frank Huang, Ms. Chelisa Cheung, Ms. Jae Liu, and Mr. Leo Lin for their generous support and contributions throughout the project.

I am also appreciative of the assistance provided by student helpers: Mr. Ping Liang, Ms. Wenhui Wang, Ms. Yanru Xie, Ms. Jiamin Wu, and Ms. Yuning Wu for their key roles in data collection.

I would like to acknowledge the University Research Facility in Behavioral and Systems Neuroscience for its generous support, especially Dr. Tommy Lam and Dr. Celia Dong for their timely technical assistance and advice.

My heartfelt thanks extend to Prof. Chris Maher and Dr. Adrian Traeger for their kind mentorship and valuable input on research design and academic writing during my attachment.

I owe my deepest gratitude to my family, my fiancée Yawen, and my friends, whose continuous encouragement and support have sustained me through the many phases of this doctoral journey.

Table of Contents

CERTIFICATE OF ORIGINALITY I

Abstract II

List of Research Output during the Course of Study IV

Acknowledgements X

Table of Contents XI

List of Tables XV

List of Figures XVI

List of Appendices XVII

List of Abbreviations XIX

Chapter 1: General Introduction 1

1.1 Background 1

1.2 Dissertation Objectives 5

1.3 Outline of this Dissertation 5

Chapter 2: Literature Review 8

2.1 Chronic Pain 8

2.2 Sleep and Insomnia 19

2.3 Interactions between Sleep and Pain 21

2.4 Managements for Sleep and Pain 24

Chapter 3: The Differential Effects of Sleep Deprivation on Pain Perception in Individuals with or without Chronic Pain: A Systematic Review and Meta-Analysis 27

3.1 Abstract 29

3.2 Introduction 30

3.3 Methods 32
3.4 Results 36
3.5 Discussion 43
3.6 Conclusions 50
3.7 Tables 52
3.8 Figures 53
Chapter 4: Differential Pain Perception among Females with or without Non-specific Chronic Low Back Pain and Comorbid Insomnia: A Quantitative Sensory Testing Analysis 55
4.1 Abstract 57
4.2 Introduction 58
4.3 Methods 60
4.4 Results 67
4.5 Discussion 71
4.6 Conclusions 76
4.7 Tables 77
4.8 Figures 81
Chapter 5: Neural Oscillations and Brain Connectivity in Females with Chronic Low Back Pain and Comorbid Insomnia 83
5.1 Abstract 84
5.2 Introduction 85
5.3 Methods 87
5.4 Results 94
5.5 Discussion 96

5.6 Conclusions 101
5.7 Tables 102
5.8 Figures 104
Chapter 6: Are Changes in Sleep Quality/Quantity or Baseline Sleep Parameters Related to Changes in Clinical Outcomes in Individuals with Nonspecific Chronic Low Back Pain? A Systematic Review 106
6.1 Abstract 108
6.2 Introduction 109
6.3 Methods 111
6.4 Results 116
6.5 Discussion 122
6.6 Conclusions 127
6.7 Tables 128
6.8 Figures 139
Chapter 7 Comparative Effectiveness of Non-Pharmacological Interventions on Sleep in Individuals with Chronic Musculoskeletal Pain: A Systematic Review with Network Meta-Analysis 140
7.1 Abstract 142
7.2 Introduction 143
7.3 Methods 144
7.4 Results 148
7.5 Discussion 155
7.6 Conclusions 159

7.7 Tables 160
7.8 Figures 164
Chapter 8 The Efficacy and Safety of Repetitive Transcranial Magnetic Stimulation (rTMS) in Managing Individuals with Chronic Low Back Pain and Comorbid Insomnia: A Pilot Randomized Controlled Trial 166
8.1 Abstract 167
8.2 Introduction 168
8.3 Methods 170
8.4 Results 177
8.5 Discussion 180
8.6 Conclusions 185
8.7 Tables 186
8.8 Figures 189
Chapter 9: General Discussion and Conclusion 191
9.1 Summary of Research Findings 191
9.2 Summary of Research Findings 196
9.3 Future Research Directions 203
9.4 Limitations of the Studies 206
9.5 Conclusions 207
9.6 Figures 208
Appendices 209
References 351

List of Tables

Table 1. Effect sizes of subgroup analyses for different pain stimuli after various sleep deprivation paradigms in healthy individuals 52

Table 2. Summary of evidence regarding different sleep deprivation paradigms on the pain outcomes 52

Table 3. Demographic and clinical characteristics..... 77

Table 4. Group differences in QST measurements 79

Table 5. Hierarchical regression analysis to examine clinical variables and QST parameters within CLBP+I (n=25)..... 80

Table 6. Demographic and clinical characteristics..... 102

Table 7. Hierarchical regression analysis to examine clinical variables and brain measures within CLBP+I (n=25) 103

Table 8. Study characteristics of the included studies 128

Table 9. Associations between sleep quantity/quality and LBP-related outcome measures 132

Table 10. Grade evidence profile of the relation between sleep quantity/quality and LBP-related outcome measures..... 136

Table 11. Definitions of each intervention and control..... 160

Table 12. General characteristics of included studies 162

Table 13. The league table for sleep quality at immediate post-intervention 163

Table 14. Demographic and clinical characteristics..... 186

Table 15. Means and standard deviations for patient-reported outcome measures 187

Table 16. Means and standard deviations for sleep parameters and pain perception 188

List of Figures

Figure 1. A flow chart of literature searches 53

Figure 2. The effects of total sleep deprivation on pain threshold in healthy individuals 54

Figure 3. The effects of total sleep deprivation on pain tolerance in healthy individuals 54

Figure 4. Z-sore QST at low back (a) and remote (b) sites 81

Figure 5. Global power analysis and peak alpha frequency 104

Figure 6. Functional connectivity strength across three networks at the theta band 104

Figure 7. Global graph theory-based measures of functional connectivity 105

Figure 8. A flow chart of literature searches 139

Figure 9. A flow chart of literature searches 164

Figure 10. The network plot for sleep quality at immediate post-intervention 165

Figure 11. CONSORT flow chart of the study procedure 189

Figure 12. Patient-reported outcome measures over time 190

Figure 13. Management in chronic pain and sleep 208

Figure 14. Future research directions 208

List of Appendices

Appendix 1. Search strategy in Chapter 3 209

Appendix 2. Level of evidence in Chapter 3 210

Appendix 3. Study characteristics of the included studies in Chapter 3 211

Appendix 4. Risk of bias assessment for the included studies in Chapter 3 218

Appendix 5. A funnel plot of the publication bias for articles in Chapter 3 220

Appendix 6. Meta-analysis results in Chapter 3 221

Appendix 7. Intra-rater reliability of QST in Chapter 4 228

Appendix 8. Sensitivity analyese of QST in Chapter 4 229

Appendix 9. One-way ANOVA of functional connectivity with post-hoc analyses in Chaper 5 232

Appendix 10. One-way ANOVA of brain network measures with post-hoc analyses in Chaper 5 234

Appendix 11. Search strategy in Chapter 6..... 237

Appendix 12. Outcome measures of included studies in Chapter 6 238

Appendix 13. Risk of bias assessment for the included studies in Chapter 6..... 240

Appendix 14. Search strategy in Chapter 7 241

Appendix 15. Additional details on Methods in Chapter 7..... 242

Appendix 16. Study characteristics of the included studies in Chapter 7..... 243

Appendix 17. Risk of bias assessment for the included studies in Chapter 7..... 265

Appendix 18. Comparison-adjusted funnel plots in Chapter 7..... 270

Appendix 19. Pairwise meta-analyses in Chapter 7..... 275

Appendix 20. Assessment of transitivity in Chapter 7 284

Appendix 21. Assessment of heterogeneity in Chapter 7 286

Appendix 22. Assessment of inconsistency in Chapter 7 288
Appendix 23. Network plots in Chapter 7 289
Appendix 24. Rank results and SUCRA in Chapter 7 296
Appendix 25. League tables of the network meta-analysis in Chapter 7 314
Appendix 26. Adverse events in Chapter 7 326
Appendix 27. Sensitivity analyses for sleep quality in Chapter 7 330
Appendix 28. Meta-regression in Chapter 7 334
Appendix 29. Grading the evidence of the network meta-analysis in Chapter 7 335
Appendix 30. Adverse events of rTMS in Chapter 8 349
Appendix 31. Exploratory association between outcome measures in Chapter 8 350

List of Abbreviations

ACC: Anterior Cingulate Cortex

AEC: Amplitude Envelope Correlation

ANCOVA: Analysis of Covariance

ANOVA: Analysis of Variance

AOR: Adjusted Odds Ratio

BMI: Body Mass Index

CBT: Cognitive Behavioral Therapy

CINeMA: the Confidence in Network Meta-Analysis

CLBP: Chronic Low Back Pain

CLBP+: Chronic Low Back Pain alone

CLBP+I: Chronic Low Back Pain Comorbid Insomnia

CONSORT: Consolidated Standards of Reporting Trials

CPM: Conditioned Pain Modulation

CPT: Cold Pain Threshold

CS: Conditioning Stimulus

DFNS: German Research Network on Neuropathic Pain

DASS: Depression Anxiety Stress Scale

DLPFC: Dorsolateral Prefrontal Cortex

DMN: Default Model Network

DSM-5: Diagnostic and Statistical Manual of Mental Disorders 5th edition

dwPLI: Debiased Weighted Phase Lag Index

EEG: Electroencephalography

ES: Effect Size

FABQ: Fear-Avoidance Beliefs Questionnaire

fMRI: Functional Magnetic Resonance Imaging

FPN: Frontoparietal Network

GRADE: Grading of Recommendations Assessment Development and Evaluation

GRC: Global Rating of Change Scale

fMRI: Functional Magnetic Resonance Imaging

HPT: Heat Pain Threshold

ICA: Independent Component Analysis

ICC: Intraclass Correlation Coefficient

ICD: International Classification of Diseases

IQR: Interquartile Range

Insomnia+: Insomnia alone

ISI: Insomnia Severity Index

k: Kappa Coefficient

LBP: Low Back Pain

M1: Primary Motor Cortex

MCC: Midcingulate Cortex

MNI: Montreal Neurologic Institute

MOOSE: Meta-analysis Of Observational Studies in Epidemiology reporting

MPT: Mechanical Pain Threshold

MRI: Magnetic Resonance Imaging

NAW: Number of Awakenings

NMA: Network Meta-Analysis

NPRS: Numerical Pain Rating Scale

NREM: Non-Rapid Eye Movement

OR: Odds Ratio

PAG: Periaqueductal Gray

PCC: Posterior Cingulate Cortex

PCS: Pain Catastrophizing Scale

PGI: Global Impression of Pain Rating

PICOS: Populations, Intervention, Comparison, Outcomes, and Study Design

PPT: Pressure Pain Threshold

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: International Prospective Register of Systematic Reviews

PSQI: Pittsburgh Sleep Quality Index

QST: Quantitative Sensory Testing

QUIPS: Quality of Prognosis Studies Risk of Bias Assessment Instrument for Prognostic Factor Studies

RCT: Randomized Controlled Trial

REM: Rapid Eye Movement

RMDQ: Roland Morris Disability Questionnaire

RMT: Resting Motor Threshold

RoB: Cochrane Collaboration Risk of Bias

ROBINS-I: Risk of Bias in Non-randomized Studies of Interventions

rTMS: Repetitive Transcranial Magnetic Stimulation (rTMS)

RVM: Rostroventromedial Medulla

S1: Primary Sensory Cortex

S2: Secondary Sensory Cortex

SD: Standard Deviation

SE: Sleep Efficiency

SMD: Standardized Mean Differences (SMD)

SN: Salience Network

SOL: Sleep Onset Latency

SUCRA: Surface Under the Cumulative Ranking curves

tDCS: Transcranial Direct Current Stimulation

TS: Test Stimuli

TSP: Temporal Summation of Pain

TSP-M: Temporal Summation of Mechanical Pain

TSP-H: Temporal Summation of Heat Pain

TST: Total Sleep Time

UOR: Unadjusted Odds Ratio

VAS: Visual Analog Scale

VIF: Variance Inflation Factor

WASO: Wake Time After Sleep Onset

YLD: Years Lived with Disability

95% CI: 95% Confidence Interval

Chapter 1: General Introduction

1.1 Background

Chronic pain is a major global health challenge and remains one of the leading contributors to years lived with disability worldwide [1], affecting approximately 11.0 to 43.5% of individuals across diverse populations [2]. It is one of the most frequent reasons for people seeking medical care, imposing a tremendous burden on individuals and society [3]. Empirical evidence underscores strong associations between chronic pain and co-occurring symptoms, such as depression, anxiety, maladaptive pain-related thoughts, sleep disturbances, and cognitive impairment [2, 4, 5]. Compared to asymptomatic individuals, those with chronic pain are significantly more prone to experience these comorbidities [1, 2], which in turn contribute to diminished health status, increased functional impairment, and greater work absenteeism [6, 7]. Therefore, it is paramount to understand the interplay between chronic pain and its common comorbidities so as to improve clinical management and patient outcomes.

Sleep disturbance, especially insomnia, represents one of the most common comorbidities, impacting more than 70% of people living with chronic pain [8]. Emerging evidence indicates that sleep disturbance not only increases the risk of developing chronic pain [9] but also exacerbates pain intensity, functional disability, and poor prognosis in this population [10, 11]. Furthermore, comorbidity with chronic pain and insomnia is associated with greater emotional distress and dysregulated pain processing [12, 13]. These maladaptive psychological and physiological alterations likely contribute to increased healthcare utilization and challenges in pain management. For instance, a longitudinal study reported a 2.1-fold higher hospitalization rate in patients with comorbid conditions compared to those without sleep disturbances [14].

Although the link between sleep and pain is well recognized, the underlying physiological mechanisms driving this relationship remain insufficiently understood. Recent narrative reviews have highlighted several proposed pathways through which sleep disruption may heighten pain sensitivity. These include elevated production of proinflammatory cytokines, imbalances in autonomic nervous system function, the presence of negative emotional states or mood disorders, and disruptions in central nociceptive processing [15-18]. In particular, growing interest has centered on how peripheral and central pain modulation mechanisms contribute to explaining this complex interaction.

Numerous studies have employed experimental sleep deprivation paradigms to investigate alterations in pain perception and elucidate the potential causal link between disrupted sleep and pain processing [19-25]. While a previous systematic review and meta-analysis reported moderate to large effects of sleep deprivation on increasing pain sensitivity in healthy individuals [26], it pooled data across different sleep deprivation paradigms (total, partial, and selective sleep deprivation) and diverse pain-related measures (spontaneous pain intensity and sensory pain threshold). However, this approach limits the ability to discern how different sleep deprivation paradigms uniquely affect pain responses. Importantly, there is a lack of evidence regarding how sleep loss impacts pain perception in people with chronic pain.

While experimental sleep deprivation paradigms significantly elicited spontaneous pain intensity, reduced pain threshold to noxious sensory stimuli, and increased central sensitization in healthy individuals [27], such paradigms primarily involve the disruption of total or partial sleep

duration, which may not accurately reflect the sleep patterns of individuals with chronic pain. They more commonly report multiple nighttime awakenings instead of complete or partial sleep deprivation [28-30]. Moreover, individuals with chronic pain have already exhibited peripheral or central sensitization and aberrant pain processing, leading to different responses to noxious stimuli compared to healthy individuals [31-33]. Therefore, the existing findings from experimental sleep deprivation in healthy individuals may not provide a precise understanding of pain perception observed in people with comorbid chronic pain and insomnia. More importantly, no neuroimaging studies have investigated how comorbid insomnia affects brain oscillatory activity during resting state in this clinical population.

Studies have indicated that recovery sleep following sleep deprivation can restore pain threshold [34-36]. A logical follow-up question arises as to whether changes in sleep parameters are prospectively linked to the respective changes in pain-related symptoms. To date, no systematic review has thoroughly synthesized the evidence regarding the longitudinal relationship between sleep and pain in individuals with (CLBP). Furthermore, existing studies have reported inconsistent findings regarding the predictive value of sleep parameters in pain-related outcomes in this population, highlighting the need for further investigation.

Given the established causal link between sleep and pain, systematic reviews of longitudinal research have consistently showed that alleviating sleep disturbances is related to reductions in pain intensity, enhanced recovery, and improved health outcomes among individuals with chronic pain [37-39]. These findings underscore that sleep may be an important therapeutic target to prevent the incidence of pain or alleviate symptoms of chronic pain. Previous

conventional meta-analyses have shown promising effects of non-pharmacological treatments addressing sleep disturbance in individuals with chronic pain [40-45]. Nevertheless, it remains unclear which non-pharmacological intervention has superior effectiveness for improving sleep problems in these cases.

Current treatment options for comorbid chronic pain and insomnia remain limited. To date, most research has centered on cognitive behavioral therapy (CBT), which is widely regarded as the most effective intervention for improving sleep quality and efficiency in individuals with chronic pain [41, 46]. However, its clinical implementation is hindered by low adherence, high costs, and a shortage of credentialed clinicians in primary care settings [47, 48]. These barriers highlight the need for novel and effective treatment strategies. Given that comorbid chronic pain and insomnia may stem from dysregulated central pain processing and abnormal brain activity [12, 49], targeted brain modulation approaches could potentially restore these imbalances and improve clinical outcomes. Repetitive transcranial magnetic stimulation (rTMS), a noninvasive neuromodulation method, could modulate cortical excitability, enhance synaptic plasticity, and alter brain network connectivity across a range of neurological and psychiatric conditions [50, 51]. When applied at specific frequencies to targeted cortical regions, rTMS has shown promise in alleviating symptoms of chronic pain and insomnia independently [52-57]. However, to date, no research has directly compared the efficacy of different rTMS protocols in individuals with comorbid CLBP and insomnia.

1.2 Dissertation Objectives

Against the above backgrounds, this project aimed to address critical gaps in the understanding and treatment of comorbid chronic pain and insomnia. The specific objectives were to (1) examine the impact of experimental sleep deprivation on pain perception in healthy individuals and those with chronic pain; (2) investigate pain perception and neurophysiological characteristics associated with comorbid CLBP and insomnia; (3) explore the prospective relationship between sleep quality/quantity and pain-related outcomes in people with CLBP; (4) evaluate the relative effectiveness of non-pharmacological treatments for improving sleep quality in individuals with chronic musculoskeletal pain; and (5) assess the feasibility and acceptability of rTMS treatment in individuals with comorbid CLBP and insomnia.

1.3 Outline of this Dissertation

To achieve these objectives, this Dissertation includes eight chapters, involving three systematic reviews, one cross-sectional study, and one pilot randomized controlled trial. The results presented in Chapters 3 through 7 have been published in peer-reviewed academic journals (i.e., The Clinical Journal of Pain, PAIN, Sleep Medicine Reviews, and Journal of Pain).

Chapter 2 provides a comprehensive literature review covering the pain pathway, quantitative sensory testing, neuroimaging findings related to chronic pain, sleep and insomnia, interplay between sleep and pain, and current approaches to managing sleep in chronic pain.

Chapter 3 is a systematic review and meta-analysis to synthesize evidence on how distinct sleep deprivation paradigm affect pain responses as measured by changes in spontaneous pain

intensity, pain threshold, pain tolerance, conditioned pain modulation, and temporal summation of pain in individuals with and without chronic pain.

Chapter 4 is a cross-sectional study using quantitative sensory testing (QST) protocol to assess pain perception among four groups of age-matched females with CLBP, insomnia, comorbid conditions, or neither. This study also explores the association between clinical variables and QST assessments within the comorbid CLBP and insomnia group.

Chapter 5 is a cross-sectional study utilizing resting-state electroencephalography (EEG) to quantify neural oscillatory activity and functional brain connectivity across four groups of age-matched females, including healthy controls, those with CLBP, insomnia, and concomitant conditions. This study also examines whether insomnia independently contributed to neural alterations within the comorbid CLBP and insomnia group.

Chapter 6 is a systematic review to evaluate the prospective associations between sleep quality and pain-related outcomes in people with CLBP. Specifically, it evaluates whether improvements in sleep measures are linked to concurrent improvements in clinical variables and whether baseline sleep predicts future pain outcomes.

Chapter 7 is a systematic review and network meta-analysis comprehensively assessing the comparative effectiveness of non-pharmacological treatments for improving sleep in individuals with chronic musculoskeletal pain.

Chapter 8 is a pilot randomized controlled trial to assess the feasibility, acceptability, and preliminary efficacy of different rTMS protocols in individuals with CLBP and comorbid with insomnia. This study also explores the preliminary effects of rTMS on pain perception, sleep parameters, and psychological outcomes.

Chapter 9 presents an integrated discussion of the key findings across studies, significance and implications of the findings, study limitations, and overall conclusions drawn from this thesis.

Chapter 2: Literature Review

2.1 Chronic Pain

2.1.1 Definition and Prevalence

Pain that persists beyond the expected healing period following a peripheral injury can result in long-lasting chronic pain. According to the International Association for the Study of Pain and the 11th edition of the International Classification of Diseases (ICD-11), chronic pain is characterized by persistent or recurrent pain lasting longer than three months [58]. To enhance the diagnostic clarity and utility in both clinical and research setting, the ICD-11 delineates seven distinct codes representing the most prevalent and clinically significant groups of chronic pain conditions [58-65]. This classification system provides a standardized framework that facilitates advances in research, guides health policy, and supports the delivery of more effective, individualized patient care.

The prevalence of chronic pain varies widely, ranging from 11.0 to 43.5% across different populations and regions [2]. In the United States, statistics from the Centers for Disease Control and Prevention indicate that approximately 20.4% of adults suffer from chronic pain [66], while a systematic review in the United Kingdom identified a prevalence as high as 43.5% [67]. In China, a large cross-sectional study estimated a point prevalence of 31.5% [68], which aligns with the prevalence rate observed in low- and middle-income countries (33.0%) [69]. Chronic pain is not only highly prevalent but also a major contributor to global years lived with disability, imposing a tremendous burden on individuals and healthcare system [1]. Four of the top six contributors to YLD—low back pain, musculoskeletal disorders, migraine, and neck pain—are chronic pain conditions [70]. The economic impact is profound, with annual costs attributed to

chronic pain estimated between US$560 billion and US$635 billion, surpassing expenses associated with heart disease (US$309 billion), cancer (US$243 billion), and diabetes (US$188 billion) [71].

Individuals with chronic pain tend to utilize healthcare services more frequently and present with greater comorbidity compared to asymptomatic individuals [1, 2]. Research has reported that chronic pain ranks among the leading reasons for medical consultations, with three of the top ten causes of healthcare visits (osteoarthritis, back pain, and headaches) [3]. Moreover, chronic pain frequently coexists with a range of other symptoms involving depression, anxiety, catastrophizing, poor sleep, and cognitive dysfunctions [2, 4]. These comorbidities further exacerbate declines in health status, impair daily functioning, and increase work absenteeism [6, 7]. These patterns are consistent with the biopsychosocial framework of chronic pain, which underscores the multi-dimensional and dynamic interaction between chronic pain and biological, psychological, and social factors in shaping the pain experience and its consequences [72]. Given the high prevalence, substantial impact, and complex nature of chronic pain, there is an urgent need for advances in understanding and managing this condition.

2.1.2 Pain Pathway

Pain perception arises from the dynamic integration of sensory, affective, and cognitive components, mediated by complex interactions within ascending and descending pathways of the nervous system [73]. Noxious signals originating in peripheral tissues are conveyed to the central nervous system through ascending pain pathways [74, 75]. This process is initiated by the activation of primary afferent nociceptors in the periphery, specialized to detect harmful

mechanical, thermal, or chemical stimuli [76]. Nociceptors are broadly classified into two types based on axonal diameter, degree of myelination, and conduction velocity: Aδ fibers and C fibers [76, 77]. Myelinated, medium-diameter Aδ fibers respond to intense pressure and extreme temperatures, conducting impulses at speeds of 5-30 m/s [75, 78]. In contrast, unmyelinated, small-diameter C fibers, with a slow conduction speed of around 1 m/s, can be activated by various noxious stimuli, including high-intensity mechanical, thermal, or chemical stimuli [75, 78]. Following peripheral activation, nociceptive signals enter the spinal cord's dorsal horn, synapsing onto second-order neurons [74, 75]. These signals are subsequently relayed to supraspinal structures via two principal ascending tracts: the spinothalamic and spinoreticulothalamic pathways [74, 75]. The spinothalamic tract, located within the lateral funiculus of the spinal cord, conveys nociceptive information to the thalamus and subsequently to the somatosensory cortex, which processes the sensory-discriminative aspects of pain [75, 79, 80]. In parallel, the spinoreticulothalamic tract, primarily situated in the medial funiculus, projects to limbic structures such as the cingulate and insular cortices through connections with the parabrachial nucleus and amygdala [75, 79, 80]. This medial pathway is essential for processing the affective-motivational components of pain, shaping its emotional and behavioral responses [75].

Following processing in the brainstem and thalamus, nociceptive signals ascend to the cerebral cortex for higher-order integration. Importantly, no single cortical region is exclusively responsible for processing noxious stimuli [81]. Rather, pain perception emerges from the coordinated activation of a distributed network of brain regions, including the primary (S1) and secondary (S2) somatosensory cortices, anterior cingulate cortex (ACC), midcingulate cortex

(MCC), posterior cingulate cortex (PCC), prefrontal cortex, insula, motor cortex, supplementary motor area, thalamus, cerebellum, basal ganglia, and amygdala [82-84]. This interconnected network, traditionally referred to as the “pain matrix”, has been proposed to underpin the multidimensional experience of pain, encompassing its sensory, affective, and cognitive dimensions [73, 85].

However, the functional specificity of the “pain matrix” has been questioned. The extent to which the observed brain activations reflect nociceptive processing versus broader stimulus-related responses remains uncertain [75]. Notably, Notably, similar patterns of cortical activation have been elicited by non-noxious, attention-demanding, or emotionally salient stimuli, suggesting that these regions may participate in general salience detection rather than being uniquely pain-specific [77]. In light of these findings, the concept of dynamic pain connectome has been proposed to challenge the “pain matrix” notion. This model emphasizes that neural communication occurs across the large-scale network, incorporating pain- and attention-related circuits [86, 87]. The brain dynamics engage in spontaneous and fluctuating patterns of neural activity across multiple timescales, which offers valuable insights into the neural mechanisms of pain perception and modulation [86, 87].

The descending inhibitory pain pathway refers to a top-down modulatory system in which supraspinal regions (e.g., the brainstem and higher cortical areas) project to the spinal cord’s dorsal horn to suppress incoming nociceptive signals [88]. Often referred to as the endogenous descending anti-nociceptive network, this system encompasses several key brain regions such as the rostral and pregenual anterior cingulate cortex, periaqueductal gray (PAG), parahippocampal

area, hypothalamus, and the rostral ventromedial brainstem [79, 89]. Among these, the PAG plays a central role, serving as a key hub that integrates afferent signals from cortical structures, the amygdala, and the hypothalamus to modulate pain [89, 90]. Projections from the PAG to the spinal cord via the RVM activate the endogenous opioid system, thereby suppressing pain [89, 91]. Within the RVM, three physiologically distinct neuron populations—on-cells, off-cells, and neutral cells—mediate this modulatory process, characterized by their differential responses to noxious stimuli [92]. Specifically, activation of off-cells leads to the inhibition of pain transmission, as observed in response to analgesic doses of morphine or PAG stimulation [92-94]. In contrast, on-cells activation contributes to the descending facilitation of pain, which can be activated by nociceptive signals or different pain models [92-94]. Overall, the dynamic interplay between ascending nociceptive and descending modulatory pathways is fundamental to the regulation of normal nociceptive processing. Disruption of this balance is increasingly recognized as a critical contributor to the onset and persistence of chronic pain conditions.

2.1.3 Quantitative Sensory Testing for Chronic Pain

Pain assessment primarily relies on self-report instruments due to its subjective nature of pain experience [95, 96]. However, commonly used patient-reported outcome measures (e.g., the McGill Pain Questionnaire, the Numeric Pain Rating Scale, and the Visual Analogue Scale) only capture the severity of internal pain experience but offer limited insight into the underlying mechanisms contributing to pain [95]. In contrast, quantitative sensory testing (QST) provides a standardized, laboratory-based approach to evaluating pain perception that may reflect the functional status and excitability of both central and peripheral pain pathways [97-100]. QST

encompasses a range of psychophysical methods designed to assess and quantify sensory function by measuring perceptual responses (e.g., suprathreshold, threshold, and tolerance) across diverse types of stimuli (e.g., thermal, pressure, mechanical, electrical, and vibration stimuli). Importantly, data derived from QST hold the potential to serve as diagnostic, predictive, and prognostic biomarkers that enhance our understanding of pain pathophysiology and facilitate the development of optimal treatment strategies tailored to individuals with chronic pain [101-105].

The German Research Network on Neuropathic Pain (DFNS) has developed the most systematic and extensive quantitative sensory testing (QST) protocol. This standardized framework encompasses a range of assessments, including thermal detection thresholds (cold, warmth, and thermal sensory limen), mechanical detection thresholds (touch and vibration), thermal pain thresholds (cold and heat), mechanical pain thresholds (pressure and pinprick), and the temporal summation of pinprick stimuli [97, 98]. The DFNS protocol has demonstrated acceptable to excellent inter-rater and test-retest reliability across diverse chronic pain conditions [106-109]. Recent frameworks classify QST into static and dynamic modalities based on the nature of the stimuli and sensory responses assessed [100, 110]. Static QST focuses on determining sensory thresholds or pain-magnitude ratings in response to given stimuli [100]. These tests provide information about an individual's pain perception and the basal state of their nociceptive system [100]. Heightened sensitivity to sensory stimuli within the area of injury or damage reflects peripheral sensitization, whereas increased sensitivity beyond the affected area indicates central sensitization [31, 106]. In contrast, dynamic QST evaluates the ability of the central nervous system to modulate pain in response to sequential or concurrent noxious stimuli [100, 110]. The

most commonly used dynamic tests include temporal summation of pain (TSP) and conditioned pain modulation (CPM). TSP reflects facilitation of ascending nociceptive pathways, while CPM can serve as a proxy measure for the endogenous descending inhibitory control [31, 106, 111]. Together, static and dynamic QST approaches provide insights into the mechanisms underlying pain modulation and the interplay between peripheral and central nervous system contributions to pain perception.

Emerging evidence from QST supports the presence of both peripheral and central sensitization across a range of chronic pain conditions. Specifically, individuals with chronic pain exhibit significantly reduced pain thresholds within affected regions compared to those without pain, as evidenced by diminished sensitivity to pressure and heat stimuli in the lumbar region among those with CLBP [13, 106, 112, 113]. Additionally, recent systematic reviews have identified widespread sensory abnormalities in individuals with chronic pain compared to asymptomatic populations, including lower pain thresholds at remote sites, diminished efficiency of CPM, and enhanced TSP [114-116]. However, considerable inter-individual and inter-condition variability exists in the prevalence and magnitude of peripheral and central sensitization [117-119]. In certain conditions such as fibromyalgia, central sensitization features are observed in the majority of patients, while in other pain conditions, these features may only be evident in specific subgroups, either the majority in some cases (e.g., osteoarthritis) or a minority in others (e.g., shoulder pain) [31]. These results underscore alterations in the neurophysiological processing of nociceptive input in chronic pain and highlight the heterogeneous and condition-specific nature of sensitization mechanisms across different chronic pain populations.

2.1.4 Brain Imaging in Chronic Pain

Recent advances in neuroimaging substantially deepened our comprehension of the neural processes involved in chronic pain. Neuroimaging studies in humans have identified structural and functional brain abnormalities linked to chronic pain and its clinical manifestations [120-122]. Structural magnetic resonance imaging (MRI) have demonstrated associations between chronic pain and alterations in regional gray matter (e.g., decreased gray matter volume, concentration, or density in certain brain areas) and regional white matter (e.g., disruption in structural integrity, myelination, or connectivity of the fiber pathways) [122-126]. Notably, gray matter atrophy has been observed in brain regions related to the sensory, emotional, and cognitive dimensions of pain processing. These regions include S1, S2, ACC, MCC, PCC, prefrontal cortex, thalamus, anterior and posterior insula, amygdala, and hippocampus [122, 123]. These structural alterations may reflect the impact of chronic pain on brain areas critical to pain perception, emotional responses, and cognitive appraisal. Studies have also demonstrated that white matter abnormalities, particularly within prefrontal areas and corticolimbic regions, are related to the transmission of pain signals and the transition from acute to chronic pain states [124-126]. Beyond structural alterations, functional MRI (fMRI) utilizing task-based and resting-state paradigms has revealed abnormal neural activation and connectivity patterns in those experiencing chronic pain. Systematic reviews of task-based fMRI studies have reported aberrant activation to noxious stimuli in key pain-processing areas, including S1, S2, ACC, prefrontal cortex, thalamus, and insular cortex [84, 127]. Furthermore, resting-state fMRI studies have uncovered disruptions in functional connectivity within and between large-scale brain networks, particularly within the dynamic pain connectome (default model network (DMN), salience network (SN), and antinociceptive system) [86, 87]. However, it is important to acknowledge

that alterations in brain morphometric changes and functional connectivity are not uniform across diverse chronic pain conditions [20; 212]. This heterogeneity implies that the neurophysiological underpinnings of chronic pain likely vary depending on the particular type of pain condition. Therefore, a nuanced and individualized approach is essential for investigating and addressing the neurophysiological features of each specific pain condition.

Compared to MRI and fMRI, electroencephalography (EEG) provides a more accessible and cost-effective neuroimaging modality with superior temporal resolution in the millisecond range [128, 129]. This high temporal precision makes EEG particularly well-suited for capturing rapid spatiotemporal brain activity and holds promise for identifying neurophysiological biomarkers to aid in the diagnosis and evaluation of treatment responses in individuals with chronic pain [128]. Among EEG applications in pain research, one of the most widely adopted paradigms involves recording cerebral responses to transient noxious stimuli, such as brief thermal stimuli [128, 130]. This approach yields valuable insights into the temporal sequence of pain processing, characterized by stimulus-evoked changes in amplitude, latency, and neural oscillatory activity [131]. Time-domain analyses of these evoked potentials have identified characteristic components, including the early negative peak (N1) occurring 50-200 ms post-stimulus, the subsequent negative peak (N2) at 200-400 ms, and the positive peak (P2) at 300-500 ms, along with their respective latencies [33, 132-134]. The early components predominantly capture the sensory-discriminative dimension of pain, while later components are more closely associated with affective-motivational appraisal [33]. Recent systematic reviews have reported a significant elevation in early- and late-phase somatosensory evoked potentials in individuals with chronic pain relative to asymptomatic individuals [33]. These findings indicate that chronic pain is

characterized by disrupted sensory processing and aberrant cognitive-emotional modulation of nociceptive input [33, 134, 135].

Beyond time-domain analyses, time-frequency analyses have been employed to explore non-phase-locked modulations of ongoing neural oscillations across multiple frequency bands, including theta (4.0–8.0 Hz), alpha (8.0–13.0 Hz), beta (14.0–30.0 Hz), and gamma (30.0–100.0 Hz) [131, 136-138]. These oscillatory activities are thought to reflect the dynamic coordination of functional networks through the segregation and integration of distributed brain regions [139]. Previous studies demonstrated that gamma-band oscillations in the sensorimotor cortex, induced by brief stimuli, were associated with subjective pain perception and stimulus intensity [139, 140]. These analyses provide complementary information regarding the dynamic processes by which nociceptive information is integrated with contextual and cognitive factors to shape the pain experience [128, 141]. However, cortical responses elicited by transient noxious stimuli may not precisely represent pain perception or ongoing clinical pain experiences. Instead, these responses predominantly reflect the salience or defensive actions triggered by the noxious stimuli [142, 143].

Novel experimental pain paradigms employing longer-lasting noxious stimulation offer valuable opportunities to investigate the neural mechanisms underlying ongoing pain experiences [144-147]. Previous research in healthy individuals found that decreases in alpha and beta oscillatory activity within the sensorimotor cortex during prolonged pain stimulation corresponded with objective stimulus intensity, whereas increases in gamma oscillations within prefrontal areas encoded subjective pain perception [130, 144-149]. Furthermore, recent studies demonstrated

alterations in functional connectivity within alpha and beta frequency bands in response to prolonged pain [150, 151]. Importantly, the patterns of brain activity during tonic noxious stimulation significantly differ from those elicited by brief stimuli [146-149]. Despite these advances, the systematic characterization of cortical oscillatory dynamics during tonic pain has largely been restricted to healthy populations. There is limited evidence on how tonic pain is neurophysiologically represented in individuals suffering from chronic pain, highlighting the need for additional research in this area.

Resting-state EEG recordings offer a valuable approach to investigating the neurophysiological alterations associated with chronic pain. In contrast to task-based approaches that depend on external inputs, resting-state EEG measures spontaneous neural activity, providing a representation that better reflects the ongoing symptoms experienced in chronic pain [129, 152]. These recordings capture intrinsic oscillatory patterns and synchrony within brain networks, serving as potential biomarkers for the objective diagnosis and personalized management of chronic pain [128]. A typical oscillatory pattern in chronic pain is thalamocortical dysrhythmia, characterized by a shift from the alpha to theta band activity in thalamocortical circuits, accompanied by increased beta and gamma oscillations in surrounding areas [134, 141, 153-158]. However, these patterns have not been consistently observed across studies, potentially due to insufficient consideration of comorbidities and condition-specific factors [32]. Additionally, most studies primarily focused on oscillatory brain activity rather than investigating connectivity patterns in the context of chronic pain [32, 141, 159]. To better understand the neurophysiological mechanisms underlying chronic pain, future research should systematically account for comorbidities and examine brain connectivity and network dynamics.

2.2 **Sleep and Insomnia**

2.2.1 Sleep and Health

Sleep is an inherent aspect of human life, with individuals spending roughly one-third of their lifetime asleep. It plays a vital role in maintaining both our mental and physical well-being. The National Sleep Foundation advises that adults obtain between seven and nine hours of sleep each night [160]. However, inadequate sleep can profoundly impair various cognitive functions, including attention, working memory, emotional regulation, and learning [161-164]. For example, sleep deprivation can amplify amygdala reactivity in response to negative emotional stimuli, which leads to over-generalized emotional sensitivity and distorted interpretations of facial expressions [161, 164]. Moreover, poor sleep is linked to a heightened risk of developing a variety of physical or mental disorders, such as hypertension, cardiovascular disease, diabetes, depression, obesity, and even premature mortality [165, 166]. Thus, obtaining high-quality, sufficient sleep is vital for restoring optimal functioning and reducing the risk of chronic health problems.

2.2.2 Insomnia Disorder

Insomnia is a highly prevalent sleep disorder and poses a significant public health concern. Around one-third of the population suffers from insomnia symptoms, while an estimated 6.0% to 10.0% meet the diagnostic criteria for a sleep disorder [167, 168]. Epidemiological studies across European countries have revealed considerable variations in the prevalence of insomnia, ranging from 5.7% in Germany to 19.0% in France. These differences could largely be attributed to differences in how insomnia is defined and diagnosed [169]. The Diagnostic and Statistical

Manual of Mental Disorders, Fifth Edition (DSM-5), defines insomnia based on these criteria: (1) trouble initiating sleep, maintaining sleep, or early awakening after sleep onset; (2) symptoms present on at least three nights per week for a duration of three months or longer; and (3) impaired daytime functioning, encompassing fatigue, cognitive impairment, or mood disturbances [167].

Previous studies has demonstrated insomnia as a strong risk contributor for mental health disorders [170], cardiovascular disease [171], and diabetes [172]. It frequently coexists with psychiatric, medical, and neurological conditions and substance use disorders, such as depressive disorders, chronic pain, neurodegenerative diseases, and opioid use [169]. Due to the frequent complaints of daytime symptoms associated with poor sleep, numerous studies have consistently demonstrated that insomnia significantly impairs daily functioning, leading to fatigue, irritability, reduced work productivity, and diminished quality of life [173, 174]. These impairments not only drive individuals to seek healthcare but also contribute to substantial burdens at both the individual and societal levels [175]. The average annual direct and indirect costs are estimated at $1,431 for individuals with insomnia symptoms and $5,010 for those diagnosed with insomnia disorder, compared to $421 for individuals without insomnia [176].

Given the high prevalence and significant consequences of insomnia, several potential mechanisms have been proposed to elucidate its underlying causes, such as heritability, genetic variants, childhood adversity, circadian dysfunction, impaired functioning of the homeostatic sleep regulation, and malfunctioning emotional and motivational regulation [30, 48]. Among these concepts, the hyperarousal model emerges as a well-established maintenance factor of

insomnia disorder [177-179]. Individuals with insomnia often exhibit heightened cognitive preoccupation with sleep-related difficulties and persistent rumination about their sleep complaints, which can be attributed to increased physiological, cognitive, or cortical arousal during sleep and wakefulness [177-179]. Physiological studies have demonstrated dysregulation in the sympathetic nervous system (e.g., altered heart rate and heart rate variability) and the hypothalamic-pituitary-adrenal axis (e.g., elevated levels of cortisol and adrenocorticotropic hormone) in individuals with insomnia disorder [180, 181]. Furthermore, a recent systematic review of resting-state EEG studies reported increased theta, alpha, beta, and gamma oscillations in individuals with insomnia relative to healthy sleepers across wakefulness and different sleep stages [152]. Complementary findings from an fMRI review by *Fasiello* et al. revealed impaired functional connectivity patterns in insomnia, characterized by increased activity within the DMN, SN, and sensorimotor network, along with decreased connectivity in the frontoparietal network [182]. Collectively, these findings underscore disruptions in both physiological regulation and brain network activity, reinforcing the concept that hyperarousal plays a central role in insomnia.

2.3 Interactions between Sleep and Pain

2.3.1 The Relationship between Sleep and Pain

Sleep disturbance, especially insomnia, is a common biological factor that affects over 70% of individuals with chronic pain [8]. The conventional perspective acknowledges a reciprocal relationship between sleep and pain, where sleep disturbance predicts subsequent pain symptoms and vice versa [10, 37, 183]. However, recent systematic reviews have challenged this notion, demonstrating that self-reported sleep quality on a given night is predictive of increased pain

intensity the next day, while variations in pain levels experienced the day before do not have a significant impact on sleep quality the following night [11, 184]. Prospective studies further support this unidirectional association: baseline sleep disturbances have been shown to predict the future onset of pain conditions but not vice versa [185-187]. Experimental sleep deprivation paradigms in healthy individuals have similarly demonstrated that inadequate sleep increases spontaneous pain complaints and lowers pain thresholds [19-25]. Considering the widespread occurrence of sleep disturbances in chronic pain and the causality between sleep and pain, recent systematic reviews of longitudinal studies have found that alleviating sleep problems corresponds with reductions in pain intensity, improved recovery, and enhanced health outcomes across both clinical and general populations [37-39, 188]. These results emphasize sleep as a key contributor and a target for therapeutic intervention in preventing pain development and alleviating symptoms associated with chronic pain.

2.3.2 Potential Mechanisms between Sleep and Pain

While the link between sleep and pain is well-established, the underlying mechanisms remain poorly understood. Recent narrative reviews have identified multiple biological and psychological pathways that might explain how sleep disturbances affect pain perception. These include impaired endogenous pain modulation, elevated concentrations of proinflammatory cytokines (e.g., IL-6, TNF-α, and C-reactive protein), negative affect or mood disorders (e.g., depression and anxiety), dysregulation of endogenous substances (e.g., dopamine, orexin, melatonin, vitamin D), altered in brain networks responsible for processing pain, as well as additional factors (e.g., fatigue, reduced physical activity, and dysregulation of the hypothalamus-pituitary-adrenal axis) [15, 16]. Among these mechanisms, disruptions in

peripheral and central pain processing appear particularly interesting. Cross-sectional studies have found that patients with osteoarthritis and comorbid insomnia exhibit enhanced central sensitization and reduced cold pain tolerance compared to those without insomnia [189, 190]. These findings are consistent with experimental studies in healthy individuals, in which sleep deprivation induces both central (e.g., elevated TSP, diminished CPM) and peripheral (e.g., lowered pain thresholds and tolerance) sensitization [27].

Neuroimaging studies have further elucidated how sleep deprivation affects brain mechanisms involved in pain modulation and transmission in healthy individuals. These investigations have demonstrated that heightened pain sensitivity following sleep deprivation is linked to alterations in brain activity during nociceptive processing [19, 191]. For instance, *Krause et al.* demonstrated that increased pain sensitivity following sleep deprivation correlated with greater activation in the S1, alongside reduced activity in the anterior insula and thalamus [19]. These brain regions are key components of the ascending pathway, contributing to the sensory and emotional aspects of pain perception [79, 192]. Complementary evidence from another fMRI study showed that heightened thermal pain sensitivity resulting from sleep fragmentation was linked to stronger functional connectivity in the executive control network, suggesting that cognitive systems also contribute to the modulation of pain under conditions of disrupted sleep [191].

However, existing EEG evidence reveals paradoxical findings regarding how sleep deprivation influences pain-related psychophysical and neurophysiological responses in healthy subjects. Conventional time-domain analyses have demonstrated reduced amplitude of laser-evoked

potentials, even as subjective reports of pain intensity remain unchanged or are heightened following sleep restriction [193-195]. In contrast, EEG studies using time-frequency domain analyses have revealed that increased electrical-evoked potentials are associated with increased subjective pain intensity after partial sleep deprivation [196, 197]. Taken together with these findings, the existing neuroimaging evidence regarding sleep and pain is sparse and contradictory. They have primarily concentrated on how experimental sleep deprivation influences cortical pain responses in healthy subjects. However, it remains unclear the neurophysiological mechanisms underlying the modulation in clinical populations. Addressing this gap is essential for advancing our understanding of the sleep-pain interactions and could contribute to the design of precise diagnostic tools and treatment approaches for comorbid conditions.

2.4 Managements for Sleep and Pain

2.4.1 Pharmacological Approaches

Pharmacological treatments are commonly used to manage chronic pain and sleep conditions, which have shown short-term benefits in enhancing sleep quality and alleviating sleep disturbances among chronic pain [198-200]. Pharmacological interventions targeting insomnia include $GABA_A$ receptor agonists, non-benzodiazepine hypnotics, melatonin receptor agonists, antidepressants, benzodiazepines, and gabapentinoids [16]. A randomized controlled trial found that eszopiclone significantly improved nearly all sleep measures and pain intensity among individuals with concurrent CLBP and insomnia [201]. Additionally, improvements in pain ratings were significantly correlated with improvements in sleep quality. However, the available evidence backing pharmacological therapies for people with comorbid chronic pain and

insomnia remains limited and inconsistent [16]. More importantly, prolonged use of these medications is generally discouraged due to risks of tolerance, dependence, and adverse effects such as sedation, impaired balance, and cognitive dysfunction [198, 202]. Consequently, non-pharmacological interventions may offer a preferable alternative, providing therapeutic benefits with a more favorable side-effect profile.

2.4.2 Non-pharmacological Approaches

Cognitive behavioral therapy (CBT) is widely endorsed as the first-line treatment for chronic insomnia and is implemented to address sleep disturbances in individuals with chronic pain [42, 203, 204]. Its efficacy has been extensively validated, demonstrating superior improvements in sleep quality and efficiency among people with chronic pain and coexisting insomnia [41, 44, 205, 206]. Multiple systematic reviews have demonstrated that CBT significantly improves various sleep parameters (e.g., sleep quality, sleep efficiency, and wake time after sleep onset) and simultaneously reduces pain intensity when compared to control conditions [41, 44, 205]. A recent network meta-analysis further compared various CBT protocols and found that CBT for insomnia yielded the most favorable improvements across multiple domains, including sleep outcomes, pain intensity, functional disability, and depressive symptoms, compared to CBT for insomnia and pain, CBT for pain, and the control group [206]. Despite its strong evidence base, the widespread implementation of CBT is hindered by challenges such as limited accessibility, high costs, low patient adherence, and the lack of credentialed clinicians in primary care settings [47, 48, 204]. These limitations underscore the need for continued research into innovative and effective interventions to address the complex interplay between chronic pain and sleep disturbance.

Previous pairwise meta-analyses have suggested that exercise [207], mind-body exercise [208], non-invasive brain stimulation techniques [207, 209], mindfulness-based psychotherapy [207], and relaxation [210] can effectively improve sleep quality in people with chronic pain. However, observed benefits are often modest and there is limited evidence supporting their efficacy specifically in populations with comorbid conditions [17]. Given that comorbid chronic pain and insomnia may involve dysregulated central pain processing and abnormal neural oscillations [12, 49], targeted brain modulation approaches could potentially restore these imbalances and improve clinical outcomes. Non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have gained attention as promising treatment options. These safe and acceptable interventions could modulate cortical excitability, synaptic plasticity, and functional connectivity across a range of neurological and neuropsychiatric disorders [50, 51]. Applying rTMS at tailored frequencies to precise brain regions has shown effectiveness in treating chronic pain or insomnia separately [52-57]. However, the potential efficacy of rTMS on sleep and pain in individuals with comorbid conditions remain uncertain [15, 17]. Further experimental studies are warranted to explore their effects on coexisting populations, thereby advancing our understanding of the complex interplay between these conditions.

Chapter 3: The Differential Effects of Sleep Deprivation on Pain Perception in Individuals with or without Chronic Pain: A Systematic Review and Meta-Analysis

This chapter has been published by the author of this thesis as an article in the journal "*Sleep Medicine Reviews*" in September 2022.

Sleep Medicine Reviews 66 (2022) 101695

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

The differential effects of sleep deprivation on pain perception in individuals with or without chronic pain: A systematic review and meta-analysis

Jeremy R. Chang [a], Siu-Ngor Fu [a], Xun Li [a], Shirley X. Li [b], Xiaoyue Wang [c], Zhixing Zhou [a], Sabina M. Pinto [a], Dino Samartzis [d], Jaro Karppinen [e, f, g], Arnold YL. Wong [a, *]

[a] Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong, China
[b] Sleep Research Clinic and Laboratory, Department of Psychology, The University of Hong Kong, Hong Kong, China
[c] Department of Rehabilitation, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China
[d] Department of Orthopedic Surgery, Rush University Medical Centre, Chicago, USA
[e] Medical Research Center, Oulu University Hospital and University of Oulu, Oulu, Finland
[f] Rehabilitation Services of South Karelia Social and Health Care District, Lappeenranta, Finland
[g] Finnish Institute of Occupational Health, Oulu, Finland

ARTICLE INFO

Article history:
Received 29 June 2022
Received in revised form
9 September 2022
Accepted 11 September 2022
Available online 27 September 2022

Keywords:
Sleep deprivation
Pain perception
Pain sensitization
Chronic pain
meta-Analysis

ABSTRACT

Many experimental sleep deprivation (SD) studies were conducted to clarify the causal relationship between sleep and pain. This systematic review and meta-analysis aimed to update the evidence regarding the effects of different experimental SD paradigms on various pain outcomes. Five databases were searched from their inception to June 2022. Separate random-effects models were used to estimate the pooled effect sizes (ES) of different experimental SD paradigms on various pain outcomes Thirty-one studies involving 699 healthy individuals and 47 individuals with chronic pain were included. For healthy individuals, limited evidence substantiated that total SD significantly reduced pain threshold and tolerance (ES 0.74–0.95), while moderate evidence supported that partial SD significantly increased spontaneous pain intensity (ES 0.30). Very limited to moderate evidence showed that sleep fragmentation significantly increased peripheral and central sensitization in healthy individuals (ES 0.42–0.79). Further, there was very limited evidence that total or partial SD significantly aggravated spontaneous pain intensity in people with chronic pain. Our results accentuated that different SD paradigms differentially increased subjective pain intensity and worsened peripheral/central pain sensitization in healthy individuals, whereas the corresponding findings in people with chronic pain remain uncertain. Further rigorous studies are warranted to quantify their relationships in clinical populations.

1. Introduction

Numerous studies have investigated the association between sleep and pain in the last two decades. While some researchers have suggested a reciprocal relationship, others have proposed that pain could be worsened by sleep disturbance [1,2]. Recently, growing evidence has suggested that sleep disturbance predicts the onset or aggravation of pain [1,3]. A recent systematic review revealed that poor self-reported sleep quality on the prior night predicted increased pain intensity, whereas changes in pain intensity on the previous day were not significantly related to the sleep quality on the subsequent night [3,4]. Some cohort studies also reported that baseline self-reported sleep disturbances predicted the onset of chronic pain in healthy individuals or pain aggravation in patients with chronic pain at follow-ups [5–7]. These findings highlight the importance of improving sleep to prevent or alleviate pain [8].

While the causal relationship between sleep disturbance and pain perception requires further validation, the effects of sleep disturbance on increased pain perception may be attributed to pain sensitization [9,10]. Studies reported that insufficient sleep resulting from total sleep deprivation (SD) [10,11], partial SD [12,13],

* Corresponding author. Department of Rehabilitation Sciences, Hong Kong Polytechnic University, Hung Hom, Hong Kong, China.
E-mail address: arnold.wong@ (AYL. Wong).

https://doi.org/10.1016/j.smrv.2022.101695

3.1 Abstract

Background: Many experimental sleep deprivation studies were conducted to clarify the causal relationship between sleep and pain. This systematic review and meta-analysis aimed to update the evidence regarding the effects of different experimental sleep deprivation paradigms on various pain outcomes involving spontaneous pain intensity, pain threshold, pain tolerance, conditioned pain modulation, and temporal summation.

Methods: Web of Science, Embase, Medline, PsycINFO, and CINAHL databases were searched from their inception to June 2022. Two independent reviewers screened publications, extracted data, and assessed the methodological qualities of the included studies.Separate random-effects models were used to estimate the pooled effect sizes (ES) of different experimental sleep deprivation paradigms on various pain outcomes.

Results: Thirty-one studies involving 699 healthy individuals and 47 patients with chronic pain were included. For healthy individuals, limited evidence substantiated that total sleep deprivation significantly reduced pain threshold and tolerance (ES = 0.74-0.95), while moderate evidence supported that partial sleep deprivation significantly increased spontaneous pain intensity (ES = 0.30). Very limited to moderate evidence showed that sleep fragmentation significantly increased peripheral and central sensitization in healthy individuals (ES = 0.42-0.79). Further, there was very limited evidence that total or partial sleep deprivation significantly aggravated spontaneous pain intensity in people with chronic pain.

Conclusions: Our results accentuated that different sleep deprivation paradigms differentially increased subjective pain intensity and worsened peripheral/central pain sensitization in healthy individuals, whereas the corresponding findings in people with chronic pain remain uncertain. Further rigorous studies are warranted to quantify their relationships in clinical populations.

Keywords: sleep deprivation; pain perception; pain sensitization; chronic pain; meta-analysis.

3.2 Introduction

Numerous studies have investigated the association between sleep and pain in the last two decades. While some researchers have suggested a reciprocal relationship, others have proposed that pain could be worsened by sleep disturbance [183, 211]. Recently, growing evidence has suggested that sleep disturbance predicts the onset or aggravation of pain [11, 183]. A recent systematic review revealed that poor self-reported sleep quality on the prior night predicted increased pain intensity, whereas changes in pain intensity on the previous day were not significantly related to the sleep quality on the subsequent night [11, 212]. Some cohort studies also reported that baseline self-reported sleep disturbances predicted the onset of chronic pain in healthy individuals or pain aggravation in patients with chronic pain at follow-ups [187, 213, 214]. These findings highlight the importance of improving sleep to prevent or alleviate pain [38].

While the causal relationship between sleep disturbance and pain perception requires further validation, the effects of sleep disturbance on increased pain perception may be attributed to pain sensitization [15, 19]. Studies reported that insufficient sleep resulting from total sleep deprivation [19, 20], partial sleep deprivation [21, 22], selective sleep deprivation [23, 24], or sleep fragmentation [22, 25] significantly increased spontaneous pain complaints or temporal summation of pain (TSP), as well as decreased mechanical and/or thermal pain thresholds in healthy individuals. However, since prior studies used diverse experimental sleep deprivation

paradigms and pain measurement protocols, it was difficult to draw robust conclusions regarding the effects of sleep deprivation on pain perception.

Although a prior systematic review and meta-analysis concluded that sleep deprivation had medium to large effects on pain perception [26], it was limited by: (1) no pre-registration of the review protocol in a registry; (2) not following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines; (3) no reporting of inter-reviewer reliability; and (4) no evaluation of the methodological quality of the included quasi-experimental studies. Importantly, they synthesized data across different sleep deprivation paradigms (total, partial, and selective sleep deprivation) and pain-related outcomes (spontaneous pain intensity and sensory pain threshold), which precluded the understanding of differential pain responses to different sleep deprivation paradigms. Furthermore, because the literature search in that review was back in December 2014 and increasingly more new relevant studies have been published since then, it is necessary to conduct an updated systematic review to summarize the latest evidence on this topic.

Given the high prevalence of sleep disturbances and a close interaction between sleep and pain in people with chronic pain [8], it is logical to ask whether the post-sleep deprivation pain responses differ between people with and without chronic pain. However, no systematic review has summarized the evidence regarding the effects of sleep deprivation on pain perception in people with chronic pain. Therefore, the current systematic review and meta-analysis aimed to update and separately summarize the evidence regarding the effects of each sleep deprivation paradigm on pain perception as measured by changes in spontaneous pain intensity, pain

threshold, pain tolerance, conditioned pain modulation (CPM), and TSP in individuals with and without chronic pain that last for at least three months.

3.3 Methods

This systematic review was conducted according to the PRISMA guidelines [215, 216]. The protocol was registered with PROSPERO (CRD42020179080).

3.3.1 Search Strategies

Web of Science, Embase, Medline (via EBSCO), PsycINFO, and CINAHL databases were searched systematically from their inception to 2 June 2022. An experienced research librarian assisted in the development of the search strategy. Key terms and their synonyms from medical subject headings or free-text terms were combined by appropriate truncation and Boolean operators in the title and abstract fields: “sleep deprivation” and “pain perception” (**Table S1.1**). Additionally, forward citation tracking using Web of Science and manual screening of the reference lists were performed to identify additional eligible publications. The corresponding authors of the included studies were contacted by email to identify more relevant articles or solicit raw data.

3.3.2 Study Selection and Eligibility Criteria

Two independent reviewers screened the titles and abstracts to determine their eligibility for full-text screening. Piloting on the first 100 citations of titles and abstracts was performed to ensure a reasonable agreement between both reviewers. The kappa coefficient (k) was used to determine poor (0-0.20), fair (0.21-0.40), moderate (0.41-60), good (0.61-80), or excellent (0.81 to 1.00)

agreement [217]. Disagreements between the two reviewers were resolved through discussions. A third reviewer (A.W.) adjudicated persistent disagreements. Full-text screening followed the same procedures.

Studies were included if they (1) recruited participants aged 18 years or older who were healthy or had non-cancer pain lasting for at least three months [58]; (2) involved experimentally induced reduction of sleep duration in study participants; (3) included at least one assessment time point with normal habitual sleep as the baseline value or control condition; (4) assessed at least one pain outcome as the dependent variable; (5) were randomized controlled trials (RCTs) or quasi-experimental studies; and (6) were published in peer-reviewed journals. Studies were excluded if they (1) included participants with shift work or neurological disorders that affect sleep; (2) used drugs for sleep deprivation; (3) were narrative or systematic reviews, observational studies, case reports, letters to the editor, or conference abstracts; or (4) had no full-text articles even after contacting the corresponding authors. If multiple publications reported data from the same cohort, only the study with the most relevant information would be included.

3.3.3 Data Extraction

One reviewer extracted data from the included studies using a standardized form. The second reviewer independently verified the results. Any disagreements were resolved by consensus or consulting a third reviewer. Prior to the data extraction, ten studies were randomly selected to pilot the form. The extracted data included: (1) bibliometric data (e.g., authors, year of publication, and country); (2) participants' characteristics (e.g., age, sex, diagnosis of chronic

pain, and sample size); (3) study design; (4) methods used to manipulate the sleep duration, and the description of the control or baseline condition (e.g., type, setting, and duration); (5) pain measures and instruments (e.g., types of pain and sites of stimulation); and (6) results of pain measures at baseline and after sleep manipulation.

Additionally, for studies involving multiple sleep deprivation paradigms on the same cohort, relevant data were extracted separately based on different sleep manipulation methods. Second, if studies measured pain outcomes multiple times during one sleep paradigm, results from the last time point were extracted for data synthesis. Third, when there was incomplete or unclear data in a given study, the corresponding author was contacted at least three times over a week by emails to request relevant information. If they did not respond, the data was estimated from graphs presented in the paper using OriginPro software (OriginThe lab, 2021).

3.3.4 Risk of Bias Assessments

Two reviewers independently assessed the methodological quality of the included studies. A third reviewer was consulted if disagreements persisted. The methodological quality of RCTs and randomized cross-over studies was evaluated by the Cochrane Collaboration risk of bias (RoB) 2.0 tool [218]. The Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used to assess the methodological quality of quasi-experimental studies [219]. The inter-reviewer reliability was analyzed by a kappa coefficient. The percentage consistency was estimated by the number of agreements in each domain.

3.3.5 Data Synthesis

From the statistical perspective, when data is transformed into a unified metric, the effect sizes (ES) of the same intervention can be compared and pooled across studies regardless of the study design [220, 221]. This method has been adopted to synthesize data in previous meta-analyses [161, 222]. Therefore, the current review transformed all data into ES (Cohen's *d*) for meta-analyses. The overall ES of each sleep deprivation paradigm (total, partial, selective sleep deprivation, or sleep fragmentation) on each pain outcome was separately estimated by Hedges' g, which was interpreted as small (ES = 0.2-0.49), medium (ES = 0.5-0.79), or large (ES ≥ 0.8) [223]. Positive ES indicated pain sensitization after sleep deprivation, while negative ES indicated pain inhibition. If an included study only reported a nonsignificant difference without the actual data, ES was estimated by Wilson and Lipsey's method [222]. If an included study reported results in separate subgroups (e.g., gender, sleep deprivation, or stimuli sites), the ES of each subgroup was presented separately as an independent experiment.

All statistical analyses were performed using STATA (version 15.0, Stata Corp, TX, USA). Q-Statistic was used to examine the homogeneity across studies, which was quantified by I^2, and the results were interpreted as low (25-50%), moderate (51-75%), and high (> 75%) heterogeneity [224]. Because the methods of sleep deprivation or pain measurements were diverse, random-effect models were used to account for the variance across studies [224]. Forest plots displayed data as the effect sizes and 95% confidence intervals (95% CIs). If 10 or more included studies reported a given pain outcome, the potential publication bias was assessed by a funnel plot and Egger's regression test [225]. Meta-regression analysis was performed to explore the relation between the duration of sleep deprivation and pain perception when there were 10 or

more studies in a relevant meta-analysis [224]. The significant level was set at 0.05. Subgroup analyses of different types of pain stimulus tests were also conducted. A minimum of two studies were required for each subgroup analysis. If the number of included studies was less than two, meta-analyses were precluded, but the results and the corresponding level of evidence were summarized qualitatively [224, 226].

3.3.6 Quality Level of Evidence

The overall quality of evidence regarding the effects of different sleep deprivation paradigms on various pain outcomes was determined by the modified version of recommendations from the Cochrane Collaboration Back Review Group [226]. They were classified into strong, moderate, limited, very limited, conflicting, or no evidence based on the number of studies, risk of bias, and the heterogeneity of results from the included studies (**Table S1.2**).

3.4 Results

3.4.1 Literature Searches

Our database search identified 4,404 publications (**Figure 1**). Additionally, 2,474 publications were identified by forwarding citations of the included studies and the corresponding authors contacted. After removing 1,299 duplicates, 3,105 were screened for titles and abstracts. Of the 58 retrieved full-text articles, 31 studies (involving 117 sleep deprivation experiments) were included. The inter-reviewer reliability estimates for the abstract (k = 0.66) and full-text (k = 0.76) screenings were high.

3.4.2 Study characteristics

Seven RCTs, 11 randomized crossover studies, and 13 non-RCTs studies were included (**Table S1.3**). They were conducted in 10 countries (USA = 10, Germany = 5, Denmark = 4, Norway = 4, France = 3, Brazil, Canada, Israel, Japan, and South Africa). The included studies involved 699 healthy participants (344 females and 355 males), with their mean age ranging from 20.8 to 60.4 years. Only two included studies involved males (n = 38) and females (n = 9) with chronic pain (the reported mean age was 50.1 and 59.9 years) [227, 228]. Specifically, Irwin et al. included people with rheumatoid arthritis using disease-modifying antirheumatic drugs medication (55.6%), biologic agents (48.1%), steroids (14.8%), and analgesics/nonsteroidal anti-inflammatory drugs (3.7%) [228]. Busch et al. recruited people with somatoform pain with a mean pain duration of 5 years [227].

Twenty-four included studies conducted experimental sleep deprivation manipulation in laboratories, while seven studies manipulated sleep at home [20, 194-196, 229-231]. Habitual sleep without disruption was employed as the control condition in a laboratory or home setting. Twenty laboratory-based studies (65%) required participants to sleep in a laboratory for an adaptation night before the sleep deprivation manipulation. Four common sleep deprivation paradigms were total sleep deprivation (n = 15) [19-22, 193, 227, 230, 232-239], partial sleep deprivation (n = 11) [194-196, 228, 229, 231, 237, 240-243], selective sleep deprivation (n = 5) [23, 24, 193, 237, 244], and sleep fragmentation (n = 4) [25, 191, 243, 245]. Specifically, the total sleep deprivation paradigm required participants to stay awake for 24 hours (ranging from one to three days). The partial sleep deprivation paradigm usually restricts sleep for two, four, or six hours per night, lasting from one to 12 days. The selective sleep deprivation paradigm used electroencephalography (EEG) to monitor sleep stages, and participants were awakened during a

particular sleep period (e.g., at the sign of rapid eye movement (REM) sleep [193, 237, 244], non-REM (NREM) stage 4 sleep [244], slow-wave sleep (NREM stages 3 and 4) [23, 24], and all NREM sleep stages [237]). All the studies with experimentally induced sleep fragmentation adopted Smith's protocol, which consisted of a random sequence of one 60-minute awakening and several 20-minute awakenings throughout the night [25, 243].

Regarding pain perception assessments, 12 studies used the McGill pain questionnaire [228, 229], the visual analog scale [22-24, 227, 228, 233, 241], the Pennebaker inventory of limbic languidness [243, 245], and the scale for musculoskeletal symptoms [235, 244] to evaluate spontaneous generalized body pain (n = 14), headache (n = 4), joint pain (n = 3), lumbar pain (n = 3), neck/shoulder pain (n = 2), and jaw muscles pain (n = 1). The pain threshold was assessed by cold (n = 9) [20, 24, 195, 227, 232, 235, 236, 239, 240], heat (n =17) [19, 20, 22, 24, 25, 191, 193-195, 227, 231, 232, 235, 238-240, 242], pressure (n = 13) [20, 21, 23-25, 196, 227, 230, 232, 239, 240, 242, 243], or pricking stimuli (n = 6) [21, 24, 196, 232, 239, 245]. The threshold was defined as the initial pain sensation, pain intensity ratings, or threshold for reaching a specific pain intensity (e.g., VAS = 5/10cm). Pain tolerance, which was defined as unbearable pain, was measured by cold (n = 4) [22, 24, 25, 232], heat (n = 3) [234, 237, 242], or pressure (n =2) stimuli [20, 234]. For CPM, four studies used the same protocol to assess pain threshold or intensity before and after applying cold stimuli [230-232, 243]. The remaining one applied pressure stimuli [20]. Thermal [22, 195], pressure [20], or pricking stimuli [25, 232, 239] combined with self-reported pain intensity were used to assess TSP. Pain stimuli were usually given to upper limbs (n = 26), lower limbs (n = 5), face (n = 5), and lower back (n = 1).

3.4.3 Risk of Bias and Publication Bias

The methodological quality of the included RCTs and randomized crossover studies are summarized in **Figure S1.1** and **Figure S1.2**. Six of the seven included RCTs had high risk of bias [193, 229, 233, 235, 241, 243], and one had moderate risk of bias [195]. The included randomized crossover trials had high (n = 6) [21, 22, 236, 238, 240, 245] and moderate (n = 5) [25, 196, 231, 234, 242] risk of bias. The common sources of risk of bias in the RCTs were: (1) unclear randomization process; (2) unblinded assessors; and (3) no proper handling of missing data. The ROBINS-I assessments of 13 included quasi-experimental studies are presented in **Table S1.4**. Eleven and two included quasi-experimental studies had moderate [19, 20, 23, 24, 194, 227, 228, 230, 232, 237, 238], and serious risk of bias [191, 244], respectively. Their common sources of risk of bias were: (1) no consideration of potential confounders; (2) no blinding of assessors; (3) no information regarding the reliability and validity of measurements; and (4) selective reporting of the results. The inter-reviewer reliability for RoB 2.0 and ROBINS-I assessments was excellent (k = 1.0), with over 81% agreement for each domain.

Because the number of included studies regarding post-sleep deprivation pain outcomes was less than 10 articles except for the total sleep deprivation paradigm, the publication bias was only examined regarding the effects of total sleep deprivation on pain threshold in healthy individuals. Based on the funnel plot and the Egger test results (p = 0.08) (**Figure S1.3**), there was no publication bias.

3.4.4 Effects of Total Sleep Deprivation on Pain Perception

Fifteen studies used 41 experiments involving 235 healthy individuals and 20 people with chronic pain to investigate the effects of total sleep deprivation on pain perception. Meta-analyses of studies involving healthy individuals revealed that total sleep deprivation significantly reduced pain threshold (ES = 0.74; 95% CI: 0.47 to 1.02; $p < 0.01$; $I^2 = 70.3\%$;**Figure 2**) and pain tolerance (ES = 0.95; 95% CI: 0.18 to 1.72; $p < 0.01$; $I^2 = 75.7\%$;**Figure 3**). However, total sleep deprivation had no significant effects on spontaneous pain intensity, CPM, or TSP **(Figure S1.4 to Figure S1.6**). No meta-analysis was conducted because only one included study assessed the effects of total sleep deprivation in people with chronic somatoform pain [227]. The results found that total sleep deprivation significantly increased their spontaneous pain intensity but not their pain threshold [227].

Meta-regression analysis found no significant association between the number of experimental days of total sleep deprivation and pain threshold (coefficient = -0.089, $p = 0.854$). Subgroup analyses based on different types of pain stimuli in healthy individuals found that total sleep deprivation significant reduced cold (ES = 0.93; 95% CI: 0.41 to 1.46; $p < 0.01$; $I^2 = 64.9\%$), heat (ES = 0.73; 95% CI: 0.45 to 1.02; $p < 0.01$; $I^2 = 0\%$), pressure (ES = -0.64; 95% CI: 0.00 to 1.28; $p = 0.05$; $I^2 = 84.6\%$), or pricking pain threshold (ES = 0.80; 95% CI: 0.37 to 1.23; $p < 0.05$; $I^2 = 70.3\%$). Likewise, total sleep deprivation significantly decreased pressure pain tolerance (ES = 2.71; 95% CI: 0.43 to 4.99; $p = 0.02$; $I^2 = 78.1\%$) but had no effects on heat pain tolerance **(Table 1**).

Collectively, limited evidence supported that total sleep deprivation had medium to large effects

on decreasing pain threshold and tolerance in healthy individuals, while limited to moderate evidence substantiated no significant effects of total sleep deprivation on spontaneous pain intensity, CPM, and TSP in healthy controls. Conversely, very limited evidence showed that total sleep deprivation significantly increased spontaneous pain intensity but had no effect on pain threshold in people with chronic pain. Further, no studies investigated the effect of total sleep deprivation on other pain outcomes in this population (**Table 2**).

3.4.5 Effects of Partial Sleep Deprivation on Pain Perception

Eleven studies used 43 experiments involving 221 healthy individuals and 27 people with rheumatoid arthritis to examine the effects of partial sleep deprivation on pain perception. Meta-analyses showed that partial sleep deprivation only significantly increased spontaneous pain intensity in healthy individuals (ES = 0.30; 95% CI: 0.10 to 0.49; $p < 0.01$, $I^2 = 0\%$; Figure S1.7), but had no significant impacts on pain threshold, pain tolerance, conditioned pain modulation, or TSP (**Figure S1.7 to Figure S1.11**). One study on people with rheumatoid arthritis found that partial sleep deprivation significantly increased spontaneous pain intensity [228].

Subgroup analyses of different stimuli in healthy individuals showed that partial sleep deprivation did not significantly affect cold, heat, or pressure pain threshold. The subgroup analysis of partial sleep deprivation on heat pain tolerance showed no significant effects (**Table 1**).

Overall, there was moderate evidence that partial sleep deprivation had a significant but small

effect on increasing spontaneous pain intensity among healthy individuals but no effects on pain threshold, pain tolerance, or central sensitization. Likewise, very limited evidence suggested a significant effect of partial sleep deprivation on spontaneous pain intensity among people with chronic pain. No relevant studies investigated the effects of partial sleep deprivation on peripheral and central sensitization in people with chronic pain (**Table 2**).

3.4.6 Effects of Selective Sleep Deprivation on Pain Perception

Five included studies used 22 experiments to investigate the effects of selective sleep deprivation on pain perception among 77 healthy individuals. Meta-analyses revealed that selective sleep deprivation had no significant effects on spontaneous pain intensity, pain threshold, or pain tolerance in healthy individuals (**Figure S1.12 to Figure S1.14**). Subgroup analyses regarding the effects of selective sleep deprivation on heat and pressure pain threshold showed no significant effects (**Table 1**).

Taken together, there was moderate evidence that selective sleep deprivation did not significantly alter spontaneous pain intensity, pain threshold, or pain tolerance in healthy individuals, but its effect on central sensitization remains unclear. Likewise, no studies have investigated the effects of selective sleep deprivation on pain perception in people with chronic pain (**Table 2**).

3.4.7 Effects of Sleep Fragmentation on Pain Perception

The effects of sleep fragmentation on pain perception were tested on 156 healthy individuals (4 studies with 11 experiments). Meta-analyses showed that sleep fragmentation significantly reduced pain threshold (ES = 0.42; 95% CI: 0.13 to 0.71; $p < 0.01$; $I^2 = 0\%$; **Figure S1.15**) and

pain tolerance (ES = 0.79; 95% CI: 0.22 to 1.35; $p < 0.01$; $I^2 = 36.2\%$; **Figure S1.16**) in healthy individuals, but it had no significant effects on spontaneous pain intensity (**Figure S1.17**). Included studies found that healthy individuals showed significant decreases in CPM and increases in TSP after sleep fragmentation [25, 243].

Subgroup analyses of heat and pressure pain threshold found that sleep fragmentation significantly decreased pressure pain threshold (ES = 0.69; 95% CI: 0.13 to 1.25; $p = 0.02$; $I^2 = 0\%$) but had no effects on heat pain threshold in healthy individuals **(Table 1**).

Overall, moderate evidence substantiated that sleep fragmentation had small to medium effects on reducing pain threshold and pain tolerance in healthy individuals but had no significant effects on their spontaneous pain intensity. There was very limited evidence that healthy individuals exhibited increased central sensitization after sleep fragmentation. The effects on pain perception among people with chronic pain remain unknown (**Table 2**).

3.5 Discussion

This systematic review and meta-analysis comprehensively reviewed and updated the evidence regarding the effects of different experimental sleep deprivation paradigms on spontaneous pain intensity, pain threshold, pain tolerance, CPM, and TSP among individuals with and without chronic pain. Very limited to moderate evidence substantiated that total/partial sleep deprivation or sleep fragmentation would increase subjective pain intensity, peripheral sensitization, or central sensitization in healthy individuals. Likewise, there was very limited evidence that total or partial sleep deprivation significantly elevated spontaneous pain intensity in people with

chronic pain. However, the effects of selective sleep deprivation or sleep fragmentation on the pain perception of people with chronic pain have not been investigated. These findings underscore that different sleep deprivation paradigms result in differential increases in pain perception in individuals with and without chronic pain, which highlights the importance of understanding the mechanisms underlying sleep and pain, as well as the role of sleep intervention for chronic pain management.

Although a prior systematic review and meta-analysis concluded medium to large effects of sleep deprivation on pain perception in healthy individuals [26], their conclusion was drawn based on a mix of different sleep deprivation paradigms and pain outcome measures, which might have been affected by multiple confounders. Our review addressed this limitation and revealed that total or partial sleep deprivation, and sleep fragmentation differentially increased spontaneous pain intensity or decreased various pain thresholds/tolerances in people with or without chronic pain. For example, central sensitization was enhanced solely after sleep fragmentation in healthy individuals. Because different experimental sleep deprivation interventions mimic different real-life situations, our results imply that some people may be at a higher risk of experiencing sleep deprivation-related pain than others. For instance, total or partial sleep deprivation mimics occupation-related (e.g., nurses, miners, or truckers) and recreation-related (e.g., prolonged or overnight online gaming) sleep restriction [246, 247]. Selective sleep deprivation or sleep fragmentation imitates specific sleep patterns of patients with some clinical conditions (e.g., chronic pain or obstructive sleep apnea) [25, 191, 193, 247]. Therefore, future field studies should confirm whether various real-life sleep deprivation conditions cause differential pain perception similar to the respective experimental sleep deprivation interventions.

It is noteworthy that differential pain responses following different sleep deprivation interventions might also be ascribed to variable durations of experimental sleep deprivation paradigms, pain measurement protocols, and sex-dependent effects. Although our meta-regression analysis did not find a significant correlation between the duration of total sleep deprivation and pain threshold, the effects of experimental duration in other sleep deprivation paradigms on post-sleep deprivation pain perception remain unclear. Some included studies that used one-day selective, partial sleep deprivation, or sleep fragmentation induced no significant changes in pain perception [191, 237, 240]. These results may suggest that a short period of sleep deprivation may be insufficient to cause significant changes in pain perception [191, 193, 245]. The observed dose-response effect of sleep deprivation on pain experiences further supports this notion. For example, Simpson et al. [22] found that significant increases in spontaneous pain intensity and TSP occurred in the second and third week rather than the first week of partial sleep deprivation in healthy adults. An animal study that involved experimentally induced partial sleep deprivation in rats showed that pain sensitivity became significant from the third day onward and continued to increase till the 12^{th} day [248]. Further, different pain measurement protocols (e.g., types of painful stimuli or sites of stimuli applications) may influence the measured sleep-deprived pain perception. For instance, most studies that showed nonsignificant post-sleep deprivation changes in pain threshold or tolerance applied noxious stimuli at the proximal part of upper or lower limbs (e.g., supraspinatus, thigh, knee pads, and gluteal muscles) [24, 196, 240, 242], where the peripheral nerve conduction velocity was slower than at the distal parts [249]. The slower nerve conduction is known to be associated with the higher pain threshold and tolerance [250, 251]. Additionally, two included studies found that females were more

susceptible to the sleep-deprived effects on pain perception [25, 232], which might be attributed to the biological, psychological, and sociocultural differences between females and males in pain management [252, 253]. Higher levels of testosterone in males could induce macrophages to produce more anti-inflammatory cytokines, while higher levels of estrogen and progesterone in females have been found to be significantly associated with increased pro-inflammatory cytokines (e.g., the tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6) that resulted in hyperalgesia [252, 253]. Given the above, the existing findings should be interpreted with caution, and future studies should consider these factors in investigating the association between sleep deprivation and pain perception.

Our review found a significant increase in spontaneous pain intensity but no changes in pain threshold after total or partial sleep deprivation in people with chronic pain. These results concur with other longitudinal studies, which found that poor self-reported sleep quality on the previous night was significantly related to increased pain symptoms on the following day [11, 212]. Prospective studies with more than one-year follow-up also revealed that poorer sleep quality at baseline aggravated spontaneous pain intensity and yielded poor prognosis in patients with chronic pain [187, 213, 214]. However, our finding on pain threshold differed from some clinical studies, in which patients with chronic pain and comorbid insomnia displayed lower pain threshold than patients without insomnia [190, 254, 255]. The discrepancy might be ascribed to the fact that one included study used total sleep deprivation to interrupt sleep, whereas patients with chronic pain usually experience multiple nighttime awakenings rather than a complete or partial absence of sleep [29]. However, given that only two included studies involved people with chronic pain [227, 228], the observed association remains to be further tested in the clinical

populations. Moreover, because multiple factors (e.g., comorbidities, depression, anxiety) can modify pain perception in patients with chronic pain, their pain responses to sleep deprivation may be heterogeneous. Therefore, future studies should consider the effects of different potential confounders when exploring the impacts of various sleep deprivation paradigms on spontaneous pain intensity and peripheral pain perception in chronic pain.

No included study investigated the effects of various sleep deprivation paradigms on central sensitization in patients with chronic pain. However, some cross-sectional studies revealed that compared to patients with chronic pain alone, those with insomnia exhibited heightened central sensitization [190, 254, 255]. These findings highlight the potential negative effects of sleep disturbance on pain perception in patients with chronic pain. Nonetheless, insomnia, characterized by difficulty initiating sleep and maintaining sleep, is a unique clinical entity different from sleep deprivation [25, 191]. Further research should clarify the causation between sleep deprivation and central sensitization in this population.

Although the mechanisms underlying sleep deprivation-induced increases in pain perception remain uncertain, the post-sleep deprivation change may be related to altered pain processing in the brain [15]. A neuroimaging study in healthy individuals found that pain exacerbation after total sleep deprivation was associated with increased activity in the primary somatosensory cortex and decreased activity in the anterior insula and the thalamus [19], which are the main hubs along the ascending pathway for encoding the sensory and unpleasant emotional components of pain [79, 192]. Several included studies revealed an impaired post-sleep deprivation descending inhibitory pathway as measured by CPM [25, 230, 243]. These results

are supported by animal studies that sleep deprivation-induced pain was associated with the impaired periaqueductal gray and rostral ventral medulla descending pathway [248, 256]. Further studies should incorporate neuroimaging and pain measurements to evaluate whether the altered post-sleep deprivation pain perception originates from an imbalance between pain afferents and pain suppression in the central nervous system [79, 192].

Additionally, sleep deprivation may significantly disrupt the organization of the brain functional connectome (e.g., decreased connectivity within the default mode network and attentional network but increased activity within the salience network and sensorimotor network) [257-259]. Qi et al. found decreased global functional efficiency in the brain networks after total sleep deprivation, implying the disruption of information transfer among networks [258]. These distinct functional connectivity changes after sleep deprivation are similar to the dynamic pain connectome in patients with chronic pain [260, 261]. However, only one included study directly investigated their relationships and reported that increased pain sensitivity after sleep fragmentation was associated with decreased functional connectivity between the executive control network and the default mode network in healthy individuals [191]. Accordingly, future studies should determine the potential relationships between sleep deprivation-induced pain sensitivity and dynamic brain activity.

Other mechanisms (such as inflammation, affect, and cognition) have been proposed to explain the sleep deprivation-related increase in pain sensitivity [15, 16]. Specifically, sleep deprivation may increase the release of pro-inflammatory cytokines (e.g., IL-6, TNF-α, and C-reactive protein (CRP)) [222, 262], leading to hyperalgesia [263]. Likewise, sleep deprivation-related

negative affect and cognitive deficits may alter emotional and attentional pain modulations, which results in the exacerbation of pain unpleasantness and intensity [164, 264-266]. Interestingly, previous meta-analyses reported that different sleep deprivation paradigms have different effects on the levels of circulating inflammation markers [222], anxiety levels [162], mood, emotion [161], and performance on complex cognitive tasks [163]. For example, total sleep deprivation is associated with higher levels of anxiety and more negative emotions than partial sleep deprivation [161, 162]. Also, a longer total duration of sleep deprivation intervention results in higher levels of CRP and poorer cognitive performance [163, 222]. These findings are similar to our results, which elucidated the differential effects of four sleep deprivation paradigms on pain perception, although it remains unclear how these mediators affect the relationship between the type of sleep deprivation protocol and pain perception.

Our findings highlight that substantial heterogeneity of experimental protocols and diverse confounding factors might have affected the results [22, 240, 249]. To date, there is no consensus on the standardized definitions or implementations of sleep deprivation paradigms, recommended pain outcomes for sleep deprivation research, or proper approaches to minimize bias. A multidisciplinary international taskforce should be formed to address these issues and to improve the quality, transparency, and consistency in reporting findings. Furthermore, because the ultimate goal of scientific research is to translate its findings to clinical practice, the taskforce should also discuss the purpose of each sleep deprivation paradigm and how they can be applied to real-life scenarios and clinical conditions. For example, Smith's sleep fragmentation can be used to explore sleep deprivation-pain correlations because it is the most appropriate way to mimic sleep patterns in people with chronic pain [25, 191, 243, 245]. Our pooled results also

supported that this paradigm generated homogeneous effects across different outcomes. Collectively, a concerted effort to determine the research priorities and standardize the study protocol for sleep deprivation research can optimize resource utilization and improve clinical relevance.

Several limitations in this review should be noted. First, although subgroup analyses were conducted to discern different pain responses to various sleep deprivation paradigms, multiple factors (e.g., sex, age, duration of sleep deprivation, types of pain threshold, pain stimulation sites, and selective sleep stages) might have confounded our results [22, 240, 249]. Second, because the methodological quality of all included studies was low or moderate, and some findings were pooled from a few studies for meta-analyses (e.g., the effects of sleep fragmentation on conditioned pain modulation in healthy individuals) or summarized qualitatively only (e.g., the effects of total sleep deprivation on self-reported pain intensity in people with chronic pain), these findings should be interpreted with caution. Third, pooling data from different study designs in some meta-analyses might introduce heterogeneity or bias. However, as those studies used the same pain outcome measures to answer a given research question and all data were transformed into a unified metric [220, 221], our pooled results provided a good overview of post-sleep deprivation effects on pain perception.

3.6 Conclusions

The current systematic review and meta-analysis provided the latest evidence regarding the effects of different sleep deprivation paradigms on various pain parameters. Very limited to moderate evidence supported the significant effects of total/partial sleep deprivation or sleep

fragmentation on increasing spontaneous pain intensity, peripheral sensitization, or central sensitization in healthy individuals. Similarly, there was very limited evidence that total and partial sleep deprivation significantly increased spontaneous pain intensity in people with chronic pain. These causal relationships underscore the negative impacts of sleep deprivation on pain perception and indicate the potential benefits of improving sleep in alleviating pain in people with chronic pain.

3.7 Tables

Table 1. Effect sizes of subgroup analyses for different pain stimuli after various sleep deprivation paradigms in healthy individuals

	Total sleep deprivation		Partial sleep deprivation		Selective sleep deprivation		Sleep fragmentation	
	Threshold	Tolerance	Threshold	Tolerance	Threshold	Tolerance	Threshold	Tolerance
Cold	0.93*	NA	-0.17	NA	-0.10	NA	NA	0.79*
Heat	0.73*	0.54	0.22	0.22	0.11	NA	0.23	NA
Pressure	0.64*	2.71*	0.14	NA	NA	NA	0.69*	NA
Pricking	0.80*	NA	NA	NA	NA	NA	NA	NA

Abbreviation: NA: Not Available due to the limited number of studies.
Footnote: *: significant effects, $p < 0.05$; positive value: increased pain sensitization (i.e., decreased pain threshold or tolerance); negative value: decreased pain sensitivity (i.e., increased pain threshold or tolerance).

Table 2. Summary of evidence regarding different sleep deprivation paradigms on the pain outcomes

	Spontaneous pain intensity		Pain threshold		Pain tolerance		Conditioned pain modulation		Temporal summation of pain	
	Healthy	Chronic pain	Healthy	Chronic pain	Healthy	Chronic pain	Healthy	Chronic pain	Healthy	Chronic pain
Total sleep deprivation	Moderate (-)	Very limited (+)	Limited (+)	Very limited (-)	Limited (+)	No evidence (no study)	Limited (-)	No evidence (no study)	Limited (-)	No evidence (no study)
Partial sleep deprivation	Moderate (+)	Very limited (+)	Moderate (-)	No evidence (no study)	Moderate (-)	No evidence (no study)	Moderate (-)	No evidence (no study)	Moderate (-)	No evidence (no study)
Selective sleep deprivation	Moderate (-)	No evidence (no study)	Moderate (-)	No evidence (no study)	Moderate (-)	No evidence (no study)	No evidence (no study)	No evidence (no study)	No evidence (no study)	No evidence (no study)
Sleep fragmentation	Moderate (-)	No evidence (no study)	Moderate (+)	No evidence (no study)	Moderate (+)	No evidence (no study)	Very limited (+)	No evidence (no study)	Very limited (+)	No evidence (no study)

Footnote: +: significantly increased pain sensitivity and impaired pain modulation; -: no significant changes in pain sensitivity or pain modulation.

3.8 Figures

Figure 1. A flow chart of literature searches

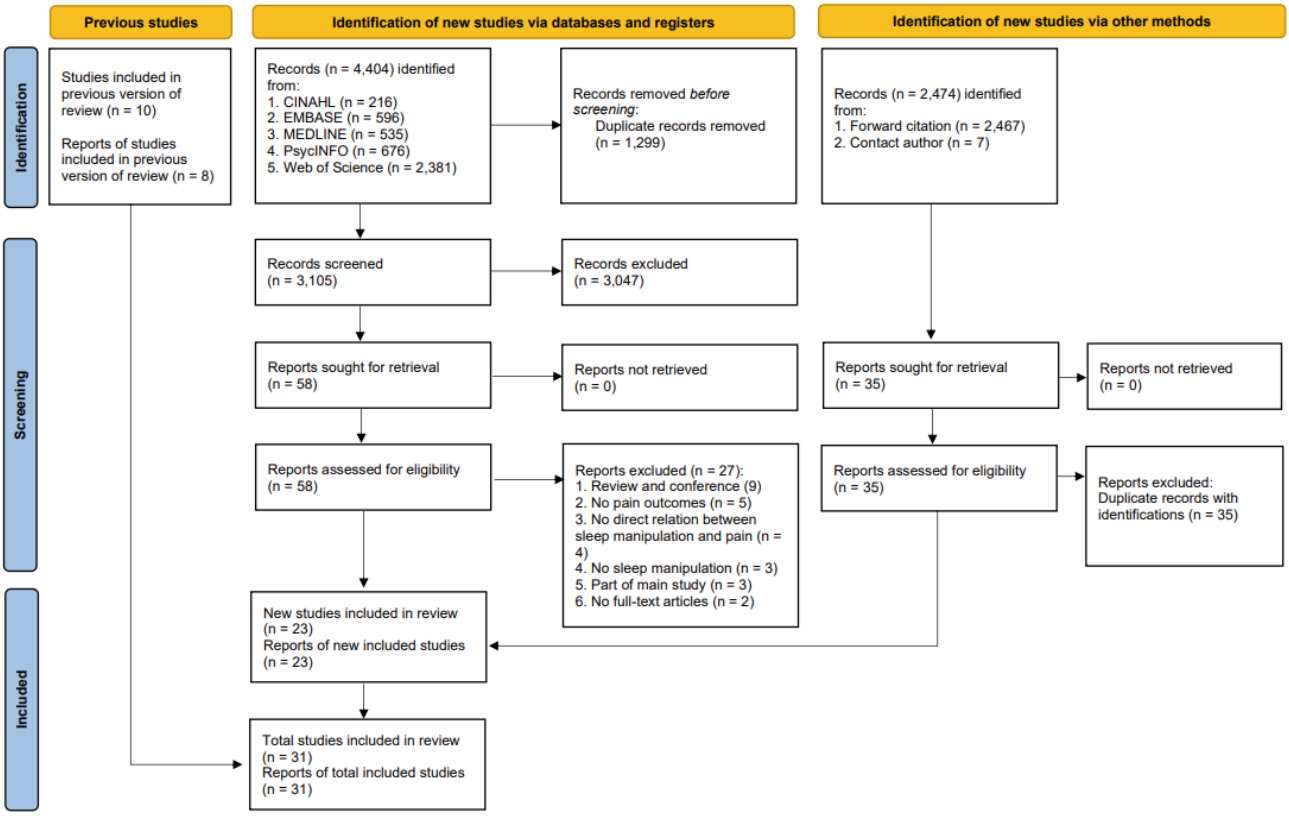
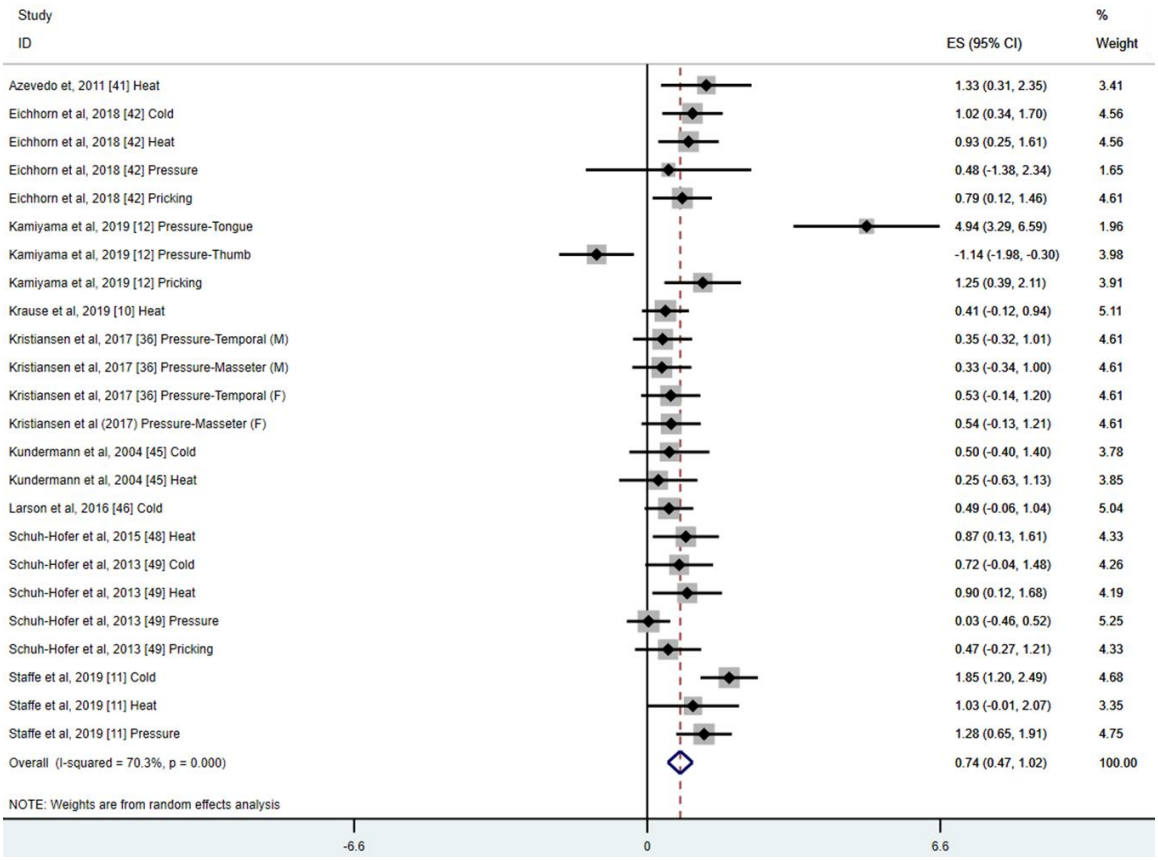
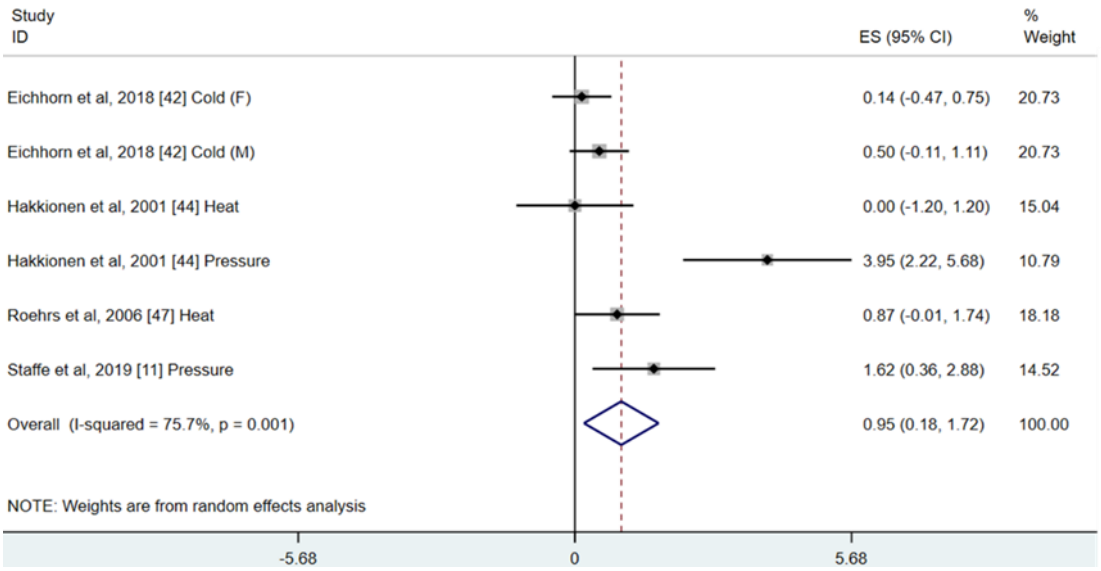


Figure 2. The effects of total sleep deprivation on pain threshold in healthy individuals



Abbreviation: F: female; M: male.

Figure 3. The effects of total sleep deprivation on pain tolerance in healthy individuals



Abbreviation: F: female; M: male.

Chapter 4: Differential Pain Perception among Females with or without Non-specific Chronic Low Back Pain and Comorbid Insomnia: A Quantitative Sensory Testing Analysis

This chapter has been published by the author of this thesis as an article in the journal "*PAIN"* in March 2025.

Part of the materials in this chapter was presented as a poster at *The 50th International Society for the Study of the Lumbar Spine Annual Meeting* on 26th-31st May 2024. Milan, Italy.

Part of the materials in this chapter was presented as a poster at *The World Physiotherapy Congress 2025* on 29th-31st May 2025. Tokyo, Japan.

Research Paper

PAIN 00 (2025) 1–10

PAIN®

OPEN

Differential pain perception among females with or without nonspecific chronic low back pain and comorbid insomnia: a quantitative sensory testing analysis

Jeremy R. Chang[a], Rachel L.C. Kwan[b], Eliza R. Sun[a], Shirley X. Li[c,d], Ping Liang[a], Jae Q.J. Liu[a], Daniel K.Y. Zheng[a], Zhixing Zhou[a], Frank F. Huang[a], Dino Samartzis[e], Siu Ngor Fu[a], Arnold Y.L. Wong[a,f,g,*]

Abstract

Sleep disturbance is a prevalent condition in individuals with chronic low back pain (CLBP). Despite a strong association between the 2 conditions, the potential mechanisms underlying the role of sleep disturbance in CLBP remain unclear. This case–control study aimed to examine pain perception among females with or without nonspecific CLBP and comorbid insomnia. One hundred females were recruited (mean age: 34.3 ± 11.4 years), with 25 individuals with concomitant CLBP and insomnia (CLBP+I), 25 with CLBP (CLBP−), 25 with insomnia (Insomnia+), and 25 healthy controls. All participants completed self-report questionnaires and quantitative sensory testing (QST). Our study found that CLBP+I exhibited lower mechanical pain and pressure pain thresholds (PPT) in both painful and nonpainful areas and impaired conditioned pain modulation (CPM) as compared to healthy controls. Similar findings were found in PPT at the back and CPM when compared to CLBP+. However, no significant differences were noted in thermal pain thresholds and temporal summation of pain across the 4 groups. Furthermore, CLBP+I and Insomnia+ displayed higher levels of functional disability, maladaptive beliefs, and negative mood than CLBP+ or healthy controls. There were significant increases in pain sensitivity to pressure stimuli, decreases in descending pain inhibitory effects, and higher levels of maladaptive psychological status in CLBP+I compared to CLBP+. These findings underscore the importance of incorporating sleep assessments as a routine practice in treating CLBP cases. Future studies are warranted to validate our findings in males, establish the diagnostic and prognostic value of QST, and probe the neurophysiological mechanisms in comorbid conditions.

Keywords: Chronic low back pain, Insomnia, Quantitative sensory testing, Conditioned pain modulation

1. Introduction

Chronic low back pain (CLBP) is one of the most common reasons for seeking healthcare consultation[22] and is associated with higher healthcare demand and more significant comorbidity than asymptomatic individuals.[24,31] Given that most CLBP cases lack identifiable medical evidence or a specific diagnosis and are labelled as nonspecific CLBP,[43] increased focus has been placed on its interactions with biological, psychological, and social factors. While CLBP is influenced by multiple contributors, including depression, anxiety, pain catastrophizing, or cognitive dysfunctions,[17,29] systematic reviews have found that over 70% of individuals with CLBP experienced sleep disturbance.[46,75] Furthermore, sleep disturbance is a stronger predictor of incident low back pain in healthy individuals[1] or worsens pain perception, disability, and prognosis in individuals with CLBP.[3,7,80] These findings highlight the importance of better understanding the role of insomnia in these populations.

Despite the well-established association between pain and sleep, the potential mechanisms underlying their correlation remain unclear. Recent narrative reviews have summarized several putative mechanisms that shed light on the impact of sleep disturbances on heightened sensitivity to pain perception.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong SAR, China, [b] School of Medical and Health Sciences, Tung Wah College, Hong Kong SAR, China, [c] Department of Psychology, Sleep Research Clinic and Laboratory, The University of Hong Kong, Hong Kong SAR, China, [d] The State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong SAR, China, [e] Department of Orthopedic Surgery, Rush University Medical Centre, Chicago, IL, United States, [f] Research Institute for Smart Ageing, The Hong Kong Polytechnic University, Hong Kong SAR, China, [g] Research Institute for Sports Science and Technology, The Hong Kong Polytechnic University, Hong Kong SAR, China

*Corresponding author. Address: Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, SAR, China. Tel.: (+852) 2766-6741. E-mail address: arnold.wong@ (A. Y.L. Wong).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

http://dx.doi.org/10.1097/j.pain.0000000000003591

Access to the article:

https://journals.lww.com/pain/fulltext/9900/differential_pain_perception_among_females_with_or.863.aspx

4.1 Abstract

Background: Sleep disturbance is a prevalent condition in individuals with chronic low back pain (CLBP). Despite a strong association between the two conditions, the potential mechanisms underlying the role of sleep disturbance in CLBP remain unclear. This cross-sectional study aimed to examine pain perception among females with or without non-specific CLBP and comorbid insomnia.

Methods: One hundred females were recruited (mean age: 34.3±11.4 years), with 25 individuals with concomitant CLBP and insomnia (CLBP+I), 25 with CLBP (CLBP+), 25 with insomnia (Insomnia+), and 25 healthy controls. All participants completed self-report questionnaires and quantitative sensory testing (QST).

Results: Our study found that CLBP+I exhibited lower mechanical pain and pressure pain thresholds (PPT) in both painful and non-painful areas and impaired conditioned pain modulation (CPM) as compared to healthy controls. Similar findings were found in PPT at the back and CPM when compared to CLBP+. However, no significant differences were noted in thermal pain thresholds and temporal summation of pain across the four groups. Furthermore, CLBP+I and Insomnia+ displayed higher levels of functional disability, maladaptive beliefs, and negative mood than CLBP+ or healthy controls.

Conclusions: There were significant increases in pain sensitivity to pressure stimuli, decreases in descending pain inhibitory effects, and higher levels of maladaptive psychological status in CLBP+I compared to CLBP+. These findings underscore the importance of incorporating sleep assessments as a routine practice in treating CLBP cases. Future studies are warranted to validate our findings in males, establish the diagnostic and prognostic value of QST, and probe the neurophysiological mechanisms in comorbid conditions.

Keywords: Chronic low back pain; Insomnia; Quantitative sensory testing; Conditioned pain modulation.

4.2 Introduction

Chronic low back pain (CLBP) is one of the most common reasons for seeking healthcare consultation [267] and is associated with higher healthcare demand and more significant comorbidity than asymptomatic individuals [268, 269]. Given that most CLBP cases lack identifiable medical evidence or a specific diagnosis and are labelled as non-specific CLBP [270], increased focus has been placed on its interactions with biological, psychological, and social factors. While CLBP is influenced by multiple contributors, including depression, anxiety, pain catastrophizing, or cognitive dysfunctions [2, 271], systematic reviews have found that over 70% of individuals with CLBP experienced sleep disturbance [8, 272]. Furthermore, sleep disturbance is a stronger predictor of incident low back pain (LBP) in healthy individuals [185], or worsens pain perception, disability, and prognosis in individuals with CLBP [10, 11, 273]. These findings highlight the importance of better understanding the role of insomnia in these populations.

Despite the well-established association between pain and sleep, the potential mechanisms underlying their correlation remain unclear. Recent narrative reviews have summarized several putative mechanisms that shed light on the impact of sleep disturbances on heightened sensitivity to pain perception. These mechanisms encompass various factors, such as the increased release of proinflammatory cytokines, dysregulation of the autonomic system, negative affect or mood disorders, and altered nociceptive processing in the brain [15-18]. Significant attention has been

given to the observed alterations in peripheral and central pain modulation. Studies found that experimental sleep deprivation paradigms increased pain sensitivity to noxious stimuli or central sensitization in individuals with or without chronic pain [22, 25, 27, 274, 275]. Likewise, a cross-sectional study in individuals with insomnia and/or knee osteoarthritis revealed that the comorbidity of pain and insomnia was associated with heightened central sensitization compared to asymptomatic individuals [190]. However, different chronic pain conditions exhibit distinct physiological and psychological profiles [117, 118]. These disease-specific characteristics may affect pain perception differently [276], limiting the generalizability of findings to individuals with CLBP. More importantly, the existing evidence regarding the association between CLBP and insomnia has primarily relied on patient-reported outcome measures, which may not fully capture the complexity and characteristics of pain perception.

Quantitative Sensory Testing (QST) is a reliable and validated method to investigate the physiological underpinnings of pain in individuals with CLBP [107, 277], and it can predict pain development, disability, and negative affect for musculoskeletal pain [101]. To our knowledge, no study has examined pain perception in individuals with non-specific CLBP and comorbid insomnia. Considering the sex-differentiated effects on pain perception [25, 275] and the high prevalence of chronic pain or insomnia in females [278, 279], the present cross-sectional study aimed to determine the pain perception characteristics in the four groups of age-matched females using a standardized and validated QST protocol. Additionally, we explored the relationship between insomnia and QST parameters in individuals with comorbid conditions, controlling for pain-related outcomes and psychological factors.

4.3 Methods

4.3.1 Study Design

This cross-sectional study was approved by the Institutional Review Board of The Hong Kong Polytechnique University (HSEARS20220731001) and conducted in accordance with the Declaration of Helsinki. Data collection took place at a laboratory on the campus between September 2022 and November 2023. Potential participants underwent an initial telephone screening with a subsequent medical history interview and physical examinations to determine their eligibility. These screening procedures were conducted by a physiotherapist under the supervision of physicians specialized in sleep or pain medicine. All participants provided written informed consent before the data collection.

4.3.2 Participants

One hundred Chinese female participants were recruited through posters posted on the campus and referrals from collaborating physicians. Based on the presence or absence of non-specific CLBP and insomnia, participants were categorized into four groups: (1) participants with non-specific CLBP and insomnia (CLBP+I, n = 25); (2) participants with non-specific CLBP without insomnia (CLBP+, n = 25); (3) participants with insomnia without non-specific CLBP (Insomnia+, n = 25); (4) healthy participants without non-specific CLBP and insomnia (Control, n = 25). The general inclusion criteria for all participants were females aged between 18 and 65 years. Exclusion criteria were: (1) specific or serious cause of pain conditions (e.g., malignancy, postsurgical or posttraumatic pain, complex regional pain syndrome, spondylarthritis, or spinal fracture); (2) other clinically diagnosed sleep disorders (e.g., sleep apnea or restless leg syndrome); (3) a history of or any existing psychiatric, neurological, or physical disorders

directly related to the onset of insomnia (e.g., substance abuse, alcohol abuse, or inflammatory diseases); (4) women with suspected/confirmed pregnancy or who is currently nursing; (5) receiving treatments for insomnia or pain for less than one month before study enrollment; (6) high variability in the sleep pattern due to occupational or recreational factors [280]; or (7) body mass index (BMI) exceeded 30 kg/m^2 [281].

Healthy individuals were free from acute pain, injury, or a history of chronic pain within the past 12 months [190]. They also did not have any clinically diagnosed sleep disorders, with scores on the Insomnia Severity Index (ISI) ≤ 10 [282] and the Pittsburgh Sleep Quality Index (PSQI) ≤ 5 [283]. Non-specific CLBP was defined as pain located between the 12^{th} ribs and gluteal creases without identifiable pathoanatomical causes, persisting for at least three months and occurring on pain more than half of the days in the past four weeks [270, 284, 285]. Participants reported an average pain intensity of more than 3 points on the 11-point Numerical Pain Rating Scale (NPRS) over the last week before enrollment [286], where 0 and 10 indicated no pain and the worst imaginable pain, respectively. For participants with insomnia, the Brief Insomnia Questionnaire was used to determine their insomnia status based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders 5^{th} edition (DSM-5) [167, 287]. All the participants were instructed to maintain their regular sleep patterns, adhere to their usual medication regimen, and refrain from excessive physical activity or alcohol 48 hours before the data collection [288]. To account for potential menstrual cycle effects on pain perception, data collection was scheduled outside of their menstruation periods [289]. No participants had used hormonal contraceptives in the month prior to enrollment.

4.3.3 Clinical and Psychological Assessments

Participants completed a battery of self-report measures to assess demography, LBP-related disability, sleep, and psychological wellbeing, including the NPRS [290], Roland Morris Disability Questionnaire (RMDQ) [291], Fear-Avoidance Beliefs Questionnaire (FABQ) [292], Pain Catastrophizing Scale (PCS) [293], ISI [282], PSQI [283], and Depression Anxiety Stress Scale (DASS) [294]. All questionnaires employed in this study have been cross-culturally adapted into Chinese and demonstrated acceptable reliability and validity [295-300].

4.3.4 Quantitative Sensory Testing (QST) Protocol

The experimental sensory testing followed a standardized protocol established by the German Research Network on Neuropathic Pain (DFNS) [97, 98], incorporating methodologies from previous studies conducted on individuals with CLBP [277, 301]. To assess the intra-rater reliability of the operator, a pilot QST protocol was conducted in 10 healthy individuals with a 5-day interval between two sessions, yielding Intraclass Correlation Coefficients ranging from 0.76 to 0.97 (**Table S2.1**). All QST assessments were conducted by the same researcher, who was blinded to the subgroup classification of the participants, in a quiet laboratory maintained at a consistent temperature of 23 ± 2℃. Participants were unaware of the recorded values for each assessment and were instructed to lie in a prone position on a treatment table during the measurements. To ensure understanding of the testing procedure, each participant underwent a 10-minute practice trial on the dominant forearm (not tested). The pain thresholds assessments were conducted on two body sites, with the remote site assessed first (thermal stimuli at the extensor carpi radialis longus muscle [118], pressure stimuli at the thenar eminence of the non-dominant hand [302], and mechanical stimuli at the dorsum of the non-dominant hand [303]),

followed by the most symptomatic part of the lumbar region (for participants without non-specific CLBP: the stimuli were applied at 5 cm lateral to the non-dominant side of the L1 to L5 spinous process) [304, 305]. Temporal summation of pain (TSP) or conditioned pain modulation (CPM) were assessed with stimuli applied on the remote site. The stimulator was slightly moved to an adjacent area after each sequence of trials to minimize receptor fatigue or habituation [103]. The following order of testing with the same equipment and standardized instructions was used to ensure the uniformity of assessments: cold pain threshold (CPT), heat pain threshold (HPT), mechanical pain threshold (MPT), pressure pain threshold (PPT), temporal summation of mechanical pain (TSP-M), temporal summation of heat pain (TSP-46 ℃ and 48 ℃), and conditioned pain modulation (CPM).

Thermal pain threshold

A 30*30-mm thermode (TSA 2, Medoc Ltd., Ramat Yishai, Israel) was used to assess CPT or HPT. The thermode was placed gently on the skin without causing deformation. The method of limits program was used to gradually increase or decrease the temperature at a rate of 1℃/second. The temperature range was set between 0 and 51℃, with a baseline temperature of 32℃. Participants were instructed to press the stop button when they perceived the thermal sensation as painful. The mean value of five consecutive trials was used in the statistical analysis.

Mechanical pain threshold

MPT was evaluated using a set of standardized weighted pinprick stimulators (MRC System GmbH, Heidelberg, Germany) with a flat contact area of 0.25mm in diameter. The stimulator consists of seven fixed intensities ranging from 8 mN to 512 mN [97]. The intensity of the

pinprick that elicited a pain sensation was recorded. The final threshold was calculated as the geometric mean of the ascending and descending stimulus intensities from five series.

Pressure pain threshold

PPT was measured by a pressure algometer (Commander EchoAlgometer, JTECH, Midvale, UT) equipped with a 1 cm^2 rubber probe. The pressure was applied at a constant rate of approximately 1 kg/cm^2 per second until participants perceived the stimulus as painful. Three trials were performed, and mean scores were calculated to determine the PPT.

Temporal summation of mechanical pain

TSP-M was assessed by the same pinprick stimulator at a fixed intensity of 256 mN on a 1 cm^2 area. Participants were instructed to rate the pain intensity using an 11-point NPRS after the first and the 10^{th} identical stimuli. A series of 10 identical stimuli were administered at a 1-second interval. If the NPRS pain rating is 0 out of 10 for three consecutive single stimuli of 256 mN, the stimulation intensity would be increased to 512 mN, and the trial would be repeated [108]. The TSP-M results were defined as the difference in NPRS between the first stimulus and the 10^{th} stimulus.

Temporal summation of heat pain

TSP-H was evaluated by a 9 cm^2 thermode (TSA 2, Medoc Ltd., Ramat Yishai, Israel) with a 13°C/second ramp rate. Participants experienced two sequences of 10 heat pulses (46 ℃ and 48 ℃) with a 5-minute interval [103, 190, 306]. A series of 10 repetitive stimuli were applied with a 2.5-second interstimulus interval at a baseline temperature of 40 ˚C for 0.5-second

duration [307, 308]. The participant was instructed to rate the pain intensity for each stimulus within the sequence using an 11-point NPRS [254]. The TSP-H was calculated as the differences in NPRS scores between the 10^{th} stimulus and the first stimulus at each temperature.

Conditioned pain modulation

CPM was assessed using painful conditioning stimuli (CS) and test stimuli (TS). The CS was noxious contact heat, applied to the dominant volar forearm between the distal third of the forearm and the ulnar styloid. The target CS temperature was set 1.1 °C above the participant's HPT for 120s [302, 309, 310]. The temperature of the CS started at 32 ℃ at baseline and increased at a ramp rate of 8°C/s to the predetermined temperature, using the TSA 2 device (Medoc Ltd., Ramat Yishai, Israel). During the CPM assessment, if participants could not tolerate the CS (i.e., pain intensity over 8 on the11-point NPRS) or if they reported a pain intensity below 4 on the 11-point NPRS, the temperature of the CS was adjusted to ensure a safe and adequate stimulus intensity [302, 309]. The TS were applied to the thenar eminence of the non-dominant hand using a pressure algometer (Commander EchoAlgometer, JTECH, Midvale, UT) to determine PPT before and immediately after removing the CS. The CPM effect was calculated by subtracting the PPT measured before the CS from the PPT measured after the CS (CPM response = $PPT_{baseline} - PPT_{post\ CS}$). A negative value indicated decreased pain sensitivity (inhibitory response or efficient CPM), while a positive value indicated increased pain sensitivity (facilitatory response or low-efficiency CPM) [311, 312].

4.3.5 Data Analysis

Statistical analysis was conducted using SPSS version 25.0 (IBM Corp., Armonk, NY). As most variables did not adhere to normal distribution based on the Shapiro-Wilks test, group differences were determined using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. The results were reported as medians, interquartile range (IQR), or percentages. The significance level of all statistical analyses was set at 0.05. Post-hoc analyses employed Bonferroni corrections to address multiple comparisons.

A logarithmic transformation was applied to MPT and PPT as suggested by previous protocols [97, 98]. Each QST-derived parameter was further transformed into a standard normal Z-score distribution, with reference to the mean and standard deviation (SD) of the healthy controls [97, 98]. The following formula was used for each QST parameter: Z-score = $(X_{participant} - Mean_{control})/SD_{control}$. For HPT, MPT, and PPT, the sign of the Z-score was reversed and multiplied by -1 to ensure consistency in the sensitivity direction and sensory function. Positive Z-score values indicate increased sensitivity to noxious stimuli compared to healthy controls (lower thresholds, gain of function), whereas negative values indicate decreased pain sensitivity (higher thresholds, loss of function). A z-score of zero corresponds to a value equivalent to the mean of healthy controls [97, 98]. Sensitivity analyses for QST were performed to assess the effect of outliers on the primary analyses. Participants outside 1.5 times IQR were classified as outliers. Furthermore, sensitivity analyses for QST were performed by excluding individuals who were underweight (BMI under 18.5 kg/m^2) or overweight (BMI over 25.0 kg/m^2) [313].

Hierarchical linear regression models were performed within CLBP+I to evaluate the unique associations between pain-related outcomes (pain duration, NPRS, and RMDQ), psychological

factors (PCS, FABQ, and DASS), and insomnia (ISI and PSQI) with QST parameters that showed statistically significant between-group differences. The dependent variable in each model was one of the QST parameters (MPT, PPT, and CPM). Pain-related outcomes were entered as independent variables in the first block (Model 1), psychological factors in the second block (Model 2), and insomnia in the third block (Model 3). The final model assessed whether insomnia was independently associated with pain sensitivity after controlling for other factors [314]. Prior to modeling, a square root transformation was applied to normalize the distribution of independent variables. To account for multicollinearity, the variance inflation factor (VIF) was examined for each independent variable, including only those with a VIF value < 5 in the model [315].

4.4 Results

4.4.1 Participants' Characteristics

The demographic and clinical characteristics of the four groups are presented in 错误!未找到引用源。. The median age across the groups ranged from 29.0 to 31.9 years. Among the participants, eight were taking medications: melatonin (n = 4), nonsteroidal anti-inflammatory drugs (n = 2), Zopiclone (n = 1), and other health-related medications (n = 1). None of the participants with CLBP reported experiencing neuropathic pain in the lower limbs. No significant between-group differences were observed in terms of age ($p = 0.994$), education levels ($p = 0.935$), working status ($p = 0.529$), and medication use ($p = 0.055$). However, CLBP+ featured a significantly higher BMI than Insomnia+ ($p_{corrected} = 0.015$).

4.4.2 Clinical and Psychological Assessments

CLBP+I and CLBP+ experienced pain for three to 26 months. The median of their average pain intensity in the last week was 5.0 (IQR: 4.0-6.0) and 4.0 (IQR: 3.0-5.0) on the NPRS, respectively. The two groups had no significant differences in the LBP duration ($p = 0.085$) and LBP intensity ($p = 0.229$). Nevertheless, CLBP+I reported significantly higher levels of functional disability ($p = 0.022$) and fear avoidance beliefs ($p = 0.048$) than CLBP+. CLBP+I also had significantly higher PCS than CLBP+ ($p_{corrected} = 0.001$) and healthy controls ($p_{corrected} = 0.011$). Regarding sleep assessments and other psychological measurements, CLBP+I and Insomnia+ exhibited significantly more severe insomnia symptoms ($p_{corrected} < 0.001$), poorer sleep quality ($p_{corrected} < 0.001$), and higher levels of emotional distress ($p_{corrected} < 0.001$) than both CLBP+ and healthy controls, whereas no significant differences in these variables were identified between CLBP+I and Insomnia+.

4.4.3 Quantitative Sensory Testing

Comparisons of pain thresholds of the back

The Kruskal-Wallis tests indicated significant between-group differences in MPT ($p < 0.001$) and PPT ($p < 0.001$), whereas no significant between-group differences were found in CPT ($p = 0.160$) and HPT ($p = 0.455$) (错误!未找到引用源。). Post-hoc analyses with Bonferroni corrections revealed that CLBP+I exhibited significantly lower MPT compared to Insomnia+ ($p_{corrected} = 0.039$) or healthy controls ($p_{corrected} < 0.001$). Furthermore, CLBP+I displayed significantly lower PPT than CLBP+ ($p_{corrected} = 0.001$), Insomnia+ ($p_{corrected} = 0.002$), and healthy controls ($p_{corrected} < 0.001$) (**Figure 4**).

Comparisons of pain thresholds of the hand

In line with the somatosensory profiles of the back, the Kruskal-Wallis tests revealed significant between-group differences in MPT ($p = 0.009$) and PPT ($p = 0.025$) at the hand (错误!未找到引用源。), while there was no significant between-group difference in CPT ($p = 0.174$) or HPT ($p = 0.067$). Compared to healthy controls, CLBP+I had significantly lower MPT ($p_{corrected} = 0.004$) and PPT ($p_{corrected} = 0.020$), indicating pain sensitization in CLBP+I. However, no significant differences were identified in other comparative analyses.

Comparisons of TSP and CPM

The four groups did not significantly differ in TSP either in response to mechanical stimuli ($p = 0.134$), 46℃ heat pain stimuli ($p = 0.621$), or 48℃ heat pain stimuli ($p = 0.456$). However, the Kruskal-Wallis test revealed significant between-group effects on CPM ($p = 0.011$). Post-hoc analyses with Bonferroni corrections demonstrated that CLBP+I exhibited significantly less inhibitory effects than CLBP+($p_{corrected} = 0.029$) or healthy controls ($p_{corrected} = 0.023$), while no significant between-group differences were observed in other analyses.

Sensitivity analyses and assessments for outliers

One outlier was identified in the MPT at the remote site (1.0%), two outliers in the PPT at the remote site (2.0%), three outliers in the PPT at the back (3.0%), five outliers in the TSP for 46°C heat pain stimuli (5.0%), nine outliers in the TSP for 48°C heat pain stimuli (9.0%), and three outliers in the CPM (3.0%). After removing these outliers, none of the comparisons exhibited alterations in their significance, although the significance level was slightly increased in PPT at the hand and CPM (**Table S2.2**). Moreover, sensitivity analyses excluding individuals who were underweight (n = 16) or overweight (n = 8) yielded results consistent with the primary analyses

for MPT, PPT, and CPM. We also identified between-group differences in CPT at the back (p = 0.027) and remote site (p = 0.030), as well as HPT at the remote site (p = 0.011) during these analyses (**Table S2.3**).

4.4.4 Associations between Clinical Variables and QST Parameters within CLBP+I

Hierarchical linear regression analyses examining associations between clinical variables and QST parameters are displayed in **Table 5**. Variance inflation factor analysis indicated no significant multicollinearity among clinical variables (1.213 to 2.029). Model 1 accounted for 39.4% of the variance in MPT at the back ($F_{3,21} = 4.547, p = 0.013$), whereas Model 2 explained 44.2% ($F_{6,18} = 2.377, p = 0.072$). None of the pain-related outcomes or psychological factors were significantly associated with mechanical pain sensitivity. The final model showed that insomnia was a significant predictor, explaining an additional 17.6% of the variance ($p = 0.049$). Higher insomnia severity was significantly associated with lower MPT at the back ($\beta = -0.519, p = 0.016$). A similar pattern was observed for MPT at the remote site, where Models 1 and 2 together explained 51.7% of the variance ($F_{6,18} = 3.144, p = 0.027$). Longer pain duration ($\beta = -0.047$, $p = 0.045$) and higher RMDQ scores ($\beta = -0.519$, $p = 0.003$) were significantly related to lower MPT. The final model revealed that insomnia accounted for an additional 21.3% of the variance ($p = 0.008$), with higher insomnia severity linked to heightened pain sensitivity at the remote site ($\beta = -0.553$, $p = 0.003$). For PPT at the back, PPT at the remote site, and CPM, the final model explained 16.0% ($F_{8,16} = 0.381, p = 0.916$), 36.4% ($F_{8,16} = 1.147, p = 0.386$), and 28.6% ($F_{8,16} = 0.802, p = 0.610$) of the variance, respectively. None of the clinical variables were significantly associated with variance in these outcomes.

4.5 Discussion

The current study investigates the pain perception characteristics among four well-characterized groups of individuals with or without non-specific CLBP or insomnia. Our results indicated that females with CLBP+I exhibited significantly heightened sensitivity to mechanical and pressure painful stimuli in both painful and non-painful areas as compared to age-matched healthy controls. Furthermore, CLBP+I displayed lower PPT at the back and more pronounced impairment in the descending pain pathway than CLBP+. Regarding psychological measurements, CLBP+I and Insomnia+ reported significantly more maladaptive beliefs or negative mood compared to CLBP+ or healthy controls. Insomnia was independently associated with MPT at both the back and remote site in CLBP+I, even after controlling for pain-related and psychological factors. These findings underscore the potential adverse effects of insomnia on pain perception in individuals with CLBP, emphasizing the importance of providing additional sleep treatments for CLBP+I.

Prior research has identified a considerable heterogeneity in pain experience among individuals with CLBP when evaluated by various QST [13, 116]. This divergence in findings may be ascribed to inter-individual differences and a lack of consideration for the complex biopsychosocial nature of CLBP [13, 116]. Given the high prevalence of sleep disturbances and the strong correlation between sleep and pain [8, 10, 11, 272, 273], subgrouping individuals with CLBP based on their sleep status can provide valuable insights into somatosensory functioning within the homogeneous subgroup, which is often overlooked. Our results revealed that compared to healthy controls, CLBP+I demonstrated lower MPT and PPT in both painful and non-painful areas. However, no significant differences were observed between CLBP+ and

healthy controls. Additionally, CLBP+I exhibited significantly lower PPT at the back than both CLBP+ and Insomnia. These findings align with a previous cluster analysis that identified a subset of CLBP patients with higher pressure pain sensitivity who were more prone to sleep disturbance [13]. Given the compelling evidence, the findings provide some support to the hypothesis that sleep may play a contributing role in heightened pain perception in individuals with chronic pain. Clinicians should be cognizant of distinct somatosensory functions in comorbid conditions and consider triaging a subgroup of CLBP+I for tailored treatments [27, 46].

Although our study revealed relatively higher sensitivity to cold or heat stimuli in CLBP+I, CLBP+, and Insomnia+ compared to healthy controls, there were no significant differences in thermal pain thresholds among the four groups. These results contradict previous studies that have demonstrated increased thermal sensitization in individuals with chronic pain [112, 119, 316] or insomnia [317] when compared to asymptomatic individuals. This discrepancy may be attributed to the influence of genetic and environmental factors on the nature of thermal pain thresholds and the variability in responses to different stimuli within heterogeneous chronic pain populations. For example, Christopher et al. pointed out that heritable components could account for 60% of the variance in cold pain and 26% in heat pain [318]. Future research should validate our current findings and determine which components of QST assessment are more sensitive as diagnostic outcomes and prognostic biomarkers for treatment response in the comorbid condition.

Regarding CPM, our study found that CLBP+I exhibited a less efficient inhibitory effect on descending pain pathways compared to CLBP+ and healthy controls, whereas no significant differences were noted between CLBP+ and healthy controls. These findings are consistent with earlier studies in chronic pain populations, suggesting that diminished endogenous pain inhibitory effect was mediated by poor sleep quality [255, 319, 320]. Surprisingly, no significant differences in TSP among the four groups were observed. These findings contrast with previous studies that revealed enhanced TSP in individuals with CLBP [112, 115, 116] or healthy individuals after sleep deprivation [20, 25]. This disparity may be attributed to differences in temporal summation measurement protocols (e.g., types of painful stimuli or sites of stimuli applications). Specifically, the current study applied the mechanical or heat painful stimuli to non-painful areas, whereas other studies found facilitated TSP in the lumbar region of individuals with CLBP [112, 116], which could potentially be confounded by peripheral sensitization. Notably, Campbell et al. combined CPM and TSP as an integrated measure of central sensitization, indicating enhanced central sensitization in individuals with keen osteoarthritis and insomnia compared to healthy controls [190]. These findings underscore that comorbid conditions might be associated with abnormal central pain processing. Further studies should explore underlying central mechanisms through neuroimaging and examine the effectiveness of interventions designed to restore central sensitization in comorbid cases.

While significant differences were found in objective pain measurements between CLBP+I and CLBP+, there were no significant differences in the duration or intensity of LBP. These findings suggest that despite variations in psychophysiological somatosensory patterns, the clinical manifestations of pain are largely similar between the two groups [304]. However, it is

noteworthy that CLBP+I displayed significantly higher levels of functional disability, fear-avoidance beliefs, pain catastrophizing thoughts, and negative mood compared to CLBP+. Likewise, Insomnia+ also displayed significantly worse conditions in these variables than healthy controls. These results align with prior research showing that insomnia alone or comorbid with knee osteoarthritis is associated with heightened attention to pain-related thoughts and elevated depressive symptoms compared to asymptomatic individuals [190]. The parallel findings in both CLBP and knee osteoarthritis imply that insomnia amplify the experience of chronic pain. Further research should explore whether similar patterns exist in other types of chronic pain conditions. Clinically, it is recommended to incorporate sleep screening as a routine assessment for individuals with chronic pain. If insomnia is present, clinicians should actively screen for maladaptive beliefs and emotional distress. This approach would enable more tailored treatments and improve outcomes for this population.

Our hierarchical regression analyses in CLBP+I revealed that insomnia significantly increased the explained variance in MPT at the back and remote site, independent of pain-related and psychological factors. Similar findings from previous studies on chronic pain suggest that insomnia is independently associated with heightened pain intensity [314, 321]. These results highlight the potential role of sleep as an independent factor in managing pain sensitivity in comorbid states. A systematic review further supports this, indicating that sleep loss-induced pain sensitivity can be reversed by recovery sleep in healthy individuals [36]. Nevertheless, the models for PPT and CPM did not reach statistical significance, possibly attributed to differences in stimulus types, the distinct mechanisms underlying different QST assessments [109], and the relatively small sample size. Future studies should explore the mechanisms by which sleep

affects various nociceptive processes using larger, more homogeneous samples. Moreover, these studies should identify biopsychosocial factors that may moderate or mediate the relationship between sleep and pain perception. Such findings would help elucidate the associations between potential mechanisms and clinical manifestations, thereby better informing clinical decision-making.

This study had several limitations that should be acknowledged. First, although insomnia diagnosis was conducted using a standardized semi-structured interview according to DSM-5 criteria, the absence of objective assessments (e.g., polysomnography) limited our ability to determine sleep states objectively. Second, our study did not incorporate neuroimaging biomarkers or consider other biopsychosocial factors such as different menstrual phases, household matters, and lifestyle. Subsequent studies are warranted to explore these aspects to gain insight into the neurophysiology of central pain mechanisms and biopsychosocial factors in distinct subgroups. Third, our study controlled for potential confounders such as age, sex, and pain type, which may limit the generalizability of our results to older adults, males, or other types of musculoskeletal pain. Further studies are warranted to investigate potential sex-specific effects on pain perception in different comorbid pain conditions. Likewise, our cohort had a low proportion of individuals using medications or with serious medical histories, and results may not be representative of those with undergoing pharmacological treatment or more complex medical profiles. Finally, although the TSP-heat paradigm utilized in our study was developed based on existing evidence [103, 190, 302, 309], the observed decline in pain intensity during the final stimuli may primarily reflect habituation processes rather than temporal summation [322]. Therefore, future studies should optimize stimulus parameters for evoking TSP-heat (e.g.,

stimulus frequency, baseline temperature, peak temperature, or peak duration) and to explore its effects in comorbid states.

4.6 Conclusions

In summary, this is the first empirical investigation to examine differential pain perception among females with or without non-specific CLBP and comorbid insomnia. Our results indicate a potential association between CLBP and insomnia, possibly involving a reduction in PPT and impairment of the descending pain-inhibitory pathway. Female individuals with CLBP and comorbid insomnia also reported higher levels of functional disability, maladaptive beliefs, and emotional distress compared to those with CLBP alone. These findings highlight the importance of incorporating sleep assessments into routine screening for individuals with CLBP and considering sleep as a target for therapeutic interventions to restore psychophysiological functions in comorbid conditions. Further studies are needed to explore the diagnostic and prognostic value of QST, investigate the underlying neural mechanisms, and adopt a biopsychosocial approach to understanding and managing in individuals with comorbid conditions.

4.7 Tables

Table 3. Demographic and clinical characteristics

	Healthy control (n=25)	**Insomnia+ (n=25)**	**CLBP+ (n=25)**	**CLBP+I (n=25)**	***p* value**
Age, median (IQR)	29.3 (26.9 to 46.8)	31.9 (26.2 to 39.6)	29.6 (24.9 to 35.0)	29.0 (27.2 to 40.3)	0.944
Body mass index, median (IQR)	20.5 (19.1 to 22.2)	19.3 (18.3 to 21.0)	21.2 (20.2 to 23.1)	21.3 (19.2 to 24.0)	**0.015**
Education (≥ bachelor), %	92.0	92.0	92.0	88.0	0.935
Working status, %					0.529
Employed	96.0	92.0	88.0	96.0	
Unemployed	0.0	4.0	0.0	0.0	
Retired	4.0	4.0	12.0	4.0	
Medication use, %					0.055
None	100.0	80.0	96.0	92.0	
Nonsteroidal anti-inflammatory drug	0.0	0.0	4.0	4.0	
Melatonin or Zopiclone	0.0	16.0	0.0	4.0	
Medications for other health conditions	0.0	4.0	0.0	0.0	
Duration of pain, median (IQR)	-	-	18.0 (8.0 to 36.0)	24.0 (9.0 to 54.0)	0.085
Average pain intensity during last week, median (IQR)	-	-	4.0 (3.0 to 5.0)	5.0 (4.0 to 6.0)	0.229
Roland Morris Disability Questionnaire, median (IQR)	-	-	5.0 (5.0 to 8.0)	8.0 (6.5 to 11.0)	**0.022**
Fear-Avoidance Beliefs Questionnaire, median (IQR)					
Total score	-	-	32.0 (21.0 to 41.5)	39.0 (32.0 to 45.0)	**0.048**
Physical activity subscale	-	-	15.0 (12.0 to 18.5)	16.0 (13.0 to 18.5)	0.320
Work subscale	-	-	18.0 (10.5 to 25.0)	23.0 (18.5 to 27.0)	**0.027**
Pain Catastrophizing Scale, median (IQR)	14.0 (5.5 to 22.5)	19.0 (14.5 to 29.0)	13.0 (6.5 to 21.0)	24.0 (19.0 to 26.0)	**0.001**
Insomnia Severity Index, median (IQR)	2.0 (1.0 to 3.0)	16.0 (13.5 to 19.5)	4.0 (2.0 to 7.0)	14.0 (12.0 to 16.5)	**< 0.001**
Pittsburgh Sleep Quality Index, median (IQR)	3.0 (2.0 to 4.0)	12.0 (10.5 to 13.0)	4.0 (3.0 to 5.0)	11.0 (10.0 to 13.0)	**< 0.001**

Depression Anxiety Stress Scale, median (IQR)					
Total score	4.0 (1.5 to 8.0)	17.0 (8.0 to 29.5)	5.0 (3.5 to 7.5)	18.0 (11.0 to 25.5)	**< 0.001**
Anxiety subscale	1.0 (0.0 to 2.0)	4.0 (1.0 to 9.0)	2.0 (0.5 to 4.0)	5.0 (2.0 to 7.0)	**< 0.001**
Depression subscale	1.0 (0.0 to 1.5)	4.0 (1.0 to 8.0)	1.0 (0.0 to 2.0)	4.0 (2.0 to 6.0)	**< 0.001**
Stress subscale	2.0 (0.5 to 4.0)	9.0 (5.0 to 13.0)	2.0 (1.0 to 4.0)	8.0 (6.0 to 12.0)	**< 0.001**

Abbreviation: CLBP+: Individuals with non-specific chronic low back pain; CLBP+I: Individuals with concomitant non-specific chronic low back pain and insomnia; Insomnia+: Individuals with insomnia; IQR: Interquartile range; QST: Quantitative sensory testing.
Footnote: Values are presented as median and interquartile range. P value was calculated by the Kruskal-Wallis test for continuous variables and by the chi-square test for categorical variables. The p-value in bold indicates a statistically significant difference among the four groups ($p < 0.05$).
Notation: Higher total scores of included questionnaires indicated poor functioning.

Table 4. Group differences in QST measurements

	Healthy control (n=25)	**Insomnia+ (n=25)**	**CLBP+ (n=25)**	**CLBP+I (n=25)**	***p* value**
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
Cold pain threshold (°C)					
Back	12.30 (0.00 to 23.84)	16.85 (5.28 to 25.72)	22.28 (10.87 to 26.70)	16.43 (6.75 to 27.49)	0.160
Remote site	10.30 (5.72 to 16.15)	14.30 (6.25 to 20.74)	17.10 (9.06 to 20.76)	12.76 (10.54 to 23.31)	0.174
Heat pain threshold (°C)					
Back	41.34 (39.90 to 42.73)	41.38 (38.71 to 42.95)	40.28 (38.68 to 42.62)	41.33 (37.45 to 42.50)	0.455
Remote site	42.90 (41.25 to 42.52)	41.14 (38.81 to 44.04)	41.60 (39.43 to 43.36)	41.48 (38.62 to 42.42)	0.067
Mechanical pain threshold (mN)					
Back	2.26 (1.98 to 2.49)	2.19 (1.75 to 2.40)	2.05 (1.69 to 2.40)	1.81 (1.37 to 2.04)	**< 0.001**
Remote site	2.11 (1.95 to 2.37)	1.99 (1.80 to 2.22)	1.96 (1.75 to 2.22)	1.85 (1.50 to 2.07)	**0.009**
Pressure pain threshold (Kg)					
Back	0.74 (0.64 to 0.82)	0.68 (0.54 to 0.79)	0.70 (0.55 to 0.77)	0.43 (0.32 to 0.58)	**< 0.001**
Remote site	0.49 (0.39 to 0.57)	0.46 (0.33 to 0.55)	0.40 (0.32 to 0.53)	0.34 (0.23 to 0.46)	**0.025**
Temporal summation of mechanical pain	1.00 (0.00 to 2.00)	1.75 (0.50 to 3.00)	1.50 (0.00 to 2.50)	2.00 (0.50 to 2.80)	0.134
Temporal summation of heat pain (46°C)	-1.00 (-3.00 to 0.00)	-1.50 (-3.00 to 0.00)	-2.00 (-2.50 to 0.50)	-1.00 (-1.80 to 0.00)	0.621
Temporal summation of heat pain (48°C)	0.00 (-2.00 to 0.00)	-1.00 (-1.25 to 0.00)	0.00 (-1.00 to 0.00)	-0.50 (-1.50 to 0.00)	0.456
Conditioned pain modulation	-0.20 (-0.40 to 0.25)	-0.20 (-0.35 to 0.30)	-0.10 (-0.30 to 0.20)	0.20 (0.05 to 0.20)	**0.011**

Abbreviation: CLBP+: Individuals with non-specific chronic low back pain; CLBP+I: Individuals with concomitant non-specific chronic low back pain and insomnia; Insomnia+: Individuals with insomnia; IQR: Interquartile range; QST: Quantitative sensory testing.
Footnote: Values are presented as median and interquartile range. P value was calculated by the Kruskal-Wallis test. The p-value in bold indicates a statistically significant difference among the four groups ($p < 0.05$).

Table 5. Hierarchical regression analysis to examine clinical variables and QST parameters within CLBP+I (n=25)

	Pain-related outcomes (Beta)			Psychological factors (Beta)			Insomnia (Beta)		Statistics
	Pain duration	NPRS	RMDQ	PCS	FABQ	DASS	ISI	PSQI	
MPT-B									
Model 1	-0.001	-0.365	-0.277						R^2=0.394, $F_{3,21}$=4.547*
Model 2	-0.019	-0.495	-0.276	0.089	-0.003	-0.082			R^2=0.442, $F_{6,18}$=2.377, ΔR^2=0.048
Model 3	-0.031	-0.329	-0.308	-0.050	-0.002	-0.054	**-0.519***	-0.145	R^2=0.618, $F_{8,16}$=3.229*, ΔR^2=0.176*
MPT-R									
Model 1	-0.036	0.096	**-0.398****						R^2=0.425, $F_{3,21}$=5.183**
Model 2	**-0.047***	0.105	**-0.519****	0.175	0.019	-0.022			R^2=0.517, $F_{6,18}$=3.144*, ΔR^2=0.092
Model 3	**-0.056****	0.236	**-0.528****	0.036	0.018	0.014	**-0.533****	-0.285	R^2=0.730, $F_{8,16}$=5.415**, ΔR^2=0.213**
PPT-B									
Model 1	<-0.001	0.118	0.052						R^2=0.079, $F_{3,21}$=0.604
Model 2	-0.003	0.188	0.014	0.032	-0.041	0.048			R^2=0.147, $F_{6,18}$=0.519, ΔR^2=0.068
Model 3	<-0.001	0.155	0.028	0.046	-0.041	0.049	-0.044	-0.052	R^2=0.160, $F_{8,16}$=0.381, ΔR^2=0.003
PPT-R									
Model 1	-0.01	-0.072	0.086						R^2=0.078, $F_{3,21}$=0.593
Model 2	-0.015	0.098	-0.044	0.081	0.015	0.079			R^2=0.354, $F_{6,18}$=1.646, ΔR^2=0.279
Model 3	-0.015	0.102	-0.040	0.070	0.014	0.083	0.047	-0.052	R^2=0.364, $F_{8,16}$=1.147, ΔR^2=0.001
CPM									
Model 1	0.008	0.113	-0.146						R^2=0.108, $F_{3,21}$=0.847
Model 2	0.012	0.253	-0.193	-0.036	0.035	0.070			R^2=0.206, $F_{6,18}$=0.779, ΔR^2=0.098
Model 3	0.010	0.279	-0.224	-0.016	0.038	0.054	-0.093	0.216	R^2=0.286, $F_{8,16}$=0.802, ΔR^2=0.080

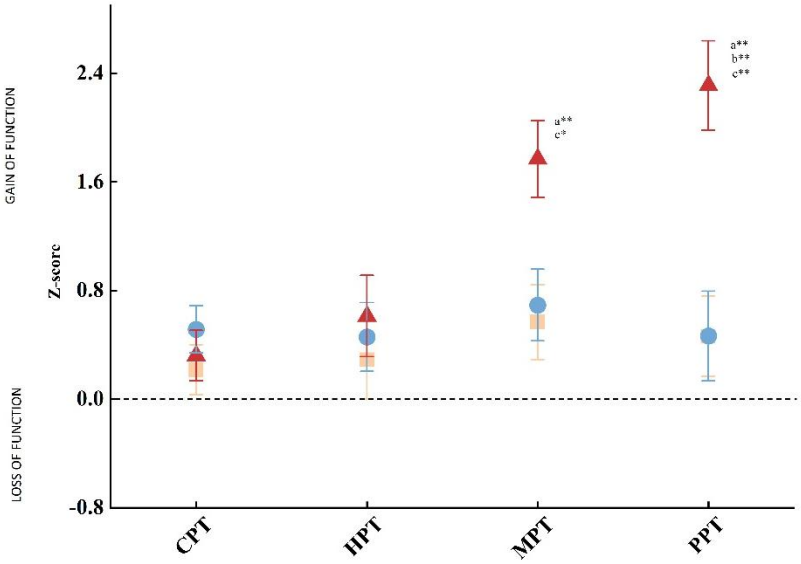
Abbreviation: CLBP+I: Individuals with concomitant non-specific chronic low back pain and insomnia; CPM: conditioned pain modulation; DASS: Depression Anxiety Stress Scale; FABQ: Fear-Avoidance Beliefs Questionnaire; ISI: Insomnia Severity Index; Insomnia+: Individuals with insomnia; MPT-B: Mechanical pain threshold at the back; MPT-R: Mechanical pain threshold at the remote site; NPRS: 11-point Numerical Pain Rating Scale; PCS: Pain Catastrophizing Scale; PSQI: Pittsburgh Sleep Quality Index; PPT-B: Pressure pain threshold at the back; PPT-R: Pressure pain threshold at the remote site; QST: Quantitative sensory testing; RMDQ: Roland Morris Disability Questionnaire.

Footnote: [a]: standardized beta; *: $p < 0.05$; **: $p < 0.01$.

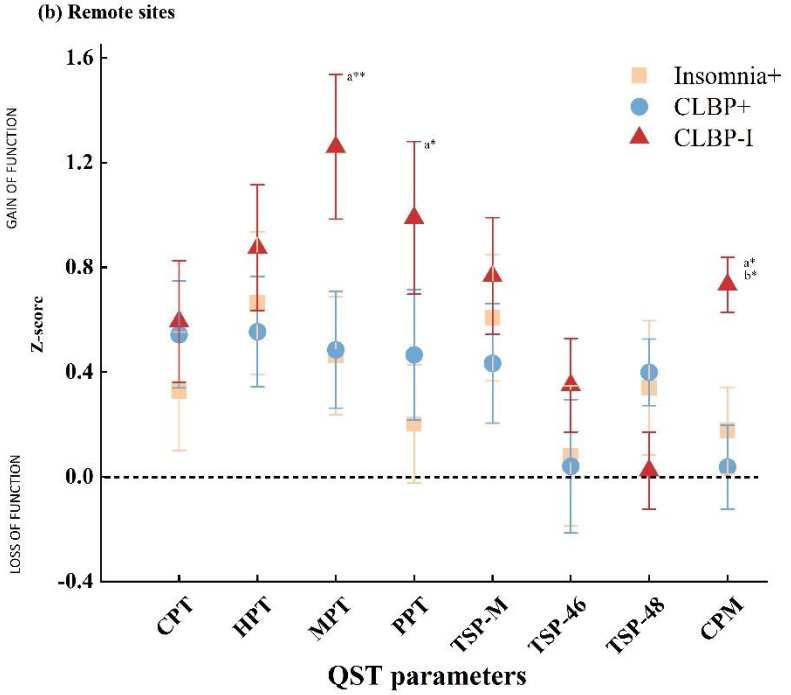
4.8 Figures

Figure 4. Z-sore QST at low back (a) and remote (b) sites

(a) Low back site



(b) Remote sites



Abbreviation: CLBP+: Individuals with non-specific chronic low back pain; CLBP+I: Individuals with non-specific chronic low back pain and insomnia; CPT: Cold pain threshold; CPM: conditioned pain modulation; HPT: Heat pain threshold; Insomnia+: Individuals with insomnia; MPT: Mechanical pain threshold; PPT: Pressure pain threshold; QST: Quantitative sensory testing; TSP-M: Temporal summation of mechanical pain; TSP-46: Temporal summation of heat pain (46°C); TSP-48: Temporal summation of heat pain (48°C).
Footnote: Values are presented as mean and standard error. Z values were standardized according to the mean

and standard deviation of the healthy controls. A positive Z-score value indicates increased sensitivity to noxious stimuli compared to healthy controls (lower thresholds, gain of function), whereas a negative value indicates decreased sensitivity (higher thresholds, loss of function). *Concerning CPM, a positive value represents decreased CPM (facilitatory response or lower efficiency), while a negative value represents increased CPM (inhibitory response or greater efficiency).* a: A significant difference between the CLBP+I group and healthy controls; b: A significant difference between the CLBP+I and CLBP groups; and c: A significant difference between the CLBP+I and Insomnia groups. *: $p < 0.05$; **: $p < 0.01$.

Chapter 5: Neural Oscillations and Brain Connectivity in Females with Chronic Low Back Pain and Comorbid Insomnia

This chapter has been published by the author of this thesis as an article in the journal "*Journal of Pain*" in July 2025 (In press).

Part of the materials in this chapter was presented orally at *The World Physiotherapy Congress 2025* on 29th-31st May 2025. Tokyo, Japan.

5.1 Abstract

Background: Sleep disturbance is a common comorbidity in individuals with chronic low back pain (CLBP), leading to greater functional impairments and poorer prognosis. Despite a strong association between CLBP and sleep, the neurophysiological mechanisms linking these two conditions remain unclear. As resting-state brain activity can reflect underlying neurophysiological states, this cross-sectional study aimed to explore the spontaneous resting brain activity associated with CLBP and insomnia.

Methods: One hundred females were enrolled and categorized into four subgroups: (1) non-specific CLBP and insomnia (CLBP+I, n = 25); (2) non-specific CLBP alone (CLBP+, n = 25); (3) insomnia alone (Insomnia+, n = 25); and (4) controls without non-specific CLBP nor insomnia (Controls, n = 25). Participants completed clinical questionnaires and underwent resting-state electroencephalography (EEG) recordings. DISCOVER-EEG was used for preprocessing and extracting physiological brain function features automatically.

Results: CLBP+I exhibited disrupted functional connectivity at the theta band across brain networks and enhanced beta band information processing compared to other groups, reflecting brain network imbalances driven by the combined effects of CLBP and insomnia. Additionally, insomnia was independently associated with aberrant functional connectivity in CLBP+I, even after accounting for pain-related and psychological factors.

Conclusion: These findings provide new insights into the neurophysiological basis of CLBP with comorbid insomnia and lay a foundation for developing biomarkers and improving treatment strategies for this complex condition.

Keywords: Chronic low back pain; Insomnia; Electroencephalography; Spectral power; Functional connectivity.

5.2 Introduction

Chronic low back pain (CLBP) is the leading cause of years lived with disability worldwide [267, 323] and is associated with greater healthcare demand and higher rates of comorbidity compared to asymptomatic individuals [268, 269]. Up to 90% of CLBP cases lack identifiable etiology and are classified as non-specific CLBP [270]. This diagnostic uncertainty has prompted researchers to explore the interactions between biological, psychological, and social factors in CLBP. Among these factors, sleep disturbance—particularly insomnia—is highly prevalent, affecting over 70% of individuals with CLBP [8]. Insomnia not only exacerbates pain perception and functional disability in these patients but also negatively impacts prognosis [11, 188]. Furthermore, sleep problems contribute to the development of low back pain in healthy individuals [185], while improving sleep quality has been shown to enhance recovery outcomes for low back pain (LBP) [38, 188]. These findings highlight the critical role of insomnia in CLBP.

Research has shown that sleep deprivation negatively affects peripheral and central sensitization in individuals with or without chronic pain [27]. Electroencephalography (EEG) studies in healthy individuals have found that sleep deprivation-induced pain sensitivity is closely related to alterations in the amplitude of painful-evoked potentials [195-197]. However, these findings are primarily based on responses to transient nociceptive stimuli and may not adequately reflect the sustained neural alterations associated with chronic pain [128]. Therefore, the current understanding of the relationship between sleep and pain is limited to the non-clinical population with external stimuli. Further research is needed to explore the neurophysiological characteristics underlying comorbid chronic pain and insomnia in clinical contexts.

Resting-state EEG offers a promising avenue for investigating intrinsic brain activity and functional network dynamics in individuals with CLBP and insomnia. Unlike task-based paradigms that rely on external stimuli, resting-state EEG captures spontaneous brain activity, which aligns more closely with the persistent symptoms of chronic pain and insomnia [32, 152]. Studies utilizing resting-state EEG have identified neural alterations in individuals with CLBP, such as thalamocortical dysrhythmia, characterized by reduced alpha activity and increased theta activity within thalamocortical circuits [158, 324]. Likewise, research in insomnia populations has revealed abnormalities in neural oscillations and synchrony, such as increased theta, beta, and gamma power [152]. Both CLBP and insomnia have also been linked to abnormal connectivity among large-scale brain networks [182, 325, 326], particularly those involved in emotional regulation, attention allocation, and cognitive control, such as the salience network (SN), default mode network (DMN), and frontoparietal network (FPN). While CLBP and insomnia independently exhibit distinct neural signatures, no studies to date have investigated neural oscillations and brain connectivity in individuals with comorbid conditions.

Considering sex-differentiated effects on pain perception [275] and the higher prevalence of chronic pain or insomnia in females [278, 279], our study aimed to identify unique neurophysiological characteristics underlying the comorbid condition in this population. We compared neural oscillations and functional connectivity across four age-matched groups of females with or without non-specific CLBP, insomnia, and concomitant conditions, to provide insights into the interaction between chronic pain and sleep disturbance. As previous findings indicate similar neural oscillatory patterns in insomnia and chronic pain [32, 152], and impaired

pain processing in individuals with comorbid conditions compared to those with either condition alone or none [12, 49], we hypothesized that the comorbidity of CLBP and insomnia would exhibit neural activity patterns more closely aligned with thalamocortical dysrhythmia and display more pronounced abnormalities in brain connectivity. Additionally, we hypothesized that insomnia would be independently associated with the observed neural alterations in individuals with comorbid conditions, even after controlling for pain-related outcomes and psychological factors.

5.3 Methods

5.3.1 Study Design and Procedures

This case-control study was approved by the Institutional Review Board of The Hong Kong Polytechnic University (HSEARS20220731001) and conducted in accordance with the Declaration of Helsinki. Data was collected in a university laboratory between September 2022 and November 2023. Potential participants underwent telephone and clinical interviews to assess eligibility. These screening procedures were conducted by a physiotherapist under the supervision of physicians specialized in sleep or pain medicine. Eligible individuals provided written informed consent and then completed a battery of questionnaires and resting-state EEG acquisition.

5.3.2 Size Estimation and Participants

The sample size was estimated using the G*Power 3.1.9.2 (2016 Version) software [327]. In the absence of prior EEG studies in the target population, the average effect size (0.35) was derived from previous findings on central sensitization in comorbid conditions [190]. To detect between-group differences across four groups with 80% power at a two-sided alpha level of 0.05, a total

sample of 96 participants was needed. One hundred Chinese female participants were enrolled through posters posted on the campus and referrals from collaborating physicians. They were categorized into four subgroups: (1) participants with non-specific CLBP and insomnia (CLBP+I, n = 25); (2) participants with non-specific CLBP alone (CLBP+, n = 25); (3) participants with insomnia alone (Insomnia+, n = 25); and (4) participants without non-specific CLBP nor insomnia (Controls, n = 25). The general inclusion criteria were females aged between 18 and 65 years. The exclusion criteria were: (1) specific pain conditions or spinal pathologies (e.g., malignancy, postsurgical or posttraumatic pain, complex regional pain syndrome, spondylarthritis, or spinal fracture); (2) other clinically diagnosed sleep disorders (e.g., sleep apnea or restless leg syndrome); (3) a history of or existing neurological, psychopathological, or physical disorders (e.g., stroke, dementia, or substance abuse); (4) suspected or confirmed pregnancy or currently nursing; (5) receiving treatments for insomnia or pain within one month before the data collection; or (6) a body mass index exceeding 30 kg/m^2 [281].

Controls should be free from acute pain or a history of chronic pain within the past 12 months [190]. They also did not have any clinically diagnosed sleep disorders, with scores on the Insomnia Severity Index (ISI) $\leq$ 10 [282] and the Pittsburgh Sleep Quality Index (PSQI) $\leq$ 5 [283]. Non-specific CLBP was defined as pain located between the 12^{th} ribs and gluteal crease without clear nociceptive-specific cause, persisting pain for more than three months and presenting pain over half the days in the past four weeks [270, 284, 285]. Participants with non-specific CLBP should have an average pain intensity $\geq$ 4 on an 11-point Numerical Pain Rating Scale (NPRS) over the last seven days [286], where 0 and 10 indicate no pain and the worst imaginable pain, respectively. Participants' insomnia status was determined by the Brief

Insomnia Questionnaire according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (i.e., difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening after sleep onset at least three nights a week for three months, along with impaired daytime functioning) [167, 287]. To account for potential menstrual cycle effects on pain perception and brain activity, data collection was scheduled outside of their menstruation periods. All participants were instructed to maintain their regular sleep patterns, adhere to their usual medication regimen, and abstain from excessive physical activity or alcohol 48 hours before data collection. No participants had used hormonal contraceptives in the month prior to enrollment.

5.3.3 Measures

Patient-Reported Outcome Measures

Participants provided their demographic information. They also filled out the NPRS [290] and Roland Morris Disability Questionnaire (RMDQ) [291] to report their pain intensity and LBP-related disability, respectively. ISI and PSQI were used to evaluate insomnia severity and sleep quality, while Pain Catastrophizing Scale (PCS) [293] and Depression Anxiety Stress Scale (DASS) [294] were employed to assess participants' pain catastrophizing and psychological well-being, respectively. All questionnaires employed in this study have been cross-culturally adapted into Chinese and demonstrated acceptable reliability and validity [295-297, 299, 300].

EEG Data Acquisition

Resting-state EEG was recorded using the Neuroscan EEG system with a 64-channel SynAmpsRT amplifier and Ag–AgCl electrodes (ElectroCap, Ohio, United States) following the

International 10/20 system. Two additional electrodes were used to monitor ocular movement and eye blinks. The impedance for all electrodes was maintained below 10 kΩ. The ground and common reference electrodes were located at the Ground between FPz and Fz and Reference between Cz and CPz. The recording sampling frequency was 1,000 Hz using online band-pass filters between 0.01 and 250 Hz. Participants were instructed to remove all electronic and metallic objects and stay in the temperature-controlled magnetically shielded room to minimize external noise and artifacts. They were seated comfortably and instructed to maintain an upright posture, stay awake without thinking anything, and relax their bodies and jaw muscles. To minimize muscle artifacts and ensure consistent data over time, five-minute resting-state EEG recordings were acquired with eyes closed [328].

5.3.4 EEG Preprocessing and Analysis

DISCOVER-EEG, a comprehensive EEG pipeline designed for resting-state analysis, was used to automate preprocessing and extract physiologically meaningful brain function features [329]. This pipeline promotes reproducible research on brain function and has been widely adopted in chronic pain research [330, 331]. EEG data were imported into MATLAB version R2020a (The Mathworks Inc, Natick, MA, USA) and processed using EEGLAB [332], FieldTrip [333], and Brain Connectivity [334] toolboxes. The raw data were downsampled from 1,000 Hz to 250 Hz. The initial and last 10 seconds were excluded to avoid non-stationary signals and transient effects. Seven preprocessing steps preceded feature extraction: (1) line noise removal with a 50 Hz notch-reject filter; (2) high pass filtering (0.5 Hz) and bad channel rejection; (3) re-referenced to the average of all electrodes; (4) independent component analysis (ICA) with automatic rejection by ICLable toolbox (components labeled as “Muscle” or “Eye” exceeding 80%) [332];

(5) interpolation of removal channels using a spherical spline method; (6) bad time segment removal with the Artifact Subspace Reconstruction method; and (7) data segmentation into 2-second epochs with a 50% overlap [329]. An experienced EEG technologist visually inspected the preprocessed data to identify and remove bad segments. No significant between-group differences were observed in bad segments during preprocessing (**Figure S1**).

Power spectra were analyzed using Slepian multitapers with ±1 Hz frequency smoothing [329]. The frequency bands of interest included theta (4.0-8.0 Hz), alpha (8.0-13.0 Hz), beta (13.1-30.0 Hz), and gamma (30.1-80.0Hz) [335]. Global absolute power was determined by averaging the power within each frequency band across all epochs and electrodes. To minimize individual variability, relative power was calculated by dividing the absolute power in a specific frequency band by the total power of all frequency bands [336]. Additionally, the peak alpha frequency was determined by the peak maximum and the center of gravity within the alpha band [329].

Source reconstruction was estimated using an atlas-based beamforming approach to mitigate volume conduction issues [329]. The band-pass filtered data for each frequency were projected into the spatial distribution using an array-gain Linear Constrained Minimum Variance beamformer [337]. The lead field was constructed by a realistic head model based on the Montreal Neurologic Institute (MNI) template. The source model comprised 100 parcellations from the Schaefer atlas [338]. Spatial filters were created based on the covariance matrices of the band-passed filtered data and the lead field matrix. The regularization parameter was set to 5% of the covariance matrix, and the dipole orientation was fixed in the direction of the maximum variance [329]. Functional connectivity analysis employed both amplitude-based and phase-

based measures, capturing distinct and complementary communication processes within the brain [339, 340]. The amplitude-based measure was determined by orthogonalized amplitude envelope correlation (AEC), whereas the phase-based measure was computed as the debiased weighted phase lag index (dwPLI) [329]. To mitigate multiple comparison issues, we focused on three networks of interest based on prior studies in chronic pain or insomnia [182, 325]: the salience network (SN), default mode network (DMN), and frontoparietal network (FPN). Connectivity matrices were averaged across frequency bands to produce a single connectivity matrix for each band [329]. Connectivity strength was calculated as the average connectivity of one network to all other networks at each frequency band [341].

Brain network characteristics were further analyzed by thresholding the 10% of the strongest connections and binarized connectivity matrices for AEC and dwPLI, respectively [342]. By applying the graph–theory methods, we defined nodes as parcellations and edges as links between pairs of parcellations. Local graph measures were characterized as the clustering coefficient (fraction of triangles around an individual node) and degree (the number of connections of a node) within the networks of interest [329, 334]. Simultaneously, global graph measures were summarized as the global clustering coefficient (the averaging clustering coefficient of all nodes, indicating functional segregation in the network), global efficiency (the average inverse shortest path length, indicating functional integration in the network), and small-world networks (the ratio between the global clustering coefficient and global efficiency, indicating the balance of functional segregation and integration) [329, 334].

5.3.5 Statistical Analysis

Statistical analyses were performed using R 4.0.4 (R Core Team, Vienna, Austria) at a two-tailed significance level set at $\alpha = 0.05$. One-way analysis of variance (ANOVA) and the chi-square test were conducted to explore between-group differences in demographic and clinical characteristics. Group differences in EEG measures were assessed using one-way analysis of covariance (ANCOVA), controlling for the potential effects of pain catastrophizing and emotional distress. Post-hoc analyses were corrected for multiple comparisons using the Bonferroni method. For multiple comparisons within a specific EEG measure across the four frequency bands, *p*-values were adjusted using the Holm–Bonferroni method [343].

Hierarchical linear regression models were conducted within the CLBP+I group to examine the independent associations between pain-related outcomes (pain duration, NPRS, and RMDQ), psychological factors (PCS and DASS), and insomnia (ISI and PSQI) with EEG measures showing significant between-group differences. The dependent variables for EEG measures included functional connectivity at the theta band, local cluster coefficient at the beta band, and small-world networks at the beta band. Pain-related outcomes were entered as independent variables in the first block (Model 1), psychological factors in the second block (Model 2), and insomnia in the third block (Model 3). The final model assessed whether insomnia could independently predict neural alterations after controlling for other factors [314]. To ensure normality, a square root transformation was applied to the independent variables prior to analysis. Multicollinearity was evaluated using the variance inflation factor (VIF), retaining only variables with a VIF value of < 5 [315].

5.4 Results

5.4.1 Demographic and Clinical Characteristics

The demographic and clinical characteristics of the included participants are outlined in **Table 6**. No significant between-group differences were observed in terms of age ($F = 0.06$, $p = 0.944$), education levels ($\chi^2 = 3.62$, $p = 0.935$), working status ($\chi^2 = 5.12$, $p = 0.529$), and medication use ($\chi^2 = 7.61$, $p = 0.055$). The CLBP+I and Insomnia+ groups exhibited significantly more severe insomnia symptoms as measured by ISI ($p_{corrected} < 0.001$), poorer sleep quality as measured by PSQI ($p_{corrected} < 0.001$), higher pain catastrophizing as measured by PCS ($p_{corrected} < 0.001$), and greater emotional distress as measured by DASS ($p_{corrected} < 0.001$) than both the CLBP+ and Control groups, whereas there were no significant differences in pain duration ($t = 1.72$, $p = 0.094$) or pain intensity ($t = 1.95$, $p = 0.058$) between the CLBP+I and CLBP+ groups.

5.4.2 Power Spectral Analysis

One-way ANCOVA revealed no significant differences in the global absolute power across the four groups (**Figure 5A**). A significant between-group difference was initially observed in the global relative theta band ($F = 2.04$, $p = 0.014$) (**Figure 5B**), but this difference became non-significant after applying the Holm–Bonferroni correction for multiple comparisons across the four frequency bands ($p_{corrected} = 0.056$). Likewise, no significant between-group differences were found in peak alpha frequency measured by the local maximum ($F = 0.69$, $p = 0.633$) or the center of gravity ($F = 0.86$, $p = 0.513$) **(Figure 5C)**.

5.4.3 Functional Connectivity Strength

One-way ANCOVA indicated significant between-group differences in amplitude-based (AEC)

theta connectivity ($F > 3.13$, $p < 0.012$, $p_{corrected} < 0.048$) (**Figure 6**). Post-hoc analyses with Bonferroni correction showed increased amplitude-based theta connectivity in CLBP+I compared to CLBP+, Insomnia+, or Controls across multiple networks: between the SN and DMN ($p_{corrected} < 0.022$), between the SN and FPN ($p_{corrected} < 0.019$), and between the DMN and FPN ($p_{corrected} < 0.030$). No significant differences were observed across other frequency bands or among CLBP+, Insomnia+, or Controls (**Table S3.1 and Table S3.2**).

5.4.4 Graph-theory Network Analyses

Details of brain network measures are presented in **Tables S3.3 and S3.4**. One-way ANCOVA found significant between-group differences in the local clustering coefficient of amplitude-based connectivity within the FPN at the alpha band ($F = 4.10$, $p = 0.002$, $p_{corrected} = 0.006$) and the DMN at the beta band ($F = 3.71$, $p = 0.004$, $p_{corrected} = 0.016$). Post-hoc analyses with Bonferroni correction only found a significantly higher local clustering coefficient of the beta band in CLBP+I compared to Controls ($p_{corrected} = 0.015$). Regarding global graph measures (**Figure 7**), a significant between-group difference was observed in amplitude-based connectivity for small-world networks at the beta band ($F = 3.23$, $p = 0.010$, $p_{corrected} = 0.040$), with increased values in CLBP+I compared to Controls ($p_{corrected} = 0.017$). No significant differences were identified in other comparative analyses.

5.4.5 Associations between Brain Network Measures and Clinical Variables within CLBP+I

Hierarchical linear regression analyses examining associations between brain network measures and clinical variables are presented in **Table 7**. Variance inflation factor analysis indicated no significant multicollinearity among clinical variables (1.215 to 1.996). For functional

connectivity between the SN and DMN at the theta band, Models 1 and 2 collectively explained 6.2% of the variance ($F_{5,19}=0.250$, $p=0.700$). None of the pain-related outcomes or psychological factors were significantly associated with brain connectivity. However, the final model revealed that insomnia emerged as a significant predictor, explaining an additional 38.4% of the variance ($p=0.011$). Greater insomnia severity was significantly associated with increased functional connectivity between the SN and DMN ($\beta=0.028$, $p=0.0261$).

A similar pattern was observed for functional connectivity between the SN and FPN, as well as between the DMN and FPN. Models 1 and 2 together explained 2.4% ($F_{5,19}=0.095$, $p=0.960$) and 4.8% of the variance ($F_{5,19}=0.193$, $p=0.903$), respectively. The final model showed insomnia as a significant predictor, accounting for an additional 46.5% ($p=0.004$) and 36.0% ($p=0.0018$) of the variance, respectively. Higher insomnia severity was linked to increased functional connectivity between the SN and FPN at the theta band ($\beta=0.035$, $p=0.009$) and between the DMN and FPN at the theta band ($\beta=0.031$, $p=0.0259$).

For local clustering coefficient and small-world networks at the beta band, the final model explained 25.2% ($F_{7,17}=0.818$, $p=0.585$) and 14.9% ($F_{7,17}=0.425$, $p=0.873$) of the variance, respectively. None of the clinical variables were significantly associated with these outcomes.

5.5 Discussion

This study is the first to investigate the distinct neural oscillatory and brain connectivity profiles in females with or without CLBP or insomnia. Although global power analyses revealed no significant between-group differences, the comorbidity of chronic pain and insomnia was

associated with disrupted brain network connectivity. Specifically, the CLBP+I exhibited increased functional connectivity at the theta band, elevated local clustering coefficients at the beta band, and higher small-world networks at the beta band compared to CLBP+, Insomnia+, or Controls. Furthermore, insomnia was independently associated with altered functional connectivity in CLBP+I, even after controlling for pain-related and psychological factors. Our findings highlight the importance of integrated brain activity across networks, rather than isolated neural oscillations, in distinguishing comorbid states. These neurophysiological characteristics offer promise in facilitating patient phenotyping, enhancing our understanding of the neural basis of the comorbid states, and potentially guiding prognosis or personalized treatment protocols based on neurophysiological biomarkers for individuals with this condition.

Although numerous studies have examined the resting-state EEG findings in individuals with chronic pain or insomnia [32, 152, 344], there is considerable heterogeneity in power spectral analysis, often overlooking common comorbidities. Subgrouping individuals based on their unique sleep or pain profiles may provide valuable insights into the potential neurophysiological underpinnings within each homogeneous group. While our global power analyses did not detect significant between-group differences, we observed a trend of elevated theta power and reduced alpha power in CLBP+I compared to CLBP+, Insomnia+, or Controls. These trends are consistent with the thalamocortical dysrhythmia model, which proposes increased theta and decreased alpha power bands as a potential mechanism underlying chronic pain [158, 324]. The non-significant differences might be attributed to the lower sensitivity of traditional power spectral measures. A recent EEG study found that novel brain state features outperformed traditional power spectrum analysis in generalizing state classification across individuals [345].

This is further supported by findings from *Dinh et al.*, who found no group differences in global oscillatory power among chronic pain patients but identified significant alterations in brain network organization [336]. Future large-scale, international neuroimaging initiatives (e.g., ENGIMA consortium [346]) are warranted to validate our power analyses by subgrouping individuals with chronic pain based on their sleep status. Such efforts could elucidate the neurophysiological signatures of comorbid conditions and inform targeted interventions.

We observed enhanced amplitude-based connectivity at the theta band among the SN, DMN, and FPN in CLBP+I compared to the other groups, with no significant differences among the other three groups. These abnormalities in functional connectivity may be linked to abnormal pain processing [86, 87, 123] and/or hyperarousal in insomnia [30, 182]. For example, the dynamic pain connectome model highlights aberrant connectivity between the SN, DMN, and antinociceptive systems in chronic pain during the resting state [86, 87]. This model is further supported by *Bosma et al.*, who reported abnormal connectivity between the SN and DMN in patients with multiple sclerosis-related pain compared to healthy controls [347]. Additionally, a systematic review found that individuals with insomnia exhibited increased functional connectivity within the SN, DMN, and FPN, contributing to a state of hyperarousal and emotional dysregulation [182]. Given that theta band is mainly related to the down-regulation of pain inhibition [153], sleepiness [348], and cognitive processing [349], our findings supported the hypothesis that, despite feelings of sleepiness, individuals with comorbid states experience augmented cognitive or attentional processing related to ongoing pain and sleep difficulties. This may perpetuate a sustained hyperarousal state, further exacerbating their clinical condition.

Surprisingly, CLBP+I exhibited increased local clustering coefficient within the DMN and greater small-world networks in the beta band compared to Controls, indicating that comorbid states are associated with better segregation and integration of networks involved in beta-related information processing [334]. A plausible explanation for this phenomenon is maladaptive network hyper-segregation or hyper-integration in response to cortical disruptions associated with chronic pain and insomnia. Cortical neural activity dynamically adapts to variations in cognitive demands and behavioral contexts to support appropriate adaptive actions [350, 351]. However, prolonged pain and insomnia may induce systematic inflammation, heightened sensory sensitivity, decreased physical activity, maladaptive beliefs, and emotional distress [15, 17]. This multifaceted input may lead to pathological over-synchronization or dysfunctional network integration. This interpretation aligns with the proposed inverted U-shaped relationship between neural activation and mental functioning, in which both hypoactivation and hyperactivation can lead to suboptimal functioning [352]. The paucity of research using graph-theory analysis for resting-state EEG in chronic pain or insomnia prevents comparison to existing evidence and conclusive interpretations. Future studies are needed to validate our findings using advanced analytical methods.

Our hierarchical regression analyses in CLBP+I revealed that insomnia significantly increased the explained variance in functional connectivity at the theta band, independent of pain-related and psychological factors. These findings align with our recent quantitative sensory testing results, which identified insomnia as an independent predictor of heightened pain sensitivity in CLBP+I [12]. Moreover, systematic reviews have shown that sleep loss can disrupt functional connectivity and brain network organizations, although specific patterns of change vary across

studies [257, 353]. *Letzen et al.* reported that sleep deprivation enhanced functional connectivity between the DMN and FPN in healthy individuals, a change positively correlated with increased pain sensitivity [191]. These results highlight the adverse effects of insomnia on brain networks, potentially exacerbating pain sensitivity, impairing functional capacity, and worsening clinical outcomes in individuals with chronic pain. Therefore, we recommend that healthcare professionals incorporate sleep screening into routine assessments for patients with chronic pain. Early identification and targeted interventions for CLBP+I cases could mitigate the adverse effects of sleep disturbances on pain and optimize treatment outcomes [12, 46].

Several limitations should be acknowledged when interpreting our results. First, all analyses were based on cross-sectional data, which precludes the examination of causal relationships among CLBP, insomnia, and brain activity. Further longitudinal studies should determine the diagnostic and predictive value of our neurophysiological findings in CLBP+I. Second, our source reconstruction used the MNI template, which had an intrinsic limit in spatial resolution and might not fully reflect individual head shape variability. Future studies should employ individual electrode positions to enhance the precision of source reconstruction. Third, our study controlled for potential confounders, such as age, sex, and pain type, which may limit generalizability to older adults, males, or other musculoskeletal pain conditions. Further research is warranted to investigate potential age- and sex-specific effects on brain activity across various comorbid pain conditions. Finally, despite the exclusion of participants with clinically diagnosed depression or anxiety disorders, CLBP+I and Insomnia+ showed significantly higher depression and anxiety levels. The potential influence of these symptoms on the observed group differences cannot be completely discarded.

5.6 Conclusions

This is the first study to characterize oscillatory brain activity and functional connectivity across four well-defined groups. We found that females with CLBP and comorbid insomnia exhibited disrupted functional connectivity at the theta band and increased beta band information processing compared to CLBP+, Insomnia+, or Controls. These distinct neurophysiological signatures may offer promising biomarker candidates for diagnosing, monitoring, and predicting comorbid conditions. They also hold the potential for guiding personalized neuromodulation therapies, such as non-invasive brain stimulation or neurofeedback, to improve clinical outcomes in complex cases.

5.7 Tables

Table 6. Demographic and clinical characteristics

	Healthy control (n=25)	Insomnia+ (n=25)	CLBP+ (n=25)	CLBP+I (n=25)	*p* value
Age, mean (SD)	34.9 (12.2)	34.3 (11.2)	33.5 (11.9)	34.3 (11.9)	0.980
Body mass index, mean (SD)	20.8 (2.8)	19.6 (2.3)	21.6 (2.5)	21.4 (2.8)	**0.036**
Education (≥ bachelor), %	92.0	92.0	92.0	88.0	0.935
Working status, %					0.529
Employed	96.0	92.0	88.0	96.0	
Unemployed	0.0	4.0	0.0	0.0	
Retired	4.0	4.0	12.0	4.0	
Medication use, %					0.055
None	100.0	80.0	96.0	92.0	
Nonsteroidal anti-inflammatory drug	0.0	0.0	4.0	4.0	
Melatonin or Zopiclone	0.0	16.0	0.0	4.0	
Medications for other health conditions	0.0	4.0	0.0	0.0	
Duration of pain, mean (SD)	-	-	23.5 (24.1)	39.5 (39.8)	0.094
Average pain intensity during last week, mean (SD)	-	-	4.2 (1.1)	5.0 (1.5)	0.058
Roland Morris Disability Questionnaire, mean (SD)	-	-	6.7 (2.8)	8.6 (3.2)	**0.026**
Pain Catastrophizing Scale, mean (SD)	14.8 (9.9)	21.6 (12.5)	13.7 (8.4)	23.3 (6.6)	**0.001**
Insomnia Severity Index, mean (SD)	2.3 (2.1)	16.4 (3.7)	4.3 (2.9)	15.0 (3.2)	**<0.001**
Pittsburgh Sleep Quality Index, mean (SD)	2.8 (1.4)	11.5 (2.0)	3.7 (1.1)	11.2 (2.2)	**<0.001**
Depression Anxiety Stress Scale, mean (SD)	5.5 (5.7)	20.0 (13.2)	6.12 (4.7)	17.7 (8.4)	**<0.001**

Values are presented as mean and standard deviations or percentage. P value was calculated by the one-way analysis of variance or student t-test for continuous variables and by the chi-square test for categorical variables. Post-hoc analyses were performed with the Bonferroni correction. The p-value in bold indicates a statistically significant difference between groups ($p < 0.05$). Higher total scores of included questionnaires indicated poor functioning. CLBP+: Individuals with non-specific chronic low back pain; CLBP+I: Individuals with concomitant non-specific chronic low back pain and insomnia; Insomnia+: Individuals with insomnia; SD: standard deviations.

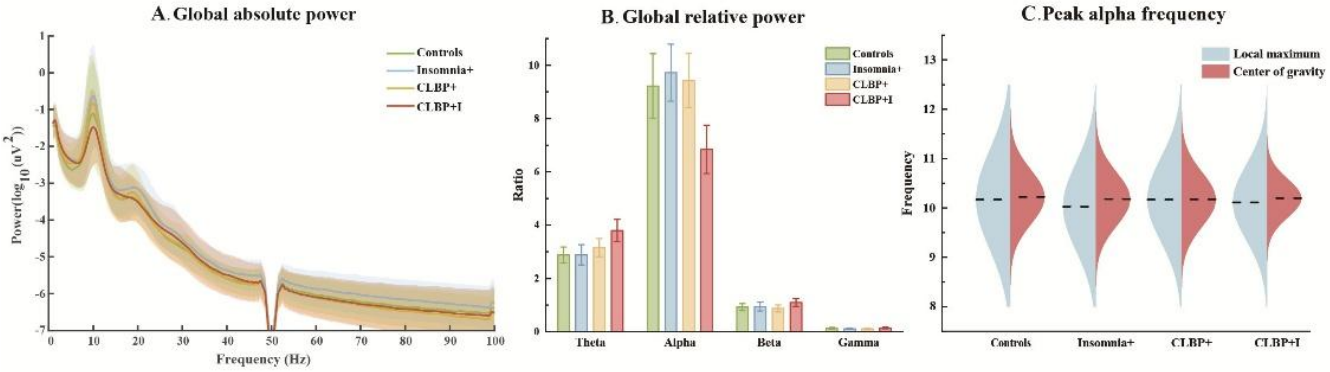
Table 7. Hierarchical regression analysis to examine clinical variables and brain measures within CLBP+I (n=25)

	Pain-related outcomes (Beta)			Psychological factors (Beta)		Insomnia (Beta)		Statistics
	Pain duration	NPRS	RMDQ	PCS	DASS	ISI	PSQI	
FC between the SN and DMN at the theta band								
Model 1	0.001	< 0.001	0.003					R^2=0.038, $F_{3,21}$=0.278
Model 2	0.004	< -0.001	0.003	0.002	< -0.001			R^2=0.062, $F_{5,19}$=0.250, ΔR^2=0.024
Model 3	-0.013	0.001	0.010	0.011	< -0.001	0.028*	0.023	R^2=0.446, $F_{7,17}$=1.954, ΔR^2=0.384*
FC between the SN and FPN at the theta band								
Model 1	0.009	0.001	-0.002					R^2=0.021, $F_{3,21}$=0.924
Model 2	0.007	< 0.001	-0.002	0.001	< -0.001			R^2=0.024, $F_{5,19}$=0.095, ΔR^2=0.002
Model 3	-0.012	0.002	0.005	0.010	< -0.001	0.035**	0.024	R^2=0.489, $F_{7,17}$=2.329, ΔR^2=0.465**
FC between the DMN and FPN at the theta band								
Model 1	0.007	0.001	0.001					R^2=0.041, $F_{3,21}$=0.300
Model 2	0.004	< 0.001	0.003	< -0.001	< 0.001			R^2=0.048, $F_{5,19}$=0.193, ΔR^2=0.007
Model 3	-0.013	0.002	0.009	0.009	< -0.001	0.031*	0.021	R^2=0.160, $F_{7,17}$=1.678, ΔR^2=0.360*
Local cluster coefficient within the DMN at the beta band								
Model 1	0.026	-0.001	-0.034					R^2=0.047, $F_{3,21}$=0.346
Model 2	0.082	0.001	-0.046	-0.017	0.004			R^2=0.198, $F_{5,19}$=0.940, ΔR^2=0.151
Model 3	0.103	-0.001	-0.052	-0.030	0.004	0.052	0.010	R^2=0.252, $F_{7,17}$=0.818, ΔR^2=0.054
Small-world networks at the beta band								
Model 1	0.149	0.038	-0.241					R^2=0.042, $F_{3,21}$=0.309
Model 2	0.549	0.052	-0.281	-0.196	0.030			R^2=0.133, $F_{5,19}$=0.584, ΔR^2=0.091
Model 3	0.440	0.060	-0.222	-0.017	0.032	0.067	0.304	R^2=0.149, $F_{7,17}$=0.425, ΔR^2=0.016

Abbreviation: CLBP+I: Individuals with concomitant non-specific chronic low back pain and insomnia; DASS: Depression Anxiety Stress Scale; DMN: Default Mode Network; FC: Functional Connectivity; FPN: Frontoparietal Network; ISI: Insomnia Severity Index; Insomnia+: Individuals with insomnia; NPRS: 11-point Numerical Pain Rating Scale; PCS: Pain Catastrophizing Scale; PSQI: Pittsburgh Sleep Quality Index; RMDQ: Roland Morris Disability Questionnaire.
Footnote: *: $p < 0.05$; **: $p < 0.01$.

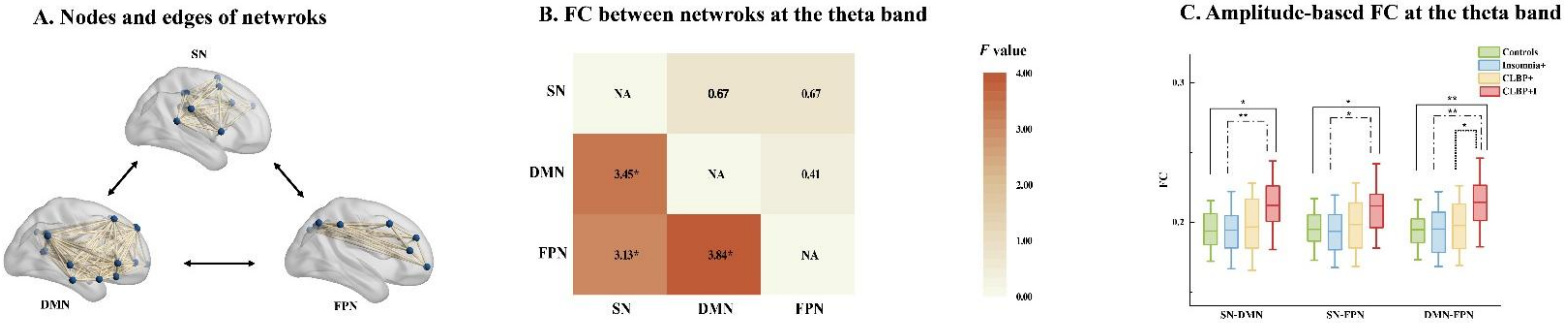
5.8 Figures

Figure 5. Global power analysis and peak alpha frequency



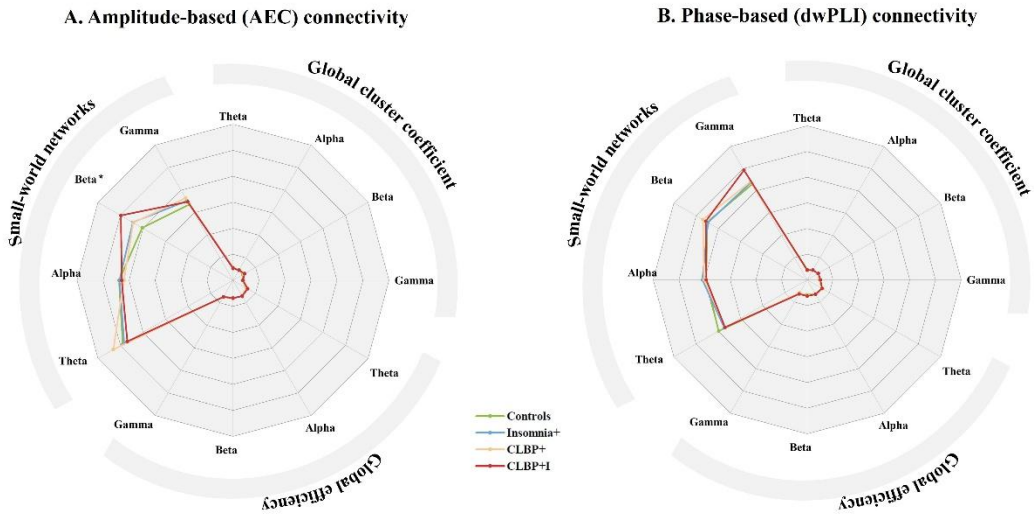
(**A)** Global absolute power spectra. (**B)** Global relative power spectra. **(C)** The violin plot of peak alpha frequency. CLBP+: Individuals with non-specific chronic low back pain; CLBP+I: Individuals with concomitant non-specific chronic low back pain and insomnia; Controls: Individuals without non-specific chronic low back pain nor insomnia; Insomnia+: Individuals with insomnia.

Figure 6. Functional connectivity strength across three networks at the theta band



(**A**) Node and edge structures across three networks. (**B**) The heat plot illustrates *F* values representing connectivity between-group differences. The lower-left section displays amplitude-based connectivity results, while the upper-right section presents phase-based connectivity findings. Bold *F*-values indicate statistically significant differences among the four groups. (**C**) Amplitude-based functional connectivity at the theta band. Significance levels with Bonferroni corrections are denoted as * ($p < 0.05$) and ** ($p < 0.01$). CLBP+: Individuals with non-specific chronic low back pain; CLBP+I: Individuals with concomitant non-specific chronic low back pain and insomnia; Controls: Individuals without non-specific chronic low back pain nor insomnia; DMN: Default mode network; FC: functional connectivity; FPN: Frontoparietal network; SN: Salience network; Insomnia+: Individuals with insomnia.

Figure 7. Global graph theory-based measures of functional connectivity



Radar plots illustrated amplitude-based **(A)** and phase-based **(B)** connectivity of three global graph measures across four frequency bands. Significance levels with Bonferroni corrections are denoted as * ($p < 0.05$). AEC: Amplitude envelope correlation; CLBP+: Individuals with non-specific chronic low back pain; CLBP+I: Individuals with concomitant non-specific chronic low back pain and insomnia; Controls: Individuals without non-specific chronic low back pain nor insomnia; dwPLI: Debiased weighted phase lag index; Insomnia+: Individuals with insomnia.

Chapter 6: Are Changes in Sleep Quality/Quantity or Baseline Sleep Parameters Related to Changes in Clinical Outcomes in Individuals with Nonspecific Chronic Low Back Pain? A Systematic Review

This chapter has been published by the author of this thesis as an article in the journal "*The Clinical Journal of Pain*" in April 2022.

Part of the materials in this chapter was presented orally at *The 17th International Forum for Back and Neck Pain Research in Primary Care* on 11th-13th November 2021. Melbourne, Australia.

Part of the materials in this chapter was presented as a poster at *The 48th International Society for the Study of the Lumbar Spine Annual Meeting* on 9th-13th May 2022. Boston, MA, USA.

Are Changes in Sleep Quality/Quantity or Baseline Sleep Parameters Related to Changes in Clinical Outcomes in Patients With Nonspecific Chronic Low Back Pain?

A Systematic Review

Jeremy R. Chang, PT, MSc, Xiaoyue Wang, PT, MSc,* Guohui Lin, PT, MSc,* Dino Samartzis, MSc, DSc,†‡§ Sabina M. Pinto, PT,* and Arnold Y.L. Wong, PT, MPhil, PhD**

Objectives: Sleep disturbance is prevalent among patients with chronic low back pain (CLBP). This systematic review aimed to summarize the evidence regarding the: (1) temporal relations between changes in sleep quality/quantity and the corresponding changes in pain and/or disability; and (2) role of baseline sleep quality/quantity in predicting future pain and/or disability in patients with CLBP.

Methods: Four databases were searched from their inception to February 2021. Two reviewers independently screened the abstract and full text, extracted data, assessed the methodological quality of the included studies, and evaluated the quality of evidence of the findings using the Grading of Recommendations Assessment Development and Evaluation (GRADE).

Results: Of 1995 identified references, 6 articles involving 1641 participants with CLBP were included. Moderate-quality evidence substantiated that improvements in self-reported sleep quality and total sleep time were significantly correlated with the corresponding LBP reduction. Low-quality evidence showed that self-reported improvements in sleep quality were related to the corresponding improvements in CLBP-related disability. There was conflicting evidence regarding the relation between baseline sleep quality/quantity and future pain/disability in patients with CLBP.

Discussion: This is the first systematic review to accentuate that improved self-reported sleep quality/quantity may be associated with improved pain/disability, although it remains unclear whether baseline sleep quality/quantity is a prognostic factor for CLBP. These findings highlight the importance of understanding the mechanisms underlying the relation between sleep and CLBP, which may inform the necessity of assessing or treating sleep disturbance in people with CLBP.

Key Words: chronic low back pain, sleep disturbance, temporal changes, prognostic factor, systematic review

(*Clin J Pain* 2022;38:292–307)

Low back pain (LBP) is a common musculoskeletal disease across the lifespan,[1–3] and the major cause of years lived with disability worldwide.[4] Although LBP is prevalent, ~90% of LBP cases are diagnosed with nonspecific LBP because no specific pathology is identified.[1,5] While most patients with LBP recover spontaneously,[1] up to 10% of LBP cases develop chronic LBP (CLBP) that last for at least 3 months.[2,3] Patients with CLBP usually have more comorbidity and impose greater economic burdens to the society than those without CLBP.[6]

While multiple factors may affect the development, maintenance, and recurrence of LBP (eg, females, older age, occupations, anxiety, depression, scoliosis, facet degeneration, Modic changes, paraspinal muscle dysfunction, and neuroinflammation),[7–13] some studies have suggested that sleep disturbance is related to the duration or intensity of LBP in patients with CLBP.[14–17] Notably, patients with higher CLBP intensity showed significantly poorer self-reported sleep quality.[18–21] Studies also found that over 55% of patients with CLBP experienced sleep disturbance,[14,18,19,22] which might manifest as insufficient sleep, frequent awakening, a long sleep latency, difficulty in initiating or maintaining sleep, and/or waking up too early.[23,24] Although speculative, poor sleep may upregulate neuroinflammatory cytokines, which are thought to be related to the pathogenesis of CLBP and aggravation of pain sensitization.[11,25–27]

Given the high prevalence of sleep disturbance in patients with CLBP, studies have evaluated the relation between subjective as well as objective sleep quality/quantity and pain/disability in patients with CLBP.[28,29] Research also showed that sleep interventions could improve various sleep parameters as measured by the Pittsburgh Sleep Quality Index (PSQI) or self-rated total sleep time (TST), pain intensity, and physical function among patients with specific or nonspecific CLBP.[30–33] For example, the addition of sleeping medication (Eszopiclone) to the pharmacologic pain regimen (Naproxen) significantly improved TST as reported in self-rated sleep diaries and pain intensity in patients with nonspecific CLBP.[32] Heapy et al[33] reported that using cognitive-behavioral therapy as a sleep intervention significantly

Received for publication May 30, 2021; revised September 13, 2021; accepted November 4, 2021.

From the *Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong SAR, China; †Department of Orthopedic Surgery; §Rush International Spine Research and Innovation Initiative, Rush University Medical Center; and ‡Rush University Graduate College, Chicago, IL.

This work was supported by the Early Career Scheme (251018/17M). The authors declare no conflict of interest.

Reprints: Arnold Y.L. Wong, PT, MPhil, PhD, Department of Rehabilitation Sciences, Hong Kong Polytechnic University, Hung Hom, Hong Kong, SAR, China (e-mail: arnold.wong@).

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.clinicalpain.com.

DOI: 10.1097/AJP.0000000000001008

Access to the article:

https://journals.lww.com/clinicalpain/abstract/2022/04000/are_changes_in_sleep_quality_quantity_or_baseline.8.aspx

6.1 Abstract

Background: Sleep disturbance is prevalent among individuals with chronic low back pain (CLBP). This systematic review aimed to summarize the evidence regarding the: (1) temporal relations between changes in sleep quality/quantity and the corresponding changes in pain and/or disability; and (2) role of baseline sleep quality/quantity in predicting future pain and/or disability in individuals with CLBP.

Methods: Medline, Embase, PsycINFO, and CINAHL were searched from their inception to February 2021. Two reviewers independently screened the abstract and full text, extracted data, assessed the methodological quality of the included studies, and evaluated the quality of evidence of the findings using the Grading of Recommendations Assessment Development and Evaluation (GRADE).

Results: Of 1,995 identified references, six articles involving 1,641 participants with CLBP were included. Moderate-quality evidence substantiated that improvements in self-reported sleep quality and total sleep time were significantly correlated with the corresponding pain reduction individuals with CLBP. Low-quality evidence showed that self-reported improvements in sleep quality were related to the corresponding improvements in CLBP-related disability. There was conflicting evidence regarding the relation between baseline sleep quality/quantity and future pain/disability in individuals with CLBP.

Conclusion: This is the first systematic review to accentuate that improved self-reported sleep quality/quantity may be associated with improved pain/disability, although it remains unclear whether baseline sleep quality/quantity is a prognostic factor for CLBP. These findings highlight the importance of understanding the mechanisms underlying the relationship between sleep and

CLBP, which may inform the necessity of assessing or treating sleep disturbance in individuals with CLBP.

Keywords: chronic low back pain; sleep disturbance; temporal changes; prognostic factor; systematic review.

6.2 Introduction

Low back pain (LBP) is a common musculoskeletal disease across the lifespan [269, 271, 354], and the major cause of years lived with disability worldwide [355]. Although LBP is prevalent, approximately 90% of LBP cases are diagnosed with non-specific LBP because no specific pathology is identified [270, 271]. While most individuals with LBP recover spontaneously[271], up to 10% of LBP cases develop chronic LBP (CLBP) that last for at least three months [269, 354]. Individuals with CLBP usually have more comorbidity and impose more significant economic burdens on society than those without CLBP [356].

While multiple factors may affect the development, maintenance, or recurrence of LBP (e.g., females, older age, occupations, anxiety, depression, scoliosis, facet degeneration, Modic changes, paraspinal muscle dysfunction, and neuroinflammation, etc.[357-363]), some studies have suggested that sleep disturbance is related to the duration or intensity of LBP in individuals with CLBP [364-367]. Notably, individuals with higher CLBP intensity showed significantly poorer self-reported sleep quality [368-371]. Studies also found that over 70% of individuals with CLBP experienced sleep disturbance [8, 272], which might manifest as insufficient sleep, frequent awakening, a long sleep latency, difficulty in initiating or maintaining sleep, and/or waking up too early [168, 372]. Although speculative, poor sleep may upregulate

neuroinflammatory cytokines, which are thought to be related to the pathogenesis of CLBP and aggravation of pain sensitization [358, 373-375].

Given the high prevalence of sleep disturbance in individuals with CLBP, studies have evaluated the relation between subjective as well as objective sleep quality/quantity and pain/disability in individuals with CLBP [376, 377]. Research also showed that sleep interventions could improve various sleep parameters measured by the Pittsburgh Sleep Quality Index (PSQI) or self-rated total sleep time, pain intensity, and physical function among individuals with specific or non-specific CLBP [201, 378-380]. For example, the addition of sleeping medication (Eszopiclone) to the pharmacologic pain regimen (Naproxen) significantly improved total sleep time as reported in self-rated sleep diaries and pain intensity in individuals with non-specific CLBP [201]. Heapy et al. reported that using cognitive behavioral therapy as a sleep intervention significantly reduced average pain intensity and PSQI scores, and improved physical function and quality of life [380]. Since insufficient sleep can reduce the analgesic effect of descending pain modulatory pathways that may result in hyperalgesia and decreased pain thresholds [381, 382], improved sleep quality/quantity may ameliorate symptoms or disability in individuals with CLBP. However, no systematic review has summarized the evidence regarding the temporal relation between improved sleep quality/quantity and associated improvements in pain/disability of individuals with CLBP.

If improved sleep quality/quantity are related to the improvements of pain intensity, self-perceived recovery and LBP-related disability in individuals with CLBP [201, 367, 383, 384], a logical follow-up question is whether baseline sleep quality/quantity of these individuals can

predict their trajectory of LBP. Recently, some prospective studies found that the presence of sleep disturbance at baseline might predict suboptimal improvement in pain severity, a heightened risk of persistent LBP, or a lower likelihood of recovery in individuals with CLBP over 12-week to 13-year periods [214, 366, 385]. However, opposite findings have also been reported [386]. These conflicting results underscore the necessity of conducting a systematic review to summarize the evidence regarding the role of baseline sleep quality/quantity in predicting the prognosis of CLBP, which can inform clinicians regarding the management of individuals with concomitant CLBP and sleep problems.

Against this background, the objectives of the current review were to summarize the evidence regarding (1) the correlation between temporal changes in sleep quality/quantity and the corresponding changes in pain intensity, quality of life and/or LBP-related disability; and (2) the role of baseline sleep quality/quantity in predicting LBP trajectory in individuals with CLBP.

6.3 Methods

The current systematic review was registered with PROSPERO (CRD42020179080). It was prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines [215, 216] and Meta-analysis Of Observational Studies in Epidemiology reporting (MOOSE) [387].

6.3.1 Search Strategy

Relevant publications were identified from Medline, Embase, PsycINFO, and CINAHL databases from their inception to February 16, 2021. The search strategy used keywords (and

related synonyms from medical subject headings: low back pain, sleep disturbance, and relation (**Table S4.1**). There was no restriction on languages. Forward citation tracking of the included studies was conducted using the Web of Science. Reference lists of the included studies were screened to identify potential publications. The corresponding authors of the included studies were contacted by emails to identify additional eligible publications.

6.3.2 Selection Criteria

Studies were included if they investigated the relations between temporal changes in sleep quality/quantity and the corresponding changes in clinical outcomes of individuals with non-specific CLBP, which was defined as pain between the 12th ribs and the gluteal crease with or without leg pain that lasted for at least three months without known pathoanatomical causes [270, 388]. The included studies should: (1) include participants with non-specific CLBP aged 18 years or older; (2) assess sleep quality/quantity by subjective or objective measurement tools; (3) measure at least one LBP-related clinical outcome other than sleep (e.g., pain, LBP-related disability, or depression); and (4) be English articles. Prospective cohort studies, case series, randomized controlled trials (RCTs), and quasi-experimental studies were eligible study designs. Studies were excluded if they: (1) involved individuals with specific LBP or non-specific LBP that lasted less than three months because their pathologies or behaviours might differ from chronic non-specific CLBP cases; (2) were cross-sectional studies, case reports, editorials, commentaries or conference proceedings; and (3) recruited < 80% of participants with non-specific CLBP in the symptomatic group unless the study provided separate data related to individuals with CLBP.

6.3.3 Study Selection and Data Extraction

Two independent reviewers screened the titles and abstracts of potential articles for full-text screening. The first 100 titles and abstracts were piloted to ensure the reviewers' agreement. The agreement was assessed by a kappa coefficient (*k*), which was classified as poor (0-0.20), fair (0.21-0.40), moderate (0.41-0.60), good (0.61-0.80); and excellent (0.81 to 1.00) [217]. If *k* was <0.60, another 100 articles were piloted. The process was repeated until the *k* was >0.60. Disagreements between these reviewers were resolved through discussion. A third reviewer was consulted for jurisdiction if disagreements persisted. The full-text articles were then screened using the same procedures.

One reviewer extracted data from the included studies, while the second reviewer verified the results. Disagreements were resolved by consensus. The extracted information included the: (1) study design; (2) participants' characteristics; (3) sample size; (4) intervention(s); (5) sleep quality/quantity variables; (6) other LBP-related clinical outcomes; (7) temporal relations between changes in sleep variables and the associated changes in LBP-related clinical outcomes; (8) statistics related to the use of baseline sleep variables in predicting future LBP-related clinical outcomes; (9) confounders involved in the analyses of relations, which might affect the strengths of the relations; and/or (10) relevant statistics (e.g., adjusted odds ratio (AOR) or unadjusted odds ratio (UOR)). If the included studies investigated multiple outcomes, only the information related to our objectives was extracted.

6.3.4 Risk of Bias Assessments

The methodological quality of the included studies was assessed by the two independent reviewers. A third reviewer was consulted if disagreements persisted. The methodological quality of prospective studies was evaluated by the Quality of Prognosis Studies Risk of Bias Assessment Instrument for Prognostic Factor Studies (QUIPS) [389, 390]. The tool comprises six domains (study population, study attrition, prognostic factor information, outcome measurement, study confounding, and statistical analysis) to evaluate potential bias in longitudinal studies [389, 390]. For the overall risk of bias, we used a similar method from previous research [391, 392]. If a study was rated with a low or moderate risk of bias and at least four domains were graded with "low risk of bias", the study was graded as having a low risk of bias (high quality). A study with two or more high-risk ratings in any of the six domains was rated as having a high risk of bias/poor quality. A study was rated as having a moderate risk of bias if the QUIPS results did not fall into the low or high risk of bias category.

The methodological quality of RCTs was assessed by the Cochrane Collaboration risk of bias (RoB) 2.0 tool for six domains: randomization process, deviation from intended interventions, missing outcomes data, measurement of the outcome, selection of the reported result, and overall bias [218]. The risk of each domain was scored as low risk of bias, some concerns of bias, or high risk of bias. A study was rated with a low overall risk of bias if all domains had low risk bias. If a study had a high risk of bias in at least one domain or some concerns for multiple domains (three or more), it was rated as a high overall risk of bias. If a study had some concerns in at least one domain but no high risk of bias, it was rated as some concerns [218].

The inter-reviewer reliability of risk of bias assessments using the QUIPS and the RoB 2.0 tool was evaluated by the kappa coefficient, while the percent agreement was estimated based on the number of agreements in the rating of each domain.

6.3.5 Data Synthesis

Meta-analyses were planned to evaluate the temporal relations between sleep variables and LBP-related clinical outcomes, as well as to determine the values of baseline sleep variables in predicting the maintenance/development of CLBP if the included studies had similar participants' characteristics, sleep parameters, LBP-related clinical outcomes, and follow-up periods. Statistical homogeneity was quantified by I^2, and the results were interpreted as low (25-50%), moderate (50-75%), and high (>75%) heterogeneity [224]. Significant heterogeneity existed when $I^2 > 50\%$ or $p < 0.1$ [224]. Random-effect models were planned for the meta-analysis. Review Manager (RevMan) v5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration) was planned to be used for meta-analysis. When a meta-analysis was inappropriate due to clinical heterogeneity (e.g., different follow-up time points), the results were summarized qualitatively. Since the included studies had very heterogenous sleep outcome measures and follow-up periods, meta-analyses were precluded, but the results were summarized narratively.

6.3.6 Grading Quality of Evidence

The overall quality of evidence regarding the relations between sleep variables and non-specific CLBP outcome measures was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [393], which is the best synthesis for judging

the quality of prognostic evidence. They were classified into four levels: high, moderate, low, or very low based on considerations involving the investigation phase, study limitations (risk of bias assessments), inconsistency, indirectness, imprecision, publication bias, moderate or large effect size, and exposure-response gradient.

6.4 Results

6.4.1 Literature Search

Database searches identified 1,995 references (**Figure 8).** After the removal of 508 duplicates, 90 references were included for full-text screening. Three prospective studies and three RCTs were included. The reasons for exclusion were: inclusion of participants without non-specific CLBP; no investigation of temporal relations between changes in sleep variables and changes in LBP-related clinical outcomes or no investigation of the role of baseline sleep variables in predicting future CLBP; inappropriate study designs; non-English articles; and no available full-text articles. The inter-reviewer reliability estimates for the abstract (k=0.74) and full-text screenings (k=0.65) were high. Forward citations of included studies yielded 78 additional citations for screening.

6.4.2 Study Characteristics

The characteristics of the included studies are reported in **Tables**

Table 8. The sample sizes of the included studies ranged from 58 to 1,356. Participants' mean ages ranged from 40.1 to 51.0 years. Follow-up durations of the included prospective studies and RCTs ranged from six to 24 months [367, 394, 395] and four to 52 weeks [201, 383, 384], respectively. These studies were conducted in Australia (n = 1), Iran (n = 1), Sweden (n =1), and

the USA (n = 3). Five included studies used yoga, stretching, education, medication, manual therapies, exercises, physiotherapy, psychological therapies, spinal injection, spinal surgery, acupuncture, and multidisciplinary pain management to treat CLBP [201, 367, 383, 384, 395]. One of them allowed participants to receive any interventions [395]. One included prospective study did not involve any intervention during the six-month study period [394]. Three included studies adjusted for confounders in analyzing the relations between sleep parameters and other LBP-related outcomes [367, 383, 384]. The most commonly adjusted confounders were age and baseline values of various clinical outcomes. Other confounders included gender, body mass index, occupation, leg symptoms, pain duration, anxiety, depression, and bothersomeness.

6.4.3 Measured Sleep Parameters

The included studies used diverse methods to evaluate sleep quality and/or quantity (**Table S4.2**). Three included studies assessed sleep quality using PSQI [367, 384, 395], which evaluates sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medication, and daytime dysfunctions [396]. One study used sleep diaries to document seven sleep parameters: total sleep time (TST), sleep onset latency (SOL), wake time after sleep onset (WASO), number of awakenings (NAW), sleep efficiency (SE), sleep quality (10-point rating), and restedness (10-point scale) [201]. This study considered TST as the primary sleep parameter because it included both the onset and maintenance of sleep [201]. Two included studies either used an item from Roland-Morris Disability Questionnaire (RMDQ) to assess sleep status [383, 394] or used two 4-point scales to assess sleep quality and quantity [394].

6.4.4 Other LBP-related Outcomes

The included studies used self-reported questionnaires/scales to rate pain, LBP-related disability, recovery, and bothersomeness (**Table S4.3**). Notably, "pain intensity" was usually measured by the 11-point pain numeric rating scale (NPRS), 100mm visual analog scale (VAS), or five-point global impression of pain rating (PGI). Four included studies assessed LBP-related disability by RMDQ [383, 384, 394, 395]. Two included studies used a global rating of change scale (GRC) to evaluate LBP recovery [367, 395]. Additionally, Rabey et al. measured bothersomeness using a seven-point scale [395].

6.4.5 Risk of Bias Assessments

The included prospective studies had high (n = 2) [394, 395] and moderate risk of bias (n = 1) [367] (**Table S4.4).** Common risks of bias were: (1) lack of information about dropout participants; (2) no consideration of confounders; and (3) unreliable measurements of prognostic factors. The inter-reviewer reliability of using QUIPS was excellent (k=1.0), with 93.7% agreement for various domain items. One included RCT had a low risk of bias [201], and two RCTs had high a risk of bias (**Figure S4.1**) [383, 384]. Common risks of bias in the included RCTs were presented at: the randomization process, handling of data, and no blinding of outcome measurements. The inter-reviewer reliability of using the RoB 2.0 tool was excellent (k=1.0), with 80% agreement for various domain items.

6.4.6 Temporal Relations between Changes in Sleep Parameters and Changes in Pain Intensity, Self-perceived Recovery, and Disability

Four studies found that changes in sleep quality/quantity were correlated with the corresponding changes in other LBP-related outcomes **(Table 9 and Table 10)** [201, 367, 383, 384].

Temporal Changes in PSQI Scores and Changes in Pain Intensity, Self-perceived Recovery, and RMDQ

A moderate-quality prospective study demonstrated that compared to individuals without sleep problems at baseline or follow-up, those developed poor sleep quality (baseline PSQI scores: < 5, but follow-up scores: ≥ 5) or showed improved sleep quality at six months (baseline PSQI scores: ≥ 5, but follow-up scores: < 5) had a higher (UOR = 2.99, 95% CI: 1.51 to 5.92; AOR = 2.88, 95% CI: 1.32 to 6.31) or lower (UOR = 0.46, 95% CI: 0.25 to 0.87; AOR = 0.49, 95% CI: 0.26 to 0.93) odds of nonrecovery/higher pain intensity (VAS > 10mm) [367]. Likewise, one RCT with a high risk of bias found that clinically meaningful improvements in NPRS scores (≥ 30%) at the six-week follow-up were significantly related to clinically meaningful improvements in PSQI scores (≥ 3 scores) at the 12- (UOR = 3.51; 95% CI: 1.73 to 7.11) and 52-week follow-ups (UOR = 1.58; 95% CI: 0.77 to 3.23) [384].

One moderate-quality prospective study reported that compared to individuals without sleep problems, those who developed or showed improved sleep quality (PSQI ≥ 5 or < 5 scores) had a significantly higher (UOR = 2.93, 95% CI: 1.53 to 5.61; AOR = 2.17, 95% CI: 1.04 to 4.52) or lower likelihood of self-perceived nonrecovery as assessed by GRC (UOR = 0.49, 95% CI: 0.31 to 0.78; AOR = 0.50, 95% CI: 0.31 to 0.81) [367].

Additionally, one low-quality RCT found that compared to individuals with < 30% reduction in RMDQ scores, those with clinical improvements in RMDQ scores (> 30% reduction from baseline) at six weeks were associated with significant clinical improvements in PSQI scores (≥ 3-point reduction) at 12 and 52 weeks, with UOR = 2.16, 95% CI: 1.18 to 3.95 and UOR = 2.18, 95% CI: 1.19 to 3.98, respectively [384].

Overall, moderate-quality evidence supported that improvements in PSQI scores over time were significantly associated with the corresponding pain reduction and self-reported recovery in individuals with CLBP. Likewise, low-quality evidence substantiated significant temporal relations between improved PSQI scores and the respective improvements in self-reported disability **(Table 10)**.

Changes in Sleep Parameters Reported in Sleep Diaries and Changes in Pain Intensity

One high-quality RCT reported that there were significant correlations between temporal improvements in sleep parameters [TST, WASO, SE, sleep quality (a 10-point scale), and restedness] and temporal improvements in pain intensity (VAS and PGI), but there were no significant relations between SOL or NUAK and pain intensity (**Table 9**) [201]. As TST was the primary outcome in this study, moderate-quality evidence suggested that increased TST was significantly related to decreased LBP intensity (VAS and PGI) in individuals with CLBP **(Table 10)**.

The Relation between Changes in the Sleep Quality Question "I sleep less well because of my back" in RMDQ and Changes in Disability

There was very low-quality evidence that the temporal improvement in sleep quality (as measured by RMDQ) was related to the subsequent improvement in LBP-related disability **(Table 10)**. Specifically, one included low-quality RCT showed that compared to the self-care group that showed inferior improvements in the total RMDQ scores, improved LBP-related sleep disturbances (the sleep question in RMDQ) at six weeks were significantly related to decreased total RMDQ scores at 12 weeks in the yoga (AOR = 2.51, 95% CI: 1.11 to 3.90) and stretching groups (AOR = 2.43, 95% CI: 1.12 to 3.74) [383].

6.4.7 Baseline Sleep Quality/Quantity in Predicting Future CLBP

Table 9 and Table 10 summarize the relationship between the baseline sleep quality/quantity and future LBP-related clinical outcomes [367, 394, 395].

Baseline PSQI Scores in Predicting Future Pain Intensity, Self-reported Recovery, Disability, or Bothersomeness

One moderate-quality cohort study found that the presence of baseline poor sleep quality (PSQI ≥ 5 scores) significantly increased the odds of nonrecovery or higher pain intensity (> 10mm on VAS) (UOR = 2.69, 95%CI: 1.72 to 4.11; AOR = 2.48, 95%CI: 1.62 to 3.70) and poor self-reported LBP recovery as measured by GRC (UOR = 1.52, 95%CI: 1.10 to 2.08; AOR = 1.50, 95%CI: 1.09 to 2.17) at the six-month follow-up [367]. Conversely, Rabey et al. reported no significant correlation between baseline PSQI scores and the ensuing NRS, GRC, RMDQ scores, or bothersomeness at the one-year follow-up [395]. Collectively, there was conflicting evidence

regarding whether baseline PSQI scores predicted pain intensity or self-reported recovery in individuals with CLBP. However, no evidence supports that baseline PSQI predicted future LBP-related disability or bothersomeness (**Table 10**).

Baseline four-point Scale of Sleep Quality/Quantity in Predicting Future LBP-related Disability

There was very low-quality evidence that baseline sleep quality (r = -0.43, $P<0.01$) or quantity (r = -0.34, $P<0.01$) as measured by a four-point scale was related to the absolute RMDQ scores at the two-year follow-up but not the percentage improvements in RMDQ scores **(Table 10)** [394].

6.5 Discussion

This is the first systematic review to reveal diverse (very low to moderate) quality of evidence regarding the associations between changes in different subjectively reported sleep parameters and the respective changes in pain intensity, self-perceived recovery, or LBP-related disability over time. However, it remains unclear whether baseline sleep quality/quantity can predict future LBP-related outcomes in individuals with CLBP. Our findings reveal a paucity of relevant research, although many individuals with CLBP experience sleep disturbance. Our results also underscore the importance of determining the causal relations between sleep and pain/function in individuals with CLBP, which may improve the assessments and treatments of these populations.

The significant relations between changes in different self-reported sleep parameters and the corresponding changes in various LBP-related outcomes revealed in the current review concurred with the findings from other chronic pain studies [43, 380, 397-399]. For instance,

Miller and Yarlas et al. found that improvements in patient-reported sleep quality were significantly associated with reduced pain and improved physical quality of life in individuals with specific CLBP following the buprenorphine transdermal patches [397, 398]. Additionally, one included RCTs with a low risk of bias found that the Spearman rank correlation coefficients between changes in various sleep parameters assessed by sleep diaries and changes in pain intensity ranged from 0.31 to 0.46 [201], indicating medium to large effect sizes [400]. Similarly, one included study with a high risk of bias revealed that clinically meaningful improvements in the PSQI scores were related to the respective clinically meaningful improvements in NPRS and RMDQ scores, although the estimated odds ratios had wide 95% CIs [384]. Collectively, these consistent findings support that sleep interventions may be an important component in managing some individuals with CLBP to improve their pain and LBP-related disability. Multiple studies have shown that pharmacological and non-pharmacological interventions for sleep could simultaneously improve sleep quality/quantity and pain intensity/physical function in individuals with chronic pain [40-45, 198, 199]. However, it remains uncertain which intervention is more effective in achieving clinically meaningful improvements in sleep quality/quantity and LBP-related clinical outcomes among individuals with CLBP.

The relationship between changes in self-reported sleep quality/quantity and changes in CLBP may be attributed to decreased pain perception after improved sleep. It is not uncommon for individuals with chronic pain to report disturbed sleep and/or reduced total sleep time [401]. Studies on healthy individuals found that sleep disturbance by forced awakenings [402, 403] or total sleep deprivation [35, 232, 382, 404] significantly increased spontaneous pain complaints, temporal summation of pain, as well as decreased mechanical and/or thermal pain thresholds. A

rat study also reported exaggerated behavioural responses to noxious stimuli after sleep deprivation but not sleep fragmentation [405]. For individuals with CLBP, studies found that poor sleep quality (assessed by electronic devices, PSQI, and sleep diaries) the night before would increase the pain intensity on the next day [212, 406]. These findings consistently indicate that insufficient sleep may alter central pain-modulatory circuits, amplify pain signals, and cause allodynia [404]. Interestingly, the effects of sleep deprivation on pain perception are reversible. Studies found that the recovery of sleep following sleep deprivation could restore the pain threshold [34-36].

Additionally, sleep deprivation may increase the release of inflammatory cytokines that may heighten pain sensitivity [407, 408], which can be reversed by sleep interventions. Sleep deprivation in healthy individuals may increase the risk of inducing systemic and cellular inflammation, as well as the production of proinflammatory cytokines [262, 409]. A recent systematic review and meta-analysis concluded that sleep disturbance in adults was significantly associated with a higher level of IL-6 and C-reactive protein in blood [408]. Further, sleep deprivation elicits low-grade neuroinflammation in the rat brain, with enhanced expression of tumor necrosis factor α (TNFα), IL-6, IL-8, IL-1β, and glial cell activation [374, 375]. Neuroinflammation is known to be related to the pathogenesis of CLBP [373]. Research has demonstrated increased brain levels of translocator protein (a marker of brain glial activation) and elevated IL-8 levels in the cerebrospinal fluid among individuals with CLBP [373, 410], which results in altered sensory processing in the brain and aggravation of pain sensitization [407, 411]. Fortunately, inflammatory response induced by sleep deprivation can also return to the baseline level after recovery from sleep in healthy participants [412, 413]. Two RCTs also

revealed that cognitive-behavioral therapy for insomnia reduced systemic and cellular inflammation levels in older adults [414, 415]. These findings highlight the potential benefits of assessing and treating sleep problems in some individuals with CLBP.

The present review found conflicting results regarding the ability of baseline PSQI scores to predict future clinical outcomes in individuals with CLBP. The discrepancy might be ascribed to differences in follow-up durations and/or adjustment of confounders in two included studies [367, 395]. Specifically, negative results were found in the included study with a longer follow-up and no adjustment for confounders [395]. Further, since certain factors (e.g., age [416], body mass index [417], physical activity level [418], baseline pain or disability level [417, 419], and anxiety [419]) are known independent prognostic factors for CLBP, studies that did not consider these confounders in their regression models might yield non-significant findings. Conversely, Pakpour et al. considered these confounders in their analysis and found that the baseline PSQI scores could predict future LBP [367]. Several prospective studies also found that baseline self-reported sleep disturbances would predict the onset of CLBP [185, 186] or chronic pain [420] in healthy individuals. Similarly, some studies have demonstrated that poorer self-reported sleep quality/quantity at baseline predicts suboptimal pain-related outcomes (e.g., future sickness absence [421], less improvement in pain interference and severity [385], lower probability of recovery from CLBP [214], and the onset of new pain or radiating pain [366]) in individuals with CLBP. However, these studies were not included in the current review because they recruited a mixed sample of people with CLBP and other chronic pain or people with specific CLBP. Future large-scale, high-quality prospective studies should be conducted to clarify whether baseline sleep quality/quantity can predict CLBP trajectory.

The current review had several strengths. First, this review protocol was registered with PROSPERO to minimize the risk of selective reporting bias. Second, comprehensive searches (including forward citation tracking and contact of the corresponding authors) were adopted to optimize the identification of eligible publications. Third, two independent reviewers followed standardized procedures to screen articles, extract data, and appraise the methodological quality of the included paper. There were several limitations in this review. First, although multiple databases were comprehensively searched, only six articles were included. The paucity of relevant research inevitably affected the quality of evidence for our findings. Second, although meta-analysis was planned, the diverse assessment tools for sleep, different follow-up time points, and LBP-related outcomes prevented the conduction of meta-analyses. Third, the current review only included English articles. Future reviews should include articles published in other languages to improve the representativeness/generalizability of findings.

While our findings have suggested the presence of significant associations between changes in self-reported sleep quality/quantity and changes in CLBP-related outcomes over time, several knowledge gaps remain to be addressed. First, all included studies used self-reported questionnaires/scales to document the sleep quality/quantity, which might be subject to recall bias or subjectivity. Future research can use wearable sleep trackers (e.g., actigraphy [422] or polysomnography [423]) to quantify various sleep parameters objectively. Second, the methodological quality of the included studies was low. Future studies should address some common risks of bias in previous research (e.g., adequate randomization and blinding, measuring potential prognostic factors, and adjusting for confounders) in order to disentangle the potential

relation between sleep and CLBP. Third, since the current evidence substantiates that changes in sleep quality/quantity are related to the corresponding changes in LBP-related outcomes, future research should investigate whether different sleep interventions would have different effects on improving sleep quality/quantity and other LBP-related outcomes in individuals with CLBP.

6.6 Conclusions

This is the first systematic review to underscore that better self-reported sleep quality/quantity is likely to be associated with improved CLBP intensity or LBP-related disability, although it remains unclear whether baseline sleep quality/quantity is related to the persistence of CLBP. Given that research in this area is still in its infancy, high-quality studies should clarify the relation between CLBP and sleep, which may identify various patient subgroups for better treatments.

6.7 Tables

Table 8. Study characteristics of the included studies

Study	Study design	Country	Characteristics of participants; average age and standard deviation; follow-ups	Intervention	Measurement of sleep quality/quantity	Measurement of clinical outcomes	Adjusted confounders	Statistical tests
Studies investigating temporal relations between changes in sleep parameters and the corresponding changes in LBP-related parameters (n=4)								
Roseen et al (2020) [384]	A secondary analysis of a 3-arm RCT	USA	Participants with nonspecific CLBP recruited from a hospital and seven community health centers (n = 320); Group A (n = 127): 46.7 ± 10.2 years; Group B (n = 129): 46.0 ± 11.4 years; Group C (n= 64): 44.3 ± 10.3 years; FU: 12 weeks, 52 weeks	Each group received a 12-week intervention program. Group A (yoga): 12 weekly 75-min classes involving yoga poses, breathing, relaxation, and meditation; practice at home for 30 min daily Group B (1-on-1 physiotherapy): fifteen 60-min appointments over the course of 12 weeks with physical therapy and aerobic exercise; home practice daily Group C (education): participants received *The Back Pain*	PSQI	1. NPRS 2. RMDQ	No	Separate univariate logistic regression models to evaluate the temporal changes in PSQI scores at 12- and 52-week follow ups with the temporal changes in scores of NPRS or RMDQ scores at 6-week FU

				Helpbook, including a chapter on solutions for sleep problems				
Pakpour et al (2018) [367]	A prospective cohort study	Iran	A convenience sample of patients with nonspecific CLBP were recruited from a chronic pain clinic and a hospital (n = 682); 41.15 ± 12.24 years; FU: 6 months	Treatments (e.g., patient education, prescription, and physiotherapy) varied due to a convenience sample of consecutive patients from two different locations	PSQI	1. GRC 2. VAS	Age, gender, BMI, occupational status, the baseline pain intensity, duration of pain, and anxiety as well as depressive symptoms (measured by HADS)	Separate logistic regression models to compare temporal changes in PSQI scores and changes in GRC or VAS
Goforth et al (2014) [201]	A double-blinded, 2-arm RCT	USA	Participants with insomnia and nonspecific CLBP were recruited through newspaper advertisements, posted announcements, and physician referrals (n = 58); Group A (n = 33): 45.7 ± 11.0 years; Group B (n =25): 40.1 ± 12.8 years; FU: 1 week, 2 weeks, 1 month	Each group received medicine with 1 month. Group A: 3 mg ESZ with NAP 500 mg twice daily and LAN 15 mg daily Group B: 3 mg placebo with NAP 500 mg twice daily and LAN 15 mg daily	1. TST 2. SOL 3. WASO 4. NUAK 5. SE 6. Sleep quality 7. Restedness	1. VAS 2. PGI	No adjustment for any confounders	Spearman correlation coefficients to evaluate the correlations between temporal changes in all sleep parameters and the corresponding changes in clinical outcomes

Sherman et al (2013) [383]	A secondary analysis of a 3-arm RCT	USA	Participants with nonspecific CLBP recruited from a health care organization (n = 192): Group A (n=78): 47 ± 9.5 years; Group B (n = 74): 49 ± 10.1 years; Group C (n = 40): 51 ± 8.4 years; FU: 6 weeks. 12 weeks, 26 weeks	Each group received a 12-week intervention: Group A: 12 weeks of weekly (once a week) yoga classes Group B: 12 weeks of weekly (once a week) intensive stretching classes Group C: a self-care book	The sleep question in RMDQ	RMDQ	Age, sex, BMI, days of LBP in the last 6 months, strenuousness of work, the presence of leg pain, the baseline RMDQ scores and bothersomeness (measured by a 11-pont scale)	A multivariate logistic regression model to investigate temporal changes in sleep disturbance score on RMDQ and changes in RMDQ
Studies investigating the role of baseline sleep quality/quantity in predicting future clinical outcomes (n=3)								
Pakpour et al (2018) [367]	A prospective cohort study	Iran	A convenience sample of people with nonspecific CLBP were recruited from a chronic pain clinic in a hospital (n = 682); 41.15 ± 12.24 years; FU: 6 months	Usual care (patient education, prescription, and physiotherapy) varied due to a convenience sample of consecutive patients	PSQI	1. GRC 2. VAS	Age, gender, BMI, occupational status, the baseline pain intensity, duration of pain, and anxiety as well as depressive symptoms (measured by HADS).	Separate logistic regression models to investigate the effect of baseline sleep status (participant with/without sleep problem) on GRC and VAS at the 6-month FU.
Nordeman et al (2017) [394]	Same as above	Sweden	Female patients with nonspecific CLBP recruited from primary healthcare (n =	No intervention	The questions related sleep quantity and quality	RMDQ	No adjustment for any confounders	Spearman correlation coefficients to evaluate the correlations between the

			123); 45±10 years; FU: 2 years					baseline sleep-related questions and the scores or percentage improvement in RMDQ at the 2-year FU
Rabey et al (2017) [395]	Same as above	Australia	Participants with axial CLBP recruited by multimedia advertisements from metropolitan, rural, clinics and hospitals (n = 266); 51 (39 - 40) years; FU: 1 years	Participants were free to undergo any intervention 1. Manual therapies 2. Exercises 3. Psychological therapies 4. Pharmacological management 5. Spinal injection 6. Spinal surgery 7. Acupuncture Multidisciplinary pain management	PSQI	1. NPRS 2. RMDQ 3. GRC 4. Bothersomeness	No adjustment for any confounders	Univariable correlation to evaluate the association between the baseline scores of PSQI and CLBP outcome measures (NPRS, RMDQ, GRC, and Bothersomeness) at the 1-year FU

Abbreviation: AOR = Adjusted Odd Ratio; CI = Confidence Interval; ESZ = Eszopiclone; FU = Follow-ups; GRC = Global Rating of Change; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Depression Rating Scale; LAN = Lansoprazole; NAP = Naproxen; NPRS = 11-point Numerical Pain Rating Scale; NUAK = Number of Awakenings; PGI = Global Impression of Pain; PSQI = Pittsburgh Sleep Quality Index; RCT = Randomized controlled trial; RMDQ = Roland-Morris Disability Questionnaire; SE = Sleep Efficiency; SOL = Sleep Onset Latency; TST = Total Sleep Time; UOR = Unadjusted odd ratio; VAS = 100mm Visual Analog Scale; WASO: Wake Time After Sleep Onset.
Footnote: [a]$P<0.10$; [b]$P<0.05$; [c]$P<0.01$

Table 9. Associations between sleep quantity/quality and LBP-related outcome measures

Sleep parameters	Study	Relations with LBP-related clinical outcomes	Statistics (e.g., odds ratio)	Effect	Strength of evidence
Changes in sleep parameters and changes in pain intensity					
PSQI global scores	Roseen et al (2020) [384]	Relation between clinically meaningful improvements (> 30% reduction from baseline) in NPRS scores at 6-wk FU (regardless of treatment groups) and clinically meaningful improvement (≥ 3-point reduction) in PSQI at the 12-wk FU (n = 320)	At 12th wk: UOR = 3.51 (95% CI 1.73 to 7.11) At 52nd wk: UOR = 1.58 (95% CI 0.77 to 3.23) (reference group: < 30% reduction in NPRS scores)	Positive relation at 12th wk only	Moderate
	Pakpour et al (2018) [367]	Relation between developing sleep problem (none at baseline, presence at 6-month FU) and nonrecovery of pain based on GRC at 6-month FU (n=354)	UOR = 2.93 (95% CI 1.53 to 5.61) AOR = 2.17 (95% CI 1.04 to 4.52) (reference group: no baseline and FU sleep problem)	Positive relation	
		Relation between resolved sleep problem (presence at baseline, absence at 6-month FU) and nonrecovery of pain based on GRC at 6-month FU (n=221)	UOR = 0.49 (95% CI 0.31 to 0.78) AOR = 0.50 (95% CI 0.31 to 0.81) (reference group: no baseline and FU sleep problem)	Positive relation	
		Relation between persistent sleep problem (presence at baseline, presence at 6-month FU) and nonrecovery of pain based on GRC at 6-month FU (n = 486)	UOR = 3.24 (95% CI 1.63 to 6.43) AOR = 2.95 (95% CI 1.48 to 5.88) (reference group: no baseline and FU sleep problem)	Positive relation	
		Relation between developing sleep problem (none at baseline, presence at 6-month FU) and pain intensity/nonrecovery of pain based on VAS at 6-month FU (n = 354)	UOR = 2.99 (95% CI 1.51 to 5.92) AOR = 2.88 (95% CI 1.32 to 6.31) (reference group: no baseline and FU sleep problem)	Positive relation	
		Relation between resolved sleep problem (presence at baseline, absence at 6-month FU) and pain intensity/nonrecovery of pain based on VAS at 6-month FU (n = 221)	UOR = 0.46 (95% CI 0.25 to 0.87) AOR = 0.49 (95% CI 0.26 to 0.93) (reference group: no baseline and FU sleep problem)	Positive relation	
		Relation between persistent sleep problem (presence at baseline, presence at 6-month	UOR = 3.73 (95% CI 1.92 to 7.26)	Positive relation	

		FU) and pain intensity/nonrecovery of pain based on VAS at 6-month FU (n = 486)	AOR = 3.45 (95% CI 1.59 to 7.46) (reference group: no baseline and FU sleep problem) Positive relation		
Total sleep time	Goforth et al (2014) [201]	Correlation between changes in total sleep time from baseline as measured by daily diary ratings of sleep and changes in pain intensity on VAS and PGI pain ratings after 1-month of insomnia and LBP treatment (n = 58)	Rho (VAS) = - 0.40[c] Rho (PGI) = - 0.46[c]	Negative relation	Moderate
Sleep onset latency	Goforth et al (2014) [201]	Correlation between changes in sleep onset latency from baseline as measured by daily diary ratings of sleep and changes in pain intensity on VAS and PGI pain ratings after 1-month of insomnia and LBP treatment (n = 58)	Rho (VAS) = - 0.05 Rho (PGI) = - 0.04	No significant relation	Moderate
Wake time after sleep onset	Goforth et al (2014) [201]	Correlation between changes in wake time after sleep onset from baseline as measured by daily diary ratings of sleep and changes in pain intensity on VAS and PGI pain ratings after 1-month of insomnia and LBP treatment (n = 58)	Rho (VAS) = 0.31[b] Rho (PGI) = 0.32[b]	Positive relation	Moderate
Number of awakenings	Goforth et al (2014) [201]	Correlation between changes in number of awakenings from baseline as measured by daily diary ratings of sleep and changes in pain intensity on VAS and PGI pain ratings after 1-month of insomnia and LBP treatment (n = 58)	Rho = 0.38[c] Rho = 0.25	Positive relation No significant relation	Moderate
Sleep efficiency	Goforth et al (2014) [201]	Correlation between changes in sleep efficiency from baseline as measured by daily diary ratings of sleep and changes in pain intensity on VAS and PGI pain ratings after 1-month of insomnia and LBP treatment (n = 58)	Rho = -0.33[b] Rho = -0.33[b]	Negative relation	Moderate
Sleep quality	Goforth et al (2014) [201]	Correlation between changes in sleep quality from baseline as measured by daily diary ratings of sleep and changes in pain intensity and PGI pain ratings on VAS after 1-month of insomnia and LBP treatment (n = 58)	Rho = -0.37[c] Rho = -0.27	Negative relation No significant relation	Moderate
Restedness	Goforth et al (2014) [201]	Correlation between changes in restedness from baseline as measured by daily diary ratings of sleep and changes in pain intensity	Rho (VAS) = -0.41[c] Rho (PGI) = -0.33[b]	Negative relation	Moderate

		on VAS and PGI pain ratings after 1-month of insomnia and LBP treatment (n = 58)			
Changes in sleep parameters and changes in LBP-related disability					
PSQI global scores	Roseen et al (2020) [384]	Relation between clinically meaningful improvement (≥ 3-point reduction) in PSQI at the 12-wk FU and clinically meaningful improvements (> 30% reduction from baseline) in RMDQ scores at 6-wk FU (regardless of treatment groups) (n = 320)	At 12th wk: UOR = 2.16 (95% CI 1.18 to 3.95) At 52nd wk: UOR = 2.18 (95% CI 1.19 to 3.98) (reference group: < 30% reduction in RMDQ scores)	Positive relation	Low
Sleep disturbance due to LBP	Sherman et al (2013) [383]	Relation between changes in sleep disturbance score on RMDQ at 6-wk FU and reduction in RMDQ scores at 12-wk FU (regardless of treatment groups) (n = 192)	Yoga: AOR = 2.51, 95% CI 1.11 to 3.90 Stretching: AOR = 2.43, 95% CI 1.12 to 3.74) (reference group: patients in the self-care group)	Positive relation	Very low
Baseline sleep parameters in predicting CLBP in the future					
PSQI global scores	Pakpour et al (2018) [367]	Baseline sleep problem to predict nonrecovery of pain based on GRC at 6-month FU (n = 682)	UOR = 1.52 (95% CI 1.10 to 2.08) AOR = 1.50 (95% CI 1.09 to 2.17) (reference group: no baseline sleep problem. PSQI < 5 points)	Predictive	Very low
		Baseline sleep problem to predict pain intensity/nonrecovery of pain based on VAS at 6-month FU (n = 682)	UOR = 2.69 (95% CI 1.72 to 4.11) AOR = 2.48 (95% CI 1.62 to 3.70) (reference group: no baseline sleep problem. PSQI < 5 points)	Predictive	Very low
	Rabey et al (2017) [395]	The baseline scores of PSQI to predict pain intensity of NPRS at the 1-year FU (n = 266).	Univariable correlation β = -0.06 (-0.12 to 0.00)[a]	Not predictive	Very low
		The baseline scores of PSQI to predict LBP-related disability of RMDQ, at the 1-year FU (n = 266).	Univariable correlation β = -0.02 (-0.15 to 0.10)[a]	Not predictive	Very low
		The baseline scores of PSQI to predict recovery of GRC at the 1-year FU (n = 266).	Univariable correlation β = 1.03 (0.97 to 1.10)[a]	Not predictive	Very low
		The baseline scores of PSQI to predict Bothersomeness at the 1-year FU (n = 266).	Univariable correlation β = 0.95 (0.88 to 1.03)[a]	Not predictive	Very low

Sleep quality	Nordeman et al (2017) [394]	The baseline sleep quality to predict the absolute scores and the percentage changes in RMDQ at the 2-year FU (n = 123)	Rho (absolute scores) = -0.43[c] Rho (changes) = -0.16[a]	Predictive Not predictive	Very low
Sleep quantity	Nordeman et al (2017) [394]	The baseline sleep quality to predict the absolute scores and the percentage changes in RMDQ at the 2-year FU (n = 123)	Rho (absolute scores) = -0.34[c] Rho = -0.18[a]	Predictive Not predictive	Very low

Abbreviation: AOR = Adjusted Odd Ratio; CI = Confidence Interval; ESZ = Eszopiclone; FU = Follow-ups; GRC = Global Rating of Change; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Depression Rating Scale; LAN = Lansoprazole; NAP = Naproxen; NPRS = 11-point Numerical Pain Rating Scale; NUAK = Number of Awakenings; PGI = Global Impression of Pain; PSQI = Pittsburgh Sleep Quality Index; RCT = Randomized controlled trial; RMDQ = Roland-Morris Disability Questionnaire; SE = Sleep Efficiency; SOL = Sleep Onset Latency; TST = Total Sleep Time; UOR = Unadjusted odd ratio; VAS = 100mm Visual Analog Scale; WASO: Wake Time After Sleep Onset.
Footnote: [a]$P<0.10$; [b]$P<0.05$; [c]$P<0.01$.

Table 10. Grade evidence profile of the relation between sleep quantity/quality and LBP-related outcome measures

Sleep parameters	CLBP outcomes	No of studies	No of participants	Univariate or Multivariable			Phase of study	GRADE factors							Overall evidence
				+	0	-		Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/large effect	Exposure gradient	
Changes in sleep parameters and changes in LBP-related outcomes															
PSQI scores	Pain intensity (VAS or NPRS)	2 [367, 384]	1002	2			2	×	✓	×	×	✓	✓	×	+++
	self-perceived pain recovery (GRC)	1 [367]	682	1			2	×	✓	×	×	✓	✓	×	+++
	LBP-related disability (RMDQ scores)	1 [384]	320	1			2	×	✓	✓	×	✓	×	×	++
Total sleep time	Pain intensity (VAS and PGI)	1 [201]	55			1	2	✓	✓	✓	×	✓	×	×	+++
Sleep onset latency	Pain intensity (VAS and PGI)	1 [201]	55		1		2	✓	✓	✓	×	✓	×	×	+++
Wake time after sleep onset	Pain intensity (VAS and PGI)	1 [201]	55	1			2	✓	✓	✓	×	✓	×	×	+++
Number of awakenings	Pain intensity (VAS)	1 [201]	55	1			2	✓	✓	✓	×	✓	×	×	+++
	Pain intensity (PGI)	1 [201]	55		1		2	✓	✓	✓	×	✓	×	×	+++

Sleep efficiency	Pain intensity (VAS and PGI)	1 [201]	55			1	2	✓	✓	✓	×	✓	×	×	+++
Sleep quality	Pain intensity (VAS)	1 [201]	55			1	2	✓	✓	✓	×	✓	×	×	+++
	Pain intensity (PGI)	1 [201]	55		1		2	✓	✓	✓	×	✓	×	×	+++
Restedness	Pain intensity (VAS and PGI)	1 [201]	55			1	2	✓	✓	✓	×	✓	×	×	+++
Sleep quality question from QMDQ	LBP-related disability (RMDQ scores)	1 [383]	192	1			1	×	✓	×	×	×	×	×	+
Baseline sl1eep parameters in predicting CLBP in the future															
PSQI scores	Pain intensity (VAS and NPRS)	2 [367, 395]	696	1		1	1 and 2	×	×	×	×	×	×	×	+
	self-perceived nonrecovery (GRC)	2 [367, 395]	696	1		1	1 and 2	×	×	×	×	×	×	×	+
	LBP-related disability (RMDQ scores)	1 [395]	266			1	1	×	✓	×	×	×	×	×	+
	Bothersomness	1 [395]	266			1	1	×	✓	×	×	×	×	×	+
4-point scale of sleep quality	LBP-related disability (RMDQ scores)	1 [394]	123	1			1	×	✓	×	×	×	×	×	+
4-point scale of	LBP-related	1 [394]	123			1	1	×	✓	×	×	×	×	×	+

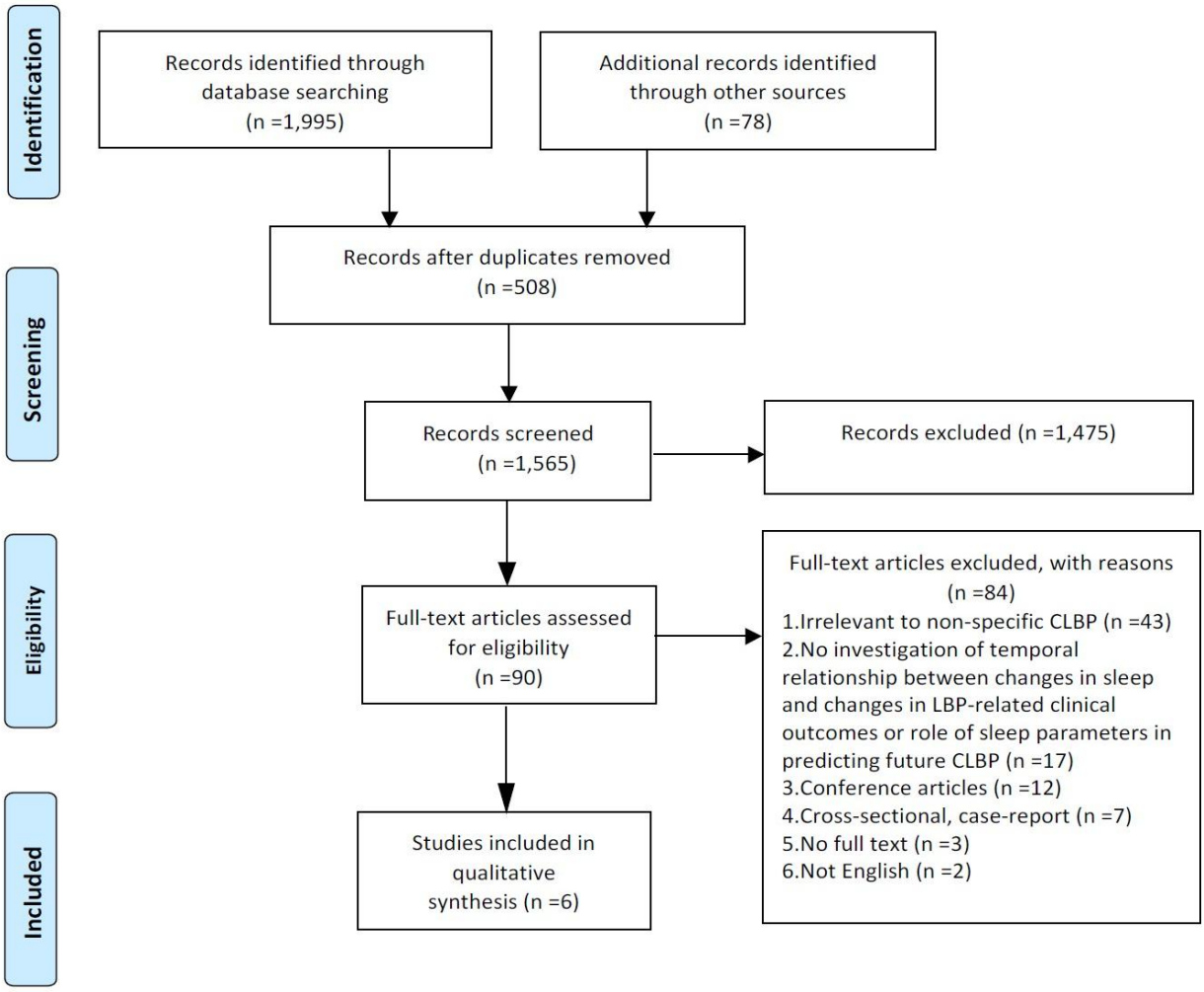
sleep quantity	disability (RMDQ scores)														

Abbreviation: GRC = Global rating of change; NPRS = 11-point Numerical Pain Rating Scale PGI = Global Impression of Pain; PSQI = Pittsburgh Sleep Quality Index; RMDQ = Roland-Morris Disability Questionnaire.

Footnote: For univariate and multivariate analyses: +, number of significant effects with a positive value; 0, number of non-significant effects; -, number of significant effects with a negative value. For GRADE factors: ✓, no serious limitations; ✕, serious limitations (or not present for moderate/large effect size, dose effect); unclear, unable to rate item based on available information. For overall quality of evidence: +, very low; ++, low; +++, moderate; ++++, high

6.8 Figures

Figure 8. A flow chart of literature searches



Chapter 7 Comparative Effectiveness of Non-Pharmacological Interventions on Sleep in Individuals with Chronic Musculoskeletal Pain: A Systematic Review with Network Meta-Analysis

This chapter has been submitted by the author of this thesis as an article in the journal "*Sleep Medicine Reviews*" in February 2024.

Part of the materials in this chapter was presented orally at *The Hong Kong Physiotherapy Association 60th Anniversary Conference* on 23rd-25th June 2023. Hong Kong, China.

Part of the materials in this chapter was presented orally at *The 13th Pan-Pacific Conference on Rehabilitation* on 23rd-24th November 2023. Chiang Mai, Thailand.

Sleep Medicine Reviews 73 (2024) 101867

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

Comparative effectiveness of non-pharmacological interventions on sleep in individuals with chronic musculoskeletal pain: A systematic review with network meta-analysis

Jeremy R. Chang [a], Yuen Kwan Cheung [b], Saurab Sharma [c,d], Shirley X. Li [e,f], Rae RY. Tao [g], Janet Lok Chun Lee [a], Eliza R. Sun [a], Sabina M. Pinto [a], Zhixing Zhou [a], Howard Fong [a], Winnie WY. Chan [a], Kangyong Zheng [a], Dino Samartzis [h], Siu-Ngor Fu [a], Arnold YL. Wong [a,*]

[a] Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong SAR, China
[b] Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, Hong Kong SAR, China
[c] School of Health Sciences, Faculty of Medicine and Health, University of New South Wales, Australia
[d] Centre for Pain IMPACT, Neuroscience Research Australia, Sydney, Australia
[e] Sleep Research Clinic and Laboratory, Department of Psychology, The University of Hong Kong, Hong Kong SAR, China
[f] The State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, China
[g] Department of Sports Science and Physical Education, The Chinese University of Hong Kong, Hong Kong SAR, China
[h] Department of Orthopedic Surgery, Rush University Medical Centre, Chicago, United States

ARTICLE INFO

Handling editor: M Vitello

Keywords:
Chronic musculoskeletal pain
Sleep quality
Non-pharmacological interventions
Network meta-analysis

ABSTRACT

This network meta-analysis aimed to estimate the comparative effectiveness of non-pharmacological interventions on sleep in individuals with chronic musculoskeletal pain. Seven databases were systematically searched up to February 2023. A random-effects network meta-analysis in a frequentist framework was performed to synthesize continuous data as standardized mean differences (SMD) along with a 95% confidence interval (95% CI). A total of 15,641 records were identified, and 107 randomized controlled trials involving 9,121 participants were included. Of 14 identified interventions, eight were significantly more effective than passive control in improving sleep quality at immediate post-intervention (SMDs = 0.67–0.74), with cognitive behavioral therapy (CBT) being the most effective treatment (SMD = 0.74, 95% CI: 0.45–1.03). Only CBT demonstrated sustained effects at short-term (SMD = 1.56; 95% CI: 0.62–2.49) and mid-term (SMD = 1.23; 95% CI: 0.44–2.03) follow-ups. Furthermore, CBT significantly improved subjective (SMD = 0.64; 95% CI: 0.25–1.03) and objective (SMD = 0.30; 95% CI: 0.01–0.59) sleep efficiency compared with passive control at immediate post-intervention. Our findings support CBT as the first-line treatment for improving sleep in individuals with chronic musculoskeletal pain, given its superior effectiveness across multiple sleep outcomes and its sustainable effects until mid-term follow-up. However, the certainty of evidence for these interventions in improving sleep quality was very low to low.

1. Introduction

Chronic musculoskeletal pain is the leading cause of years lived with disability worldwide [1,2] and is often associated with sleep disturbance [3,4]. Over 70% of individuals with chronic musculoskeletal pain experience sleep-related issues [3,4]. Research suggests that sleep disturbance is a significant predictor of the onset of painful conditions in healthy individuals [5–7] and exacerbates pain-related disability leading to poor prognosis among those with chronic musculoskeletal pain [6,8]. Additionally, improving sleep disturbance has been associated with corresponding improvements in pain intensity and clinical outcomes in individuals with chronic musculoskeletal pain [9,10]. These findings highlight the importance of targeting sleep as a therapeutic intervention to prevent chronic pain or alleviate pain symptoms.

Pharmacological treatments have been shown to have short-term effectiveness in improving sleep quality and reducing sleep disturbance among individuals with chronic pain [11,12], but they are not recommended for prolonged usage due to the potential risks of dependency and adverse effects [11,13]. Prior pairwise meta-analyses

* Corresponding author. Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hung Hom, SAR, Hong Kong, China.
E-mail address: arnold.wong@ (A.YL. Wong).

https://doi.org/10.1016/j.smrv.2023.101867
Received 5 June 2023; Received in revised form 22 September 2023; Accepted 26 September 2023
Available online 19 October 2023

Access to the article: https://www.sciencedirect.com/science/article/pii/S1087079223001235

7.1 Abstract

Background: Sleep disturbance is a prevalent condition affecting over 70% of individuals with chronic musculoskeletal pain. Non-pharmacological interventions are commonly used to manage sleep disturbance in these individuals. We aimed to estimate the comparative effectiveness of these interventions on sleep in individuals with chronic musculoskeletal pain.

Methods: CINAHL, CENTRAL, Embase, Medline, PsycINFO, Web of Science, and the WHO International Clinical Trials were systematically searched from their inception to February 2023. The primary outcomes were sleep quality and acceptability of interventions, while the secondary outcomes included other subjective or objective sleep parameters, pain intensity, disability, and safety. A random-effects network meta-analysis in a frequentist framework was performed to synthesize continuous data as standardized mean differences (SMD) and dichotomous data as the odd ratios (OR) along with 95% confidence intervals (95% CIs).

Results: A total of 15,641 records were identified, and 107 randomized controlled trials (RCTs) involving 8,121 participants were included. Of 13 identified treatments, eight were significantly more effective than passive control in improving sleep quality at immediate post-intervention (SMDs = 0.67 to 0.74), with cognitive behavioral therapy (CBT) being the most effective treatment (SMD = 0.74, 95% CI: 0.45 to 1.03). Only CBT demonstrated sustained effects at short-term (SMD = 1.56; 95% CI: 0.62 to 2.49) and mid-term (SMD = 1.23; 95%CI: 0.44 to 2.03) follow-ups. Additionally, CBT significantly improved subjective (SMD = 0.64; 95% CI: 0.25 to 1.03) and objective (SMD = 0.30; 95% CI: 0.01 to 0.59) sleep efficiency compared with passive control at immediate post-intervention. Regarding the acceptability and safety, there were no differences in all-cause discontinuations between all included interventions and passive

control, but more mild adverse events were reported in education, exercise, mind-body exercise, CBT, and physical agendas than in passive control (ORs = 3.16 to 9.76).

Conclusions: Our findings support CBT as the first-line treatment for improving sleep in individuals with chronic musculoskeletal pain, given its superior effectiveness across multiple sleep outcomes and its sustainable effects until mid-term follow-up. However, more high-quality RCTs targeting sleep are warranted to validate these findings.

Keywords: chronic musculoskeletal pain; sleep quality; non-pharmacological interventions; network meta-analysis.

7.2 Introduction

Chronic musculoskeletal pain is the leading cause of years lived with disability worldwide [424, 425] and is often associated with sleep disturbance [8, 272]. Over 70% of individuals with chronic musculoskeletal pain experience sleep-related issues [8, 272]. Research suggests that sleep disturbance is a significant predictor of the onset of painful conditions in healthy individuals [27, 37, 183] and exacerbates pain-related disability leading to poor prognosis among those with chronic musculoskeletal pain [10, 183]. Additionally, improving sleep disturbance has been associated with corresponding improvements in pain intensity and clinical outcomes in individuals with chronic musculoskeletal pain [38, 426]. These findings highlight the importance of targeting sleep as a therapeutic intervention to prevent chronic pain or alleviate pain symptoms.

Pharmacological treatments have been shown to have short-term effectiveness in improving sleep quality and reducing sleep disturbance among individuals with chronic pain [198, 199], but

they are not recommended for prolonged usage due to the potential risks of dependency and adverse effects [198, 202]. Prior pairwise meta-analyses have also demonstrated promising results for non-pharmacological interventions in addressing sleep disturbance in individuals with chronic pain [40-45]. However, these analyses only allow head-to-head comparisons of two treatments [427]. They could not estimate the comparative effectiveness of all available interventions simultaneously [427]. To address these limitations, our study conducted a systematic review and network meta-analysis (NMA) of randomized controlled trials (RCTs) to comprehensively evaluate the comparative effectiveness of non-pharmacological treatments on sleep in individuals with chronic musculoskeletal pain.

7.3 Methods

7.3.1 Search Strategy and Selection Criteria

This systematic review and NMA was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines [216] and its extension for NMA [428]. The protocol was registered with PROSPERO (CRD42023395007).

CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Medline, PsycINFO, Web of Science, and the WHO International Clinical Trials Registry Platform were searched from their inception to February 13, 2023. Three keywords and related synonyms from medical subject headings were combined using appropriate truncation and Boolean operators in the title and abstract fields: “chronic pain”, “sleep”, and “clinical trial”. The search strategies were reviewed by an experienced librarian and presented in **Appendix 14**. Additionally, the reference lists of included studies and relevant systematic reviews [40-44, 206, 429] were

manually screened to identify potential publications.

Two independent reviewers screened the titles and abstracts to determine eligibility for full-text screening. Piloting on the first 100 citations of titles and abstracts was performed to ensure a reasonable agreement between reviewers using the kappa coefficient (*k*), where the agreement was classified as (0-0.20), fair (0.21-0.40), moderate (0.41-60), good (0.61-80), or excellent (0.81 to 1.00) [217]. Any disagreements in screening were resolved by discussing with a third reviewer. The full-text screening followed the same procedures.

Inclusion and exclusion criteria were defined based on the Populations, Intervention, Comparison, Outcomes, and Study Design (PICOS) framework (**Appendix 15** for more details) [428]. Studies were included if they (1) were RCTs with a parallel-group design or cluster design involving individuals aged 18 years or older with chronic musculoskeletal pain (a duration ≥ three months) according to the multidimensional diagnostic criteria [430] and the ICD-11 for chronic pain [58]; (2) involved non-pharmacological treatments that were classified into prespecified treatment nodes based on the clinical practice guideline [431] or other NMA [432, 433] (**Table 11**); (3) had at least one control arm involving either an inactive or active intervention; (4) assessed at least one sleep parameter (e.g., sleep quality, sleep efficiency, sleep onset latency, total sleep time, or wake time after sleep onset); and (5) were published in English peer-reviewed journals. Exclusion criteria were studies (1) that involved individuals with acute pain or other types of pain [58]; (2) only included pharmacological interventions or multiple co-interventions [434]; (3) were reviews, cross-over RCTs, secondary analyses, quasi-experimental studies, or conference abstracts; or (4) had no full-text articles or insufficient data even after

contacting the corresponding authors.

7.3.2 Outcomes

The primary outcome was subjective sleep quality as assessed by valid questionnaires/scales. The secondary outcomes included other subjective and objective sleep parameters (e.g., sleep efficiency, sleep onset latency, total sleep time, or wake time after sleep onset), pain intensity, disability, the acceptability of interventions (measured as the proportion of participants who withdrew from the studies for any reason during the intervention period) [435], and the safety of interventions (measured as the proportion of participants who experienced any treatment-related adverse events during the intervention period) [436]. The primary endpoint was immediate post-intervention, while follow-up points were categorized as short-term (closest to 3 months post-intervention), mid-term (closest to 6 months post-intervention), and long-term (closest to 12 months post-intervention) follow-up [436].

7.3.3 Data Extraction and Quality Assessment

Two independent reviewers extracted data from the included studies using a standardized form. Any discrepancies were resolved by consensus or discussion with a third reviewer. The extracted data included: (1) bibliometric data; (2) study design; (3) participants' characteristics; (5) characteristics of intervention and control groups; (6) primary and secondary outcomes of interest at post-intervention and follow-up. **Appendix 15** provides details on the data extraction process. Two independent reviewers assessed the methodological quality of eligible studies using the Cochrane Collaboration risk of bias (RoB) 2.0 tool. A third reviewer was consulted if disagreements persisted. The overall risk of bias was rated as low, some concerns, or high based

on the results of each domain [218, 219].

7.3.4 Data Analysis

Pairwise meta-analysis for each outcome was first conducted using the random-effects model for available direct comparisons. The effect size was summarized as standardized mean differences (SMDs) for continuous outcomes and odds ratios (ORs) for dichotomous outcomes, accompanied by a 95% confidence interval (95% CI). The Cochrane Q test and I^2 assessed statistical heterogeneity across studies, with significant heterogeneity indicated by a $p < 0.10$ and $I^2 > 50\%$ [437].

A random-effects NMA in a frequentist framework was adopted to synthesize direct and indirect evidence simultaneously. All analyses were conducted using STATA 16.1 (Stata Corp, Texas, USA) and R 4.0.4 (R Core Team, Vienna, Austria) with the statistical package [438-440]. To check the transitivity assumption, we visually inspected the relative distribution of effect modifiers (age, sex, baseline severity of pain and sleep, duration of the treatment) across interventions and pairwise comparisons [435]. The inconsistency assumption between the indirect and direct evidence within the network was assessed using local (the node-splitting method) and global (the design-by-treatment interaction method) models [441]. The heterogeneity of the entire NMA model was estimated by a common heterogeneity variance (τ^2) as compared to empirical distributions [442, 443]. The surface under the cumulative ranking curves (SUCRA) was plotted to establish the hierarchy of each intervention in the NMA, where a larger SUCRA value indicated a higher rank for the intervention [444]. If 10 or more studies were available for a given outcome, we used a comparison-adjusted funnel plot and Egger's

regression test to evaluate small-study effects in NMA [225].

To evaluate the robustness of our primary outcome, we conducted sensitivity analyses by removing studies with a high risk of bias or with a sample size < 20. Furthermore, meta-regression analyses were performed to explore the effects of demographic characteristics (age, percentage of females, and sample size) and clinical covariates (baseline pain intensity, baseline sleep severity, and treatment duration) on sleep quality. The certainty of evidence for sleep quality was appraised within the Confidence in Network Meta-Analysis (CINeMA) framework [445, 446].

7.4 Results

7.4.1 Study Selection

Initially, 10,336 records were identified from databases and registries. After removing 1,090 duplicates, 8,246 records underwent the title and abstract screening. Subsequently, 286 full-text articles were scrutinized, and 100 studies were included. An additional 5,305 records were identified through references of the included studies and relevant reviews. Seven additional studies met the selection criteria and were included in the NMA (**Figure 9**). The inter-reviewer reliability for the abstract (k = 0.84) and full-text (k = 0.76) screening was high to excellent.

7.4.2 Study Characteristics

Table 12 presents the general characteristics of the 107 included studies, which involved a total of 8,121 participants with a mean age of 51.8 years, and 87.1% of them were female. The included studies were published from 1991 to 2022, with the majority conducted in Europe

(38.3%) and North America (32.7%). Most of the included studies focused on fibromyalgia (59.8%), osteoarthritis (11.1%), and chronic low back pain (9.3%). The majority of the included studies (80.4%) allowed participants to take medications at baseline. However, only 22.4 % of these studies detailed the inclusion criteria for sleep disturbances or insomnia. The mean scores for sleep quality and pain at baseline were transformed into standardized 100-point scales [436], with values of 54.1 (SD = 14.8) and 57.4 (SD = 14.5), respectively. The average treatment duration for the 14 interventions was 8.2 weeks (SD = 4.8). **Appendix 16** summarizes the characteristics of each included study.

7.4.3 Risk of Bias and Publication Bias

The risk of bias assessment is summarized in **Appendix 17**, with excellent inter-reviewer reliability ($k = 0.93$). Out of the 107 included studies, one (0.9%) was rated as low risk of bias, 74 (69.2%) as some concerns, and 32 (29.9%) as high risk of bias. The most common risks of bias were unclear randomization processes, unblinded assessors, and improper handling of missing data. No small-study effects were found using the comparison-adjusted funnel plots and Egger test results (

Appendix 18).

7.4.4 Pairwise Meta-analysis

The pairwise meta-analyses for primary and secondary outcomes are presented in **Appendix 19**. Significant improvements in sleep quality at immediate post-intervention were observed in CBT, exercise, manual therapy, mind-body exercise, mindfulness-based psychotherapy, and relaxation as compared to passive control (SMD = 0.38-1.79). Likewise, significant immediate post-intervention improvements in pain intensity (SMD = 0.33-0.81) and disability (SMD = 0.29-0.87) were observed for CBT, education, exercise, manual therapy, mind-body exercise, or mindfulness-based psychotherapy as compared to passive control. Regarding immediate post-intervention changes in subjective sleep parameters, CBT yielded significantly higher sleep efficiency, shorter sleep onset latency, and shorter wake time after sleep onset as compared to passive control (SMD = 0.48-0.61). However, there were no significant differences among the interventions in objective sleep parameters (assessed by actigraphy or polysomnography), acceptability, and safety.

7.4.5 NMA Assumptions

No clear evidence of violations of the transitivity assumption was found when we checked the distribution of potential modifiers across interventions and comparisons (**Appendix 20**). The common heterogeneity variance (τ^2) within the empirical distribution ranged from 0.00 to 0.48, indicating low to moderate heterogeneity (**Appendix 21**) [442, 443]. The design-by-treatment model did not detect any global inconsistency in each NMA. However, small percentages of local inconsistency were observed between some comparisons in sleep quality at immediate post-

intervention (1/36 loops), acceptability (2/35 loops), pain immediate post-intervention (1/35 loops) and at mid-term follow-up (1/17 loops), as well as disability at immediate post-intervention (1/29 loops) (**Appendix 22**).

7.4.6 NMA for Primary Outcomes

Sleep Quality

Figure 10 presents the network plot for sleep quality at immediate post-intervention, including 104 studies and 7,074 participants. **Table 13** displays the comparative effectiveness of 14 different interventions. Among these interventions, CBT, exercise, manual therapy, mind-body exercise, mindfulness-based psychotherapy, non-invasive brain stimulation, physical agents, and relaxation significantly improved sleep quality as compared to both passive control (SMD = 0.61-0.74) and inert treatment (SMD = 0.54-0.67). The ranking of treatment based on SUCRAs indicated that CBT (SUCRA = 76.5%) was the most effective treatment to improve sleep quality, followed by exercise (SUCRA = 69.2%) and mind-body exercise (SUCRA = 69.0%).

Additional information on network plots, SUCRAs, and league tables for follow-ups are presented in **Appendix 23** to **Appendix 25**. Only CBT significantly improved sleep quality at short-term (SMD = 1.56; 95% CI: 0.62-2.49) and mid-term (SMD = 1.23; 95% CI: 0.44-2.03) follow-ups as compared to passive control. CBT was ranked as the best treatment among 11 interventions (involving 24 RCTs and 1,671 participants; SUCRA = 76.5%) and nine interventions (involving 23 RCTs and 2,652 participants; SUCRA = 71.1%) at short-term and mid-term follow-ups, respectively. Results from the NMA and SUCRAs suggested that the most effective treatment for improving sleep quality at long-term follow-up was mind-body exercise

(SUCRA = 71.1%) among seven interventions (involving six RCTs and 682 participants), followed by CBT (SUCRA = 62.7%) and exercise (SUCRA = 57.9%).

7.4.7 NMA for Secondary Outcomes

Objective Sleep Parameters

Appendix 23 to **Appendix 25** summarize the results for objective sleep parameters at immediate post-intervention. Acupuncture (SMD = 0.91; 95% CI: 0.15-1.68) and CBT (SMD = 0.30; 95% CI: 0.01-0.59) significantly increased sleep efficiency as compared to passive control. Relaxation yielded significantly shorter sleep onset latency than the other seven identified interventions (SMD = 1.00-2.40). Only acupuncture showed a significantly longer total sleep time as compared to passive control (SMD = 1.01; 95% CI: 0.22-1.80) and CBT (SMD = 0.84; 95% CI: 0.13-1.54). No significant difference was found among the six identified interventions regarding wake time after sleep onset. The SUCRAs revealed that the most effective treatment for objective sleep efficiency, sleep onset latency, total sleep time, and wake time after sleep onset was acupuncture (SUCRA = 94.2%), relaxation (SUCRA = 99.5%), acupuncture (SUCRA = 94%), and physical agents (SUCRA = 85.6%), respectively.

Subjective Sleep Parameters

Appendix 23 to **Appendix 25** provide detailed information on each subjective sleep parameter at immediate post-intervention. Overall, the results showed that CBT yielded significantly superior sleep efficiency (SMD = 0.64; 95% CI: 0.25-1.03), shorter sleep onset latency (SMD = 0.70; 95% CI: 0.05-1.35), and shorter wake time after sleep onset (SMD = 0.47; 95% CI: 0.18-0.76) as compared to passive control. However, no significant difference was found across the seven

identified interventions in total sleep time. According to SUCRAs, CBT was the most effective intervention for improving sleep efficiency (SUCRA = 86.6%), sleep onset latency (SUCRA = 74.5%), and wake time after sleep (SUCRA = 87.6%).

Pain

The NMA for pain at immediate post-intervention included 99 RCTs with a total of 6,699 participants. Results indicated that 10 identified interventions significantly mitigated pain intensity as compared to control groups (SMD = 0.35-0.94), except for assistive technique, education, and inert treatment. According to SUCRA, the most effective treatment was mind-body exercise (93.2%), followed by acupuncture (86.5%) and non-invasive brain stimulation (78.9%). Detailed information for pain at follow-ups is presented in **Appendix 23** to **Appendix 25**. Acupuncture (SUCRA = 94.6%), mind-body exercise (SUCRA = 83.0%), and CBT (SUCRA = 85.4%) were the most effective treatments for pain reduction at short-term, mid-term, and long-term follow-ups, respectively.

Disability

A total of 72 RCTs involving 14 interventions and 4,945 participants contributed to the NMA for disability at immediate post-intervention. Mind-body exercise (SUCRA=95.4%), non-invasive brain stimulation (SUCRA = 80.1%), exercise (SUCRA = 73.4%), CBT (SUCRA = 65.6%), and mindfulness-based psychotherapy (SUCRA = 63.2%) had the highest probabilities of being the most effective five treatments for improving disability as compared to passive control (SMD = 0.47-0.87). The follow-up results showed that CBT (SUCRA = 78.6%) and mind-body exercise

(SUCRA = 62.2%) were the most effective treatments for improving disability at short-term and mid-term follow-ups, respectively (**Appendix 23** to **Appendix 25**).

Acceptability

The NMA for treatment acceptability included 104 studies with 14 interventions and a total of 7,803 participants. No significant difference was found between all included interventions and passive control in acceptability. However, manual therapy had significantly higher acceptability than CBT (OR = 2.81; 95% CI: 1.11-7.10) and mindfulness-based psychotherapy (OR = 2.99; 95% CI: 1.16-7.70). According to SUCRAs, the most highly ranked intervention for low dropout rate was manual therapy (SUCRA = 92.9%), followed by mind-body exercise (SUCRA = 66.8%) and education (SUCRA = 65.8%) (**Appendix 23** to **Appendix 25**).

Safety

Forty-seven RCTs involving 14 interventions with 3,425 participants reported adverse events during treatments. No included RCT reported serious adverse events. Common adverse events included pain exacerbation and psychological problems (**Appendix 26**). The NMA results showed that CBT, education, exercise, mind-body exercise, and physical agendas caused significantly more adverse events than passive control (OR = 3.16-9.76). The SUCRAs showed that passive control (SUCRA = 84.1%) had the lowest reported adverse events, followed by manual therapy (SUCRA = 70.6%) and relaxation (SUCRA = 60.9%) (**Appendix 23** to **Appendix 25**).

7.4.8 Additional Analysis

The sensitivity analyses based on the risk of bias and sample size for sleep quality were generally consistent with the original analyses (**Appendix 27**). Meta-regression for potential modifiers showed that none of the regression factors (sample size, age, gender, baseline sleep and pain severity, and treatment duration) significantly impacted the original results (**Appendix 28**). However, the certainty of evidence for interventions improving sleep quality in the estimates was very low to low (**Appendix 29**).

7.5 Discussion

This is the first NMA to quantify the comparative effectiveness of non-pharmacological interventions for sleep based on data from 8,121 individuals with chronic musculoskeletal pain in 107 RCTs. The results indicated that several non-pharmacological interventions were significantly better than passive control in improving sleep quality, sleep parameters, pain, and disability at immediate post-intervention. Given the consistent evidence across multiple sleep outcomes and time points, CBT appears to be a first-line treatment option for improving sleep in individuals with chronic musculoskeletal pain. These findings can help inform evidence-based practice and guide clinicians, healthcare providers, and policymakers in deciding on the most effective non-pharmacological interventions for sleep.

Although the available evidence consistently supports the prescription of sleep interventions for managing chronic musculoskeletal pain [183, 272, 447], there is limited guidance on which non-pharmacological intervention to recommend. Our systematic review and NMA summarized the comparative effectiveness of various non-pharmacological interventions and revealed that eight

of them significantly improved sleep quality immediately post-intervention than passive control. These findings were in line with previous pairwise meta-analyses suggesting that CBT [41, 205], mind-body exercise [208], exercise [207], non-invasive brain stimulation [207, 209], mindfulness-based psychotherapy [207], and relaxation [210] were effective in improving sleep quality in individuals with chronic musculoskeletal pain. Notably, CBT was the most effective intervention immediately post-intervention and showed sustained beneficial effects on sleep quality at short- and mid-term follow-ups. This may be attributed to the fact that CBT, especially CBT for insomnia, aims to address patients' maladaptive beliefs and behaviors that contribute to the maintenance of insomnia [448, 449], which may lead to sustained improvements in sleep over time [41, 450]. Conversely, other interventions did not show significantly better therapeutic effects than passive control at follow-ups. Further RCTs should optimize current treatment protocols and enhance long-term treatment effects on sleep quality in individuals with chronic musculoskeletal pain.

The NMA results revealed that CBT was significantly better than passive control in improving multiple sleep parameters, including subjective sleep efficiency, sleep onset latency, wake time after sleep onset, and objective sleep efficiency. These findings are consistent with previous pairwise meta-analyses of CBT for sleep in chronic pain [41, 205, 206] and collectively support that CBT may be a highly effective first-line treatment option for improving sleep in individuals with chronic musculoskeletal pain. However, our study showed inconsistent patterns between subjective and objective sleep parameters, with CBT showing more robust improvements in sleep diary-related outcomes than actigraphy- or polysomnography-measured sleep parameters, which is in line with previous meta-analyses [451, 452]. This discrepancy may be explained by

the low sensitivity of objective sleep measurements to the subjective perception of insomnia symptoms [452, 453] and the weak correlation between subjective and objective sleep measurements in both insomnia [454] and chronic pain conditions [455]. As the pooled analyses for sleep parameters in this NMA were dependent on the data from few direct comparisons, further research is needed to determine the effects of non-pharmacological interventions on these outcomes to better understand how different interventions impact subjective and objective sleep measurements in individuals with chronic musculoskeletal pain.

Our study also demonstrated that the majority of the identified interventions significantly reduced pain intensity, and five of the included interventions significantly improved disability. These results concur with previous research that improved sleep variables were associated with the corresponding alleviation of pain-related symptoms in individuals with chronic musculoskeletal pain [38, 426]. Notably, the comparative effectiveness and ranking of the included interventions varied depending on the outcome measures being evaluated (e.g., sleep quality, pain intensity, and disability). The differential effectiveness of interventions on different outcomes highlights the potential value of incorporating sleep-specific interventions and pain management to address the multifaceted symptoms of chronic musculoskeletal pain [17, 207]. These findings also indicate that further research is warranted to elucidate the effects of sleep interventions on sleep and pain-related outcomes.

When selecting treatment for improving sleep in individuals with chronic musculoskeletal pain, it is important to consider its feasibility, including high adherence and low incidence of adverse events [456]. These factors are critical aspects that can impact treatment effectiveness [457, 458].

However, there is limited evidence available on the comparative acceptability and safety of non-pharmacological interventions for sleep in individuals with chronic musculoskeletal pain. Our results indicated that manual therapy had significantly fewer all-cause discontinuations than CBT and mindfulness-based psychotherapy, which is consistent with the high attrition rates observed in psychotherapy [459]. A possible explanation is that psychological interventions typically require long-term planning and persistence to relieve symptoms, and participants may not be willing to endure the process [460]. In terms of safety, most included studies weakly defined adverse events. The NMA results demonstrated that CBT, exercise, mind-body exercise, physical agents, and education caused more adverse events than passive control. These findings underscore the need to develop strategies to improve compliance and monitor side effects of these treatments in clinical settings.

Our NMA has several limitations that should be considered when interpreting the results. First, some interventions were only investigated by a few studies (e.g., acupuncture, assistive technique, relaxation), leading to thinly connected networks and underpowered estimates to detect possible differences [461]. Second, although we classified treatments according to previous guidelines [431] and other NMA [432, 433], grouping several similar treatments as one node might introduce potential heterogeneity. Third, the risk of bias of the included studies was graded as some concerns or high, which reduced the certainty of evidence. Therefore, future research is likely to change the existing effect sizes and treatment rankings [445, 446]. Fourth, while the node-splitting method revealed some local inconsistency in certain outcomes, our NMA results should still be valid as the inconsistency was small (2.8% to 5.9%), and there were no clear transitivity violations or evident moderators [462]. Fifth, our study did not explore the

effects of different delivery characteristics of interventions (e.g., intensity, frequency, delivery type). A considerable variation in interventions might have confounded our results. Sixth, only few studies investigated the long-term effects of interventions on various sleep parameters. Future studies should evaluate the long-term effects of sleep interventions in this population. Seventh, only English articles were included, which may have limited the generalizability of our findings. However, research has found that excluding non-English studies from systematic reviews had a minimal effect on the overall conclusions [463].

7.6 Conclusions

The current systematic review and NMA provide empirical evidence supporting CBT as a first-line treatment option for sleep in individuals with chronic musculoskeletal pain, given its consistent evidence of effectiveness across multiple sleep outcomes and time points. Our findings also suggest that several alternative treatments could improve sleep quality in this population. While our findings provide the most comprehensive evidence to date to guide the choice of non-pharmacological interventions for sleep in individuals with chronic musculoskeletal pain, further high-quality RCTs targeting sleep are warranted to validate these findings. These studies should also evaluate the long-term effects of these treatment on multiple sleep parameters.

7.7 Tables

Table 11. Definitions of each intervention and control

Nodes	Definition of intervention
Acupuncture	The needles are inserted into the classical meridian, extra, painful, or trigger points. Acupressure is also classified in this group because it is based on the same acupuncture paradigm. Type: acupuncture, acupressure, auricular acupressure, dry needling, or electroacupuncture.
Assistive technique	Assistive devices are designed to improve an individual's functioning and quality of life. Type: lumbar support, mattress, or pillows.
Cognitive behavioral therapy (CBT)	Cognitive behavioral therapy is designed to solve current problems and change unhelpful patterns in cognition, behaviors, and emotional regulation. Type: CBT for pain, CBT for insomnia, CBT for pain and insomnia, cognitive therapy, behavioral therapy, exposure, or graded activity.
Education	Any kind of advice to stay active, printed educational material, pain education (neurobiology and neurophysiology of pain), or sleep hygiene.
Exercise	Exercise training is designed to improve the muscle strength, stabilization, capacity of the cardiorespiratory system, or muscle lengthening. Type: aerobic exercise (e.g., walking, cycling, jogging), resistance training, stabilization (motor control), stretching (passive, static, isometric, ballistic or proprioceptive neuromuscular facilitation), water-based exercise, or multimodal exercise (involving two or more types of exercise mentioned above).
Manual therapy	Manual therapy encompasses numerous "hands-on" treatments. Type: chiropractic, mobilization, myofascial therapy, reflexology, Shiatsu, soft tissue massage, or trigger point therapy.
Mind-body exercise	Mind-body exercise is a series of specific movements with the characteristics of slow physical movements, coordinated body, or breath awareness. Type: Pilates, Qi gong (Baduanjin or Wuqinxi), Tai Chi, or Yoga.
Mindfulness-based psychotherapy (Mindful psychotherapy)	Mindfulness-based psychotherapy or mindful psychotherapy prioritizes the holistic promotion of health and well-being, which incorporates acceptance and mindfulness-based strategies. Type: acceptance and commitment therapy or mindfulness-based stress reduction.
Non-invasive brain stimulation	Brain activity is modulated by non-invasive stimulation. Types: cranial electrotherapy stimulation, repetitive transcranial magnetic stimulation, transcranial alternating current stimulation, or transcranial direct current stimulation.
Nutritional therapy	Nutritional therapy aims to alter dietary strategy or include prescribed supplements. Type: Dietary intervention or nutritional supplements.
Physical agents	Physical modalities are applied externally on the painful points (limbs or trunk) without breaking or piercing the skin. Type: cryotherapy and therapeutic heat, cupping therapy, electromagnetic therapy, infrared radiation, laser therapy, shock-wave therapy, spa therapy (balneotherapy), transcutaneous electrical nerve stimulation, or ultrasound.

Relaxation	Relaxation techniques are therapeutic training designed to produce the body's natural relaxation response. Type: biofeedback relaxation, breathing techniques, guided imaginary intervention, music, or progressive muscle relaxation.
Inert treatment	Any kind of sham or placebo therapy.
Passive control	No treatment, waiting list control, treatment as usual, keeping daily routine activity, or standard care provided by general practitioners (eg, medications).

Table 12. General characteristics of included studies

Characteristics	**All studies (n = 107)**
Continent, n (%)	
Africa	2 (1.9)
Asia	18 (16.8)
Europe	41 (38.3)
North America	35 (32.7)
Oceania	1 (0.9)
South America	10 (9.3)
Population source, n (%)	
General population	24 (22.4)
Healthcare	46 (43.0)
Mixed	30 (28.0)
No information	7 (6.5)
Outcome measures, n (%)	
Sleep quality	104 (97.2)
Acceptability	104 (97.2)
Objective sleep parameters	11 (10.3)
Subjective sleep parameters	9 (8.4)
Pain	99 (92.5)
Disability	72 (67.3)
Safety	47 (43.9)
Follow-up periods, n (%)	
Post-intervention	105 (98.1)
Short-term (closest to 3 months)	25 (23.4)
Mid-term (closest to 6 months)	23 (21.5)
Long-term (closest to 12 months)	6 (5.6)
Total participants at baseline, n	8,121
Age of participants (year), mean (95% CI)	51.8 (50.8, 52.9)
Female participants (%), mean (95% CI)	87.1 (84.7, 89.5)
Category of chronic musculoskeletal pain, n (%)	
Ankylosing spondylitis	2 (1.9)
Chronic low back pain	10 (9.3)
Chronic myofascial pain syndrome	2 (1.9)
Chronic neck pain	1 (0.9)
Fibromyalgia	64 (59.8)
Osteoarthritis	13 (11.1)
Rheumatoid arthritis	9 (8.4)
Mixed conditions	6 (5.6)
Insomnia diagnosis, n (%)	24 (22.4)
Medications, n (%)	
Yes	86 (80.4)
No	8 (7.5)
No information	13 (12.1)

Table 13. The league table for sleep quality at immediate post-intervention

CBT														
0.06 (-0.31,0.44)	**Exercise**													
0.06 (-0.33,0.45)	-0.00 (-0.33,0.32)	**Mind-body exercise**												
0.07 (-0.50,0.64)	0.01 (-0.56,0.58)	0.01 (-0.56,0.59)	**Non-invasive brain stimulation**											
0.08 (-0.45,0.62)	0.02 (-0.51,0.56)	0.02 (-0.50,0.55)	0.01 (-0.66,0.68)	**Manual therapy**										
0.08 (-0.62,0.79)	0.02 (-0.68,0.73)	0.03 (-0.68,0.74)	0.01 (-0.72,0.74)	0.00 (-0.78,0.79)	**Acupuncture**									
0.10 (-0.33,0.53)	0.04 (-0.41,0.50)	0.05 (-0.43,0.52)	0.03 (-0.60,0.66)	0.02 (-0.57,0.61)	0.02 (-0.73,0.77)	**Mindful psychotherapy**								
0.11 (-0.37,0.60)	0.05 (-0.42,0.53)	0.06 (-0.44,0.55)	0.04 (-0.57,0.65)	0.03 (-0.52,0.58)	0.03 (-0.72,0.77)	0.01 (-0.53,0.55)	**Relaxation**							
0.13 (-0.41,0.67)	0.07 (-0.42,0.56)	0.07 (-0.47,0.61)	0.06 (-0.55,0.66)	0.05 (-0.61,0.70)	0.05 (-0.71,0.80)	0.03 (-0.58,0.63)	0.02 (-0.59,0.62)	**Physical agents**						
0.46 (-0.24,1.17)	0.40 (-0.31,1.11)	0.40 (-0.31,1.12)	0.39 (-0.35,1.13)	0.38 (-0.42,1.18)	0.38 (-0.49,1.25)	0.36 (-0.40,1.12)	0.35 (-0.41,1.10)	0.33 (-0.43,1.09)	**Nutritional therapy**					
0.47 (0.12,0.83)	**0.41 (0.02,0.80)**	**0.41 (0.03,0.80)**	0.40 (-0.20,1.00)	0.39 (-0.17,0.95)	0.39 (-0.34,1.11)	0.37 (-0.12,0.86)	0.36 (-0.15,0.86)	0.34 (-0.22,0.91)	0.01 (-0.69,0.71)	**Education**				
0.80 (-0.13,1.72)	0.74 (-0.19,1.66)	0.74 (-0.19,1.67)	0.73 (-0.26,1.71)	0.72 (-0.28,1.71)	0.71 (-0.36,1.79)	0.69 (-0.27,1.65)	0.68 (-0.28,1.65)	0.67 (-0.32,1.65)	0.34 (-0.75,1.42)	0.33 (-0.62,1.27)	**Assistive technique**			
0.67 (0.26,1.09)	**0.61 (0.20,1.02)**	**0.61 (0.19,1.04)**	**0.60 (0.21,0.99)**	**0.59 (0.05,1.13)**	0.59 (-0.03,1.20)	**0.57 (0.08,1.06)**	**0.56 (0.09,1.03)**	**0.54 (0.08,1.01)**	0.21 (-0.41,0.83)	0.20 (-0.25,0.65)	-0.13 (-1.03,0.78)	**Inert treatment**		
0.74 (0.45,1.03)	**0.68 (0.36,1.00)**	**0.68 (0.36,1.00)**	**0.67 (0.13,1.21)**	**0.66 (0.19,1.13)**	0.66 (-0.01,1.32)	**0.64 (0.24,1.03)**	**0.63 (0.20,1.06)**	**0.61 (0.10,1.12)**	0.28 (-0.41,0.97)	0.27 (-0.10,0.63)	-0.06 (-0.95,0.83)	0.07 (-0.30,0.44)	**Passive control**	

Abbreviation: CBT: Cognitive Behavioral Therapy.

Footnote: Results are presented as standardized mean difference and 95% confidence intervals. For each comparison (column vs. row) a difference > 0 indicates the intervention in the column is superior to the comparator in the row. Numbers in bold represent statistically significant results.

7.8 Figures

Figure 9. A flow chart of literature searches

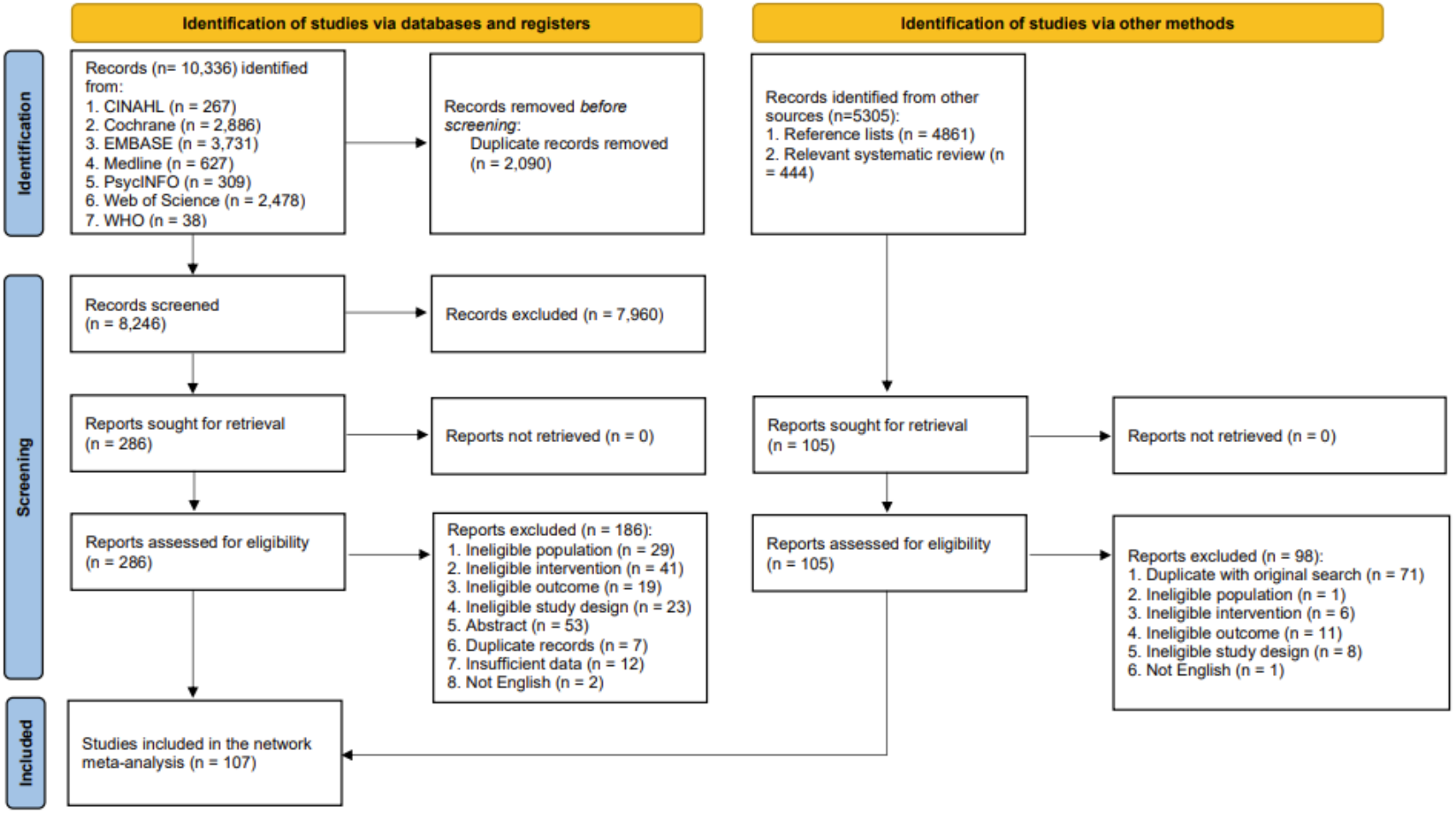
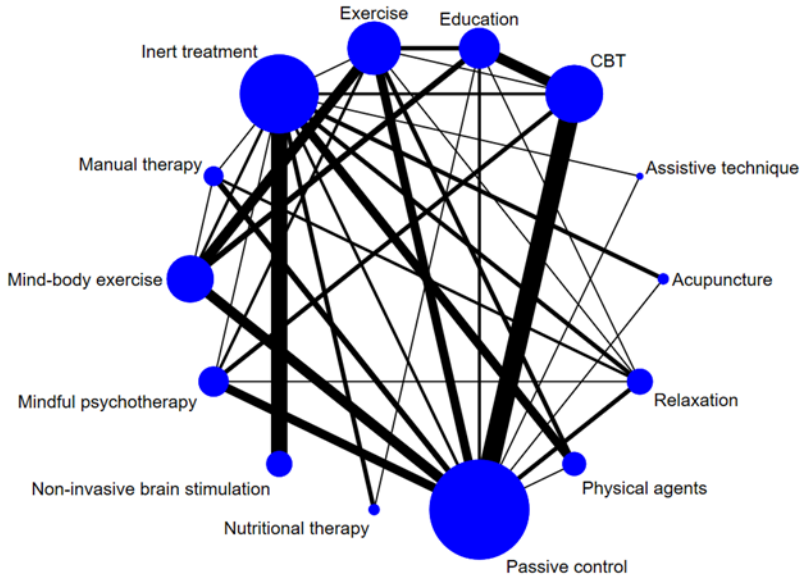


Figure 10. The network plot for sleep quality at immediate post-intervention



Abbreviation: CBT: Cognitive Behavioral Therapy.

Footnote: The size of the nodes is weighted by the number of participants for that intervention, and the width of the edges is weighted by the number of studies for that comparison.

Chapter 8 The Efficacy and Safety of Repetitive Transcranial Magnetic Stimulation (rTMS) in Managing Individuals with Chronic Low Back Pain and Comorbid Insomnia: A Pilot Randomized Controlled Trial

8.1 Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) has demonstrated effectiveness for treating chronic pain or insomnia independently. Given the high prevalence of insomnia in individuals with chronic low back pain (CLBP), this pilot randomized controlled trial assessed the feasibility, acceptability, and preliminary efficacy of rTMS targeting either the left primary motor cortex (M1) or right dorsolateral prefrontal cortex (DLPFC) in individuals with comorbid CLBP and insomnia.

Methods: Thirty-six participants were randomized to receive sham-rTMS, active M1-rTMS (10Hz, 1,500 pulses), or active DLPFC-rTMS (1Hz, 1,500 pulses) over 10 sessions for two weeks (five sessions per week), with a one-month follow-up. Primary outcomes were feasibility and acceptability. Secondary outcomes involved pain intensity, insomnia severity, disability, psychological measures, subjective and objective sleep parameters, and pain perception. This study was registered with ClinicalTrials.gov (NCT06158321).

Results: rTMS was highly feasible and acceptable, as evidenced by excellent session attendance and no participant attrition. No serious adverse events were reported. Both active M1- and DLPFC-rTMS significantly reduced pain intensity and enhanced the descending pain inhibitory pathways compared with sham stimulation. Importantly, DLPFC-rTMS was superior to sham in reducing insomnia severity, objective wake after sleep onset, and temporal summation of pain.

Conclusions: rTMS is a feasible, well-tolerated, and promising intervention for individuals with comorbid CLBP and insomnia. While both stimulation protocols yielded analgesic benefits, DLPFC-rTMS may confer additional advantages for addressing sleep disturbance.

Further full-scale randomized clinical trials are warranted to validate these preliminary findings and optimize rTMS protocols for this complex clinical population.

Key words: Repetitive transcranial magnetic stimulation; Chronic low back pain; Insomnia; Pilot randomized controlled trial; Feasibility.

8.2 Introduction

Sleep disturbance, especially insomnia, is a common complaint, impacting more than 70% of individuals with chronic low back pain (CLBP) [8]. Emerging evidence indicates that sleep disturbance raises the risk of developing chronic pain disorders [9] and worsens pain intensity, functional disability, and prognosis in individuals with CLBP [10, 11]. Additionally, the coexistence of CLBP and insomnia is linked to greater emotional distress and altered pain perception, including heightened pain sensitivity to mechanical and pressure stimuli and dysfunction in the descending pain inhibitory system [12, 13]. These maladaptive psychological and physiological alterations may contribute to increased healthcare utilization and challenges in pain management. For instance, a longitudinal study reported a 2.1-fold higher hospitalization rate in patients with these comorbid conditions relative to those without sleep disturbances, imposing substantial individual and societal burdens [14]. As such, it is imperative to attend to the comorbidity of CLBP and comorbid insomnia and develop targeted therapeutic interventions.

Current evidence for treating these comorbid conditions is limited. Most research has centered on cognitive behavioral therapy (CBT) [41]. Our recent network meta-analysis

identified CBT as the most effective treatment for enhancing sleep quality and efficiency in people with chronic musculoskeletal pain [46], yet its clinical implementation is challenged by low adherence, high costs, and a shortage of trained therapists in primary care settings [47, 48]. These limitations highlight the need for novel and effective treatment strategies. Given that comorbid chronic pain and insomnia may involve in dysregulated central pain processing and abnormal neural oscillations [12, 49], targeted brain modulation approaches could potentially restore these imbalances and improve clinical outcomes.

Repetitive transcranial magnetic stimulation (rTMS) is a well-accepted and noninvasive neurotherapeutic technique that modulates cortical excitability, synaptic plasticity, and functional connectivity across a range of neurological and neuropsychiatric disorders [50, 51]. When applied at specific frequencies to targeted brain regions, rTMS has yielded promising results for improving either chronic pain or insomnia independently [52-57]. High-frequency rTMS targeting on the primary motor cortex (M1) has been demonstrated to significantly reduce pain intensity while enhancing descending pain modulation in individuals with chronic pain [54, 55]. Conversely, the hyperarousal model in insomnia suggests that inhibitory rTMS may mitigate excessive excitatory brain activity. This is supported by systematic reviews, indicating that low-intensity rTMS over the dorsolateral prefrontal cortex (DLPFC) significantly improves sleep quality and other sleep parameters [53, 57]. However, the effectiveness of inhibitory rTMS over DLPFC for chronic pain remains inconclusive [54, 56].

To our knowledge, no studies have directly evaluated the comparative efficacy of various rTMS protocols for managing comorbid CLBP and insomnia. This pilot randomized controlled trial (RCT) primarily aimed to determine the feasibility and acceptability of utilizing different rTMS interventions—high-frequency M1-rTMS, low-frequency DLPFC-rTMS, and sham-rTMS—to individuals with comorbid CLBP and insomnia. The secondary objective was to investigate the preliminary therapeutic effects of these interventions on pain and sleep outcomes at post-treatment and at a one-month follow-up.

8.3 Methods

8.3.1 Study Design

A double-blinded, three-arm, sham-controlled pilot RCT was conducted at The Hong Kong Polytechnic University from November 2024 to June 2025. The study included a two-week intervention followed by a four-week follow-up period. It adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines [464] and extension for randomized pilot and feasibility trials [465]. The Institutional Review Board of The Hong Kong Polytechnic University approved this study (HSEARS20230819003), and it was registered on ClinicalTrials.gov under the identifier NCT06158321.

8.3.2 Participants

Chinese participants with comorbid CLBP and insomnia were recruited via posted announcements on university campus and at partner clinics across Hong Kong. The general inclusion criteria were (1) age between 18-65; (2) consent to participate in the study; (3)

stable pharmacological or nonpharmacological treatments for pain or sleep for at least one month prior to enrollment; and (4) Chinese proficiency. CLBP was defined as pain localized between the 12th ribs and gluteal creases, lasting for a minimum of three months and present on more than half of the days in the preceding four weeks [270, 284, 285]. Participants should report an average pain intensity with above 3 points on the 11-point Numerical Pain Rating Scale (NPRS) over the past week [286]. Insomnia status was assessed using the Brief Insomnia Questionnaire according to criteria of the Diagnostic and Statistical Manual of Mental Disorders 5th edition [167, 287]. Additionally, participants scored above 5 on the Pittsburgh Sleep Quality Index (PSQI) and above 10 on the Insomnia Severity Index (ISI) [283, 296, 466].

Exclusion criteria included: (1) specific CLBP causes (e.g., malignancy, spondylarthritis, or spinal fracture); (2) pregnancy or nursing; (3) history of spinal surgery; (4) presence of inflammatory or autoimmune conditions; (5) other clinically diagnosed sleep disorders; (6) self-reported history of psychiatric, neurological, or physical disorders directly linked to insomnia onset; (7) insomnia or pain treatments initiated within the past month; or (8) contraindications for rTMS [467].

8.3.3 Sample Size Estimation

A formal sample size estimation was unnecessary for pilot feasibility studies, which primarily aim to assess feasibility and acceptability [468]. The sample size was determined according to a method for preliminary pilot studies [469], which recommended a minimum of 10

participants per group for detecting large effect sizes. Therefore, we recruited 36 participants to assess feasibility.

8.3.4 Procedures

A researcher reviewed online questionnaire responses and conducted an initial telephone interview to assess eligibility. Those meeting the criteria were provided with study information and gave written informed consent before enrollment. They underwent a comprehensive screening process, including a medical history review, a brief semi-structured for assessing CLBP and insomnia, clinical examinations, and questionnaires, administrated by a physiotherapist under the guidance of sleep and pain medicine specialists. Potential participants who met the study criteria completed a sleep assessment prospectively for one week using a sleep diary and actigraphy. They were then randomly allocated into one of three intervention groups: sham-rTMS, M1-rTMS, or DLPFC-rTMS. All outcomes were collected at baseline, post-treatment, and self-reported questionnaires were additionally administered at one-month follow-up.

8.3.5 Randomization and Blinding

After screening and baseline assessments, participants were randomly allocated in a 1:1 ratio to receive either M1 or DLPFC stimulation, using a blocked random allocation sequence generated online (https://www.randomizer.org/). Within each group, participants were further randomized to receive either sham or active stimulation in a 1:2 ratio [470]. Treatment assignments were encoded in MagVenture's Research Study System according to

randomization numbers. Allocation concealment was ensured through opaque and sealed envelopes. A researcher not involved in recruitment, enrollment, data collection, intervention, and analysis conducted the randomization. Participants, interventionists, and outcome assessors were blinded to group assignments throughout the study.

8.3.6 Interventions

rTMS interventions were delivered using a MagPro magnetic stimulator (MagPro X100, Tonica Electronic, Farum, Denmark) and a figure-eight sham coil (Cool-B65 A/P). Participants seated in a semi-reclined position and were instructed to remain relaxed. Coil positioning was guided by a TMS-navigation system (LOCALITE GmbH, Sankt Augustin, Germany), targeting the left M1 (the location of the motor hotspot) and the right DLPFC (X: +38, Y: +44; Z: +26) based on Montreal Neurological Institute (MNI) coordinates [471, 472]. The coil was placed tangentially over the targeted areas, with the handle oriented 45° posterolaterally from the midline. The resting motor threshold (RMT) was measured by positioning the coil over the motor hotspot on the left or right side, identifying the minimum stimulus intensity required to elicit a motor response of at least 50 μV in the abductor pollicis brevis in five out of 10 consecutive trials [473]. The treatment protocol consisted of 10 sessions, delivered once daily for five days per week over two weeks.

The stimulation parameters for M1-rTMS followed established clinical guidelines and effective protocols for chronic pain [50, 51, 56, 474]. High-frequency (10 Hz) stimulation was delivered at 80% of the RMT, with 50 pulses per string, a 25-second inter-string interval,

and 30 trains per session, totaling 1,500 stimulation pulses over 15 minutes. For DLPFC-rTMS, low-frequency (1 Hz) stimulation was applied over the right DLPFC at 80% RMT. Each session consisted of 150 trains of 10 pulses, with a 2-second inter-train interval, resulting in 1,500 pulses over 30 minutes. The active DLPFC-rTMS protocol was based on previously validated protocols for individuals with insomnia [475, 476]. Sham stimulation used identical parameters but was delivered via a sham coil, which mimicked the auditory and sensory effects of active rTMS without cortical stimulation.

8.3.7 Outcome Measures

8.3.7.1 Primary Outcomes

8.3.7.1.1 Feasibility and Acceptability

Feasibility was evaluated based on the weekly recruitment rate (the number of participants registered for the study each week) and the eligibility rate (the proportion of registered individuals who met inclusion criteria) [477]. The study was considered feasible if at least 15 participants registered per week and the eligibility rate exceeded 30%. Adverse events were monitored and documented after each treatment session. Participants reported the severity of adverse events and their relevance to the treatment.

Acceptability was assessed by the intervention adherence rate (the proportion of participants who completed at least 90% of the treatment sessions) and the attrition rate (the percentage of participants who missed either the intervention or the assessment). The intervention was considered acceptable if adherence rate exceeded 70% and the attrition rate was below 20%

[478]. Furthermore, participants completed items assessing the acceptability of the study procedures after intervention [479, 480], including: (1) What are the rationales behind your received treatment for managing low back pain and insomnia?; (2) How would you rate the acceptability of this treatment?; (3) Will you recommend our treatment to your family or friends?; and (4) How is your overall satisfaction with the treatment? Items were scored using a 1-5 Likert scale, where higher values indicated better outcomes. Additionally, three open-ended questions were used to assess: (1) reasons for dissatisfaction with the treatment; (2) perceived barriers to current protocols; and (3) suggestions for improving adherence.

8.3.7.2 Secondary Outcomes

8.3.7.2.1 Patient-reported Outcome Measures

Participants completed a series of questionnaires at baseline, immediately post-treatment, and at one-month follow-up to evaluate the preliminary effectiveness of the intervention. These questionnaires included: pain intensity over the past week measured using NPRS [290], insomnia severity assessed by ISI [282, 296], back pain-related disability using the Roland Morris Disability Questionnaire (RMDQ) [291, 299], pain catastrophizing with the Pain Catastrophizing Scale (PCS) [293, 297], and emotional distress using the Depression Anxiety Stress Scale (DASS) [294, 300].

8.3.7.2.2 Subjective and Objective Sleep Parameters

Sleep parameters were evaluated using a one-week sleep diary [481] and ActiGraph wGT3X-BT (ActiGraph, Pensacola, USA) [482] at baseline and post-treatment. The sleep diary,

adapted from the Consensus Sleep Diary [481], was paper-and-pencil log in which participants recorded their bedtimes and wake times, the time taken to fall asleep, and the number and duration of awakenings throughout the night. Objective sleep measures were obtained via actigraphy, with participants wearing the device on their non-dominant w wrist continuously for a period of seven days. Actigraphy data were processed using ActiLife Software (version 6.11.9, Pensacola, USA, with bedtime and wake time determined based on entries in the daily sleep diary [483]. Average values for key sleep metrics, such as sleep efficiency, sleep onset latency, total sleep time, and wake after sleep onset (WASO), were calculated over the entire seven-day monitoring period.

8.3.7.2.3 Quantitative Sensory Testing Protocol (QST)

Sensory assessments followed the standardized protocol established by the German Research Network on Neuropathic Pain [97, 98]. Detailed procedures for QST have been described in our previous study [12]. QST assessments consisted of cold pain threshold (CPT), heat pain threshold (HPT), mechanical pain threshold (MPT), pressure pain threshold (PPT), temporal summation of mechanical pain (TSP), and conditioned pain modulation (CPM). Threshold assessments were conducted at two body sites, starting with the remote sites, followed by the most symptomatic site in the lower back.

8.3.8 Statistical Analysis

Descriptive statistics summarized the group characteristics, feasibility, and acceptability, with results presented as means ± standard deviation or percentages. All participants completed

evaluations at baseline, post-treatment, and follow-up, minimizing concerns about missing data bias. A two-way repeated-measures ANOVA was conducted to examine the therapeutic effects of the three rTMS protocols (sham rTMS, M1-rTMS, DLPFC-rTMS) on patient-reported outcomes over three time points (baseline, post-treatment, one-month follow-up). For sleep parameters and QST measured at only two time points, one-way ANCOVA was used to assess between-group differences at post-treatment, adjusting for baseline values according to prior recommendations [484]. Post-hoc pairwise comparisons were corrected using the Bonferroni method. To explore the interplay between sleep and pain while accounting for multiple comparisons, Pearson's correlation analyses were conducted on changes in outcomes that demonstrated statistically significant differences. Statistical procedures were carried out with IBM SPSS version 25.0 (Armonk, NY: IBM Corp), with significance defined by a two-tailed alpha of 0.05.

8.4 Results

8.4.1 Feasibility and Acceptability

Over a 16-week period, 307 candidates registered for the study through campus and clinic posters, yielding an average recruitment rate of 19.2 participants per week. Following telephone and baseline screening, 118 participants (38.4%) met the inclusion criteria. Common reasons for exclusion included subthreshold pain intensity or frequency (n=69), acute sleep disturbances (n=64), specific spinal pathology (n=17), neurological or psychiatric comorbidities (n=15), age over 65 years (n=13), and inability to contact (n=11). From the eligible cohort, the first 36 available participants completed baseline assessments and were

randomized to receive either sham-rTMS, M1-rTMS, or DLPFC-rTMS. **Figure 11** illustrates a detailed overview of the screening, enrollment, and participation process. The average age of enrolled participants was 42.1 years, and 83.3% (30/36) were female. Baseline demographic and clinical characteristics were similar among the three groups (**Table 14**).

All 36 randomized participants completed the10-session treatment protocol, post-treatment assessment, and follow-up assessment, resulting in 100.0% adherence rate and 0% attrition rate. All participants either perceived rationale or no preference for treatment rationale. Nearly all (33 out of 36 (91.7%)) participants endorsed the treatment acceptable and were satisfied with the study procedures. Over 88% of participants indicated that they would recommend the treatments to others. Open-ended questions identified three areas for potential improvement: (1) extending the overall course of treatment duration while reducing the frequency of weekly sessions (n=12), (2) offering patient education on the mechanisms of rTMS (n=6), and (3) integrating adjunctive strategies for managing pain or sleep (n=4). During the study, 11 participants (30.6%) reported 26 mild, treatment-related adverse events (**Table S6.1**). The most common adverse events were headache (38.5%), dizziness (19.2%), scalp pain (19.2%), and nocturnal arousal (15.4%). The incidence of adverse events was comparable across the three treatment groups ($\chi^2 = 1.83$, $p = 0.400$). No serious adverse events occurred during the course of the study.

8.4.2 Patient-reported Outcome Measures

Figure 12 presents patient-reported outcome measures over time. A two-way repeated measures ANOVA found a significant interaction between time and group for pain intensity ($F = 7.92$, $p < 0.001$, $\eta^2 = 0.324$, **Table 15**). Post-hoc analyses showed that both M1-rTMS ($p_{corrected} = 0.001$) and DLPFC-rTMS ($p_{corrected} < 0.001$) significantly reduced pain intensity at post-treatment compared to sham stimulation. At the one-month follow-up, only DLPFC-rTMS maintained a significant effect compared to sham-rTMS ($p_{corrected} = 0.019$). A similar interaction effect was found for insomnia severity ($F = 12.45$, $p < 0.001$, $\eta^2 = 0.430$). Post-hoc comparisons indicated significant improvements in insomnia severity for DLPFC-rTMS at post-treatment ($p_{corrected} = 0.030$) and follow-up ($p_{corrected} < 0.001$) compared to sham-rTMS. No significant interaction effects were identified for back pain-related disability ($F = 2.11$, $p = 0.089$, $\eta^2 = 0.114$), pain catastrophizing ($F = 1.35$, $p = 0.263$, $\eta^2 = 0.075$), or emotional distress ($F = 1.18$, $p = 0.330$, $\eta^2 = 0.066$). Furthermore, main effects analyses did not find significant between-group differences for these outcomes ($p > 0.276$). However, significant time effects were observed for disability ($F = 13.73$, $p < 0.001$, $\eta^2 = 0.294$), pain catastrophizing ($F = 28.40$, $p < 0.001$, $\eta^2 = 0.463$), and emotional distress ($F = 25.05$, $p < 0.001$, $\eta^2 = 0.431$), with post-hoc tests revealing improvements from baseline to post-treatment ($p_{corrected} < 0.001$) and follow-up ($p_{corrected} < 0.001$).

8.4.3 Sleep Parameters and Pain Perceptions

A one-way ANCOVA revealed significant differences in objective WASO at post-treatment across three groups ($F = 5.36$, $p = 0.010$). Post-hoc analyses with Bonferroni correction showed that DLPFC-rTMS had lower WASO compared to sham-rTMS ($p_{corrected} = 0.016$) and

M1-rTMS ($p_{corrected}$ = 0.038). Regarding quantitative sensory testing, significant group differences were observed in TSP (F = 3.53, p = 0.041) and CPM (F = 12.42, p < 0.001) at post-treatment. Specifically, both M1-rTMS ($p_{corrected}$ = 0.011) and DLPFC-rTMS ($p_{corrected}$ < 0.001) significantly enhanced descending pain inhibitory efficiency compared to sham-rTMS, while only DLPFC-rTMS showed significantly reduced TSP relative to sham-rTMS ($p_{corrected}$ = 0.037). There were no significant between-group differences in other sleep parameters or pain thresholds (**Table 16**).

8.4.4 Associations between Pain and Sleep

Correlation analyses were performed among post-treatment changes in pain intensity, insomnia severity, objective WASO, TSP, and CPM. Reduced pain intensity significantly correlated to decreased insomnia severity (r = 0.51, p = 0.002) and greater descending pain inhibitory efficiency (r = -0.46, p = 0.005). A similar association was observed between improvements in pain intensity and insomnia severity at the one-month follow-up (r = 0.38, p = 0.022). No significant correlations were found among the remaining outcomes (**Table S6.2**).

8.5 Discussion

This pilot RCT demonstrated the feasibility and acceptability of rTMS for treating individuals with comorbid CLBP and insomnia, with a 100% adherence rate and no participant attrition. Efficacy analyses revealed that both M1-rTMS and DLPFC-rTMS significantly reduced pain intensity and enhanced descending pain inhibitory pathways at post-treatment compared to

sham stimulation, whereas only DLPFC-rTMS significantly improved insomnia severity, objective WASO, and TSP. Additionally, DLPFC-rTMS maintained reductions in pain intensity and insomnia severity at the one-month follow-up. Exploratory analyses found that decreased pain intensity was significantly associated with improvements in insomnia severity and descending pain inhibition efficiency. These findings offer valuable insights into future large-scale RCTs and preliminary evidence supporting the therapeutic potential of rTMS for comorbid conditions.

Our recruitment, eligibility, attrition, and adherence rates exceeded predefined thresholds and suggested criteria [478]. Notably, over 88% of participants endorsed the intervention as rational and acceptable, and indicated that they would recommend it to others. These findings align with previous qualitative research on people with chronic musculoskeletal pain [485], reinforcing the feasibility and acceptability of rTMS for treating comorbid CLBP and insomnia. Participant feedback highlighted potential barriers to intervention implementation, including the intensive scheduling of intervention sessions, limited understanding of the mechanisms underlying rTMS, and the lack of adjunctive strategies for managing pain or sleep disturbance. Additional education is very important for this relatively novel intervention, especially for individuals with peripheral pain. A common misconception is that pain management should focus on the affected area [486]. This may lead to skepticism about the use of a brain-based intervention for alleviating distal pain. Therefore, future studies should address these barriers to increase the utility of rTMS and improve outcomes for comorbid conditions.

Our preliminary analysis indicated that both M1-rTMS and DLPFC-rTMS significantly reduced pain intensity at post-treatment compared to sham stimulation. The analgesic effects of M1-rTMS align with current clinical practice guidelines for chronic pain [51, 54, 56] and prior CLBP studies [487, 488]. Contrary to earlier guidelines that reported no analgesic benefit from DLPFC-rTMS, the present findings demonstrate significant analgesic efficacy [51, 56]. These discrepancies may be attributed to the methodological heterogeneity across studies, particularly in participant characteristics. Recent systematic reviews have highlighted variability in treatment outcomes following DLPFC-rTMS across different chronic pain populations [489, 490], with significant effects in migraine but not neuropathic pain [489]. Additionally, previous studies often overlooked comorbidities in chronic pain, resulting in a lack of specificity in targeting relevant conditions. Emerging evidence suggests that stratifying individuals by pain and sleep phenotypes reveals distinct clinical and neurophysiological profiles [12, 190], which may influence treatment responsiveness. More importantly, only DLPFC-rTMS was associated with sustained pain reduction at the one-month follow-up, whereas M1-rTMS did not yield long-term benefits. This differential trajectory supports the hypothesis that M1 stimulation produces transient analgesic effects, while DLPFC stimulation may modulate broader neural networks, generating delayed and long-lasting analgesia [51, 490-492].

Our research also found that DLPFC-rTMS had superior efficacy for improving insomnia severity and objective WASO at post-treatment compared to sham stimulation, whereas M1-

rTMS showed no such effects. These differences may be ascribed to the distinct functional roles of the cortical regions and the differential neurophysiological effects of stimulation frequencies. Specifically, M1 is responsible for sensorimotor integration and nociceptive modulation [493], while DLPFC is essential for self-awareness [494], emotion regulation [495], and arousal modulation [496]. Dysfunctional DLPFC activity is directly related to insomnia pathophysiology [30, 178, 494]. Moreover, high-frequency rTMS generally increase cortical excitability, while low-frequency rTMS typically exerts inhibitory effects [497]. The hyperarousal model of insomnia suggests that heightened somatic, cognitive, and cortical activation disrupts sleep [30, 178], implying that inhibitory neuromodulation may help restore sleep homeostasis [52, 53]. This interpretation is supported by recent RCTs using inhibitory stimulation paradigms, such as low-frequency rTMS and continuous theta burst stimulation, which have reported significant improvements in sleep parameters [498, 499]. However, four adverse events involving the exacerbation of nocturnal arousal were reported following high-frequency M1-rTMS in our study, underscoring the risk of excitatory protocols in individuals with insomnia. Collectively, our preliminary evidence suggests that low-frequency rTMS over the DLPFC may provide more effective and sustainable treatment for individuals with comorbid CLBP and insomnia than high-frequency M1 stimulation.

Our study found that both M1-rTMS and DLPFC-rTMS significantly enhanced the efficiency of descending pain inhibition. These results are consistent with prior studies showing that stimulation over M1 or DLPFC restores the inhibitory effects on pain circuits [55, 492]. Exploratory analyses further revealed that improvements in CPM were positively correlated

with pain reduction, providing empirical support for our hypothesis that restoring top-down modulation contributes to symptomatic relief in comorbid conditions [12]. Interestingly, changes in descending pain inhibition were not related to improvements in insomnia severity. This suggests that the therapeutic effects of low-frequency DLPFC-rTMS on sleep are likely mediated by distinct neurophysiological mechanisms, potentially involving decreased cortical excitability, remodeling of the underlying neural networks, or modulation of neurotransmitters such as dopamine or pineal melatonin release [52, 53]. Future research integrating brain stimulation with neurophysiological assessments is warranted to elucidate these mechanisms and clarify how rTMS exerts its effects on sleep in comorbid states.

This study has several limitations. First, the clinical outcome findings were derived from a limited sample size and should be interpreted cautiously. Larger, full-scale RCTs are warranted to validate and expand upon these preliminary results. Second, although our rTMS protocols were guided by theoretical rationale, empirical evidence, and practical considerations [52-57], the optimal stimulation parameters (e.g., stimulation frequency, targeted areas, pulses) remain uncertain [500]. Future research should compare different protocols to identify the most effective treatment configurations. Third, this study used a short-duration rTMS intervention to assess short-term outcomes. Future studies should investigate longer treatment periods with extended follow-up assessments to better understand sustained benefits. Lastly, we did not incorporate neuroimaging techniques to investigate the neurocognitive mechanisms underlying rTMS. Further research using neuroimaging is needed to elucidate the neurophysiological basis of treatment efficacy.

8.6 Conclusions

This pilot RCT demonstrated that rTMS is a feasible, well-tolerated, and safe intervention for individuals with comorbid CLBP and insomnia. Our findings highlight the importance of integrating patient education on the potential mechanisms of rTMS and adjunctive strategies for managing pain or sleep disturbances in future studies. Treatment protocols may benefit from shifting from conventional high-frequency, consecutive sessions toward those with lower frequency and extended duration. Our preliminary evidence suggests that low-frequency DLPFC-rTMS may offer more therapeutic benefits for comorbid conditions compared to high-frequency M1-rTMS and sham-rTMS. These findings underscore the need for large-scale, rigorously designed RCTs to confirm the efficacy of optimized rTMS protocols in this complex patient population.

8.7 Tables

Table 14. Demographic and clinical characteristics

	Sham rTMS (n = 12)	M1 rTMS (n = 12)	DLPFC rTMS (n = 12)
Age (year), mean (SD)	43.2 (15.8)	43.0 (14.8)	40.0 (13.8)
Female gender, n (%)	10 (83.3)	10 (83.3)	10 (83.3)
Body mass index (kg/m^2), mean (SD)	23.5 (3.0)	23.4 (5.1)	24.3 (3.7)
Education (year), mean (SD)	17.3 (3.4)	18.3 (4.5)	16.6.3 (5.2)
Working status, n (%)			
Employed	8.0 (66.7)	4.0 (33.3)	7.0 (58.3)
Unemployed	1.0 (8.3)	6.0 (50.0)	4.0 (33.3)
Retired	3.0 (25.0)	2.0 (16.7)	1.0 (8.3)
Medication use, n (%)			
None	5.0 (38.5)	6.0 (42.9)	6.0 (50.0)
Medication for pain	2.0 (15.4)	2.0 (14.3)	1.0 (8.3)
Medication for sleep	4.0 (30.8)	3.0 (21.4)	2.0 (16.6)
Medications for other health conditions1	2.0 (15.4)	3.0 (21.4)	3.0 (25.0)
Duration of pain (month), mean (SD)	73.3 (77.9)	46.8 (35.9)	48.3 (49.1)
Average pain intensity over last week, mean (SD)	5.2 (0.6)	5.3 (1.1)	5.7 (1.3)
Roland Morris Disability Questionnaire, mean (SD)	8.3 (2.7)	8.1 (3.6)	8.9 (3.5)
Insomnia Severity Index, mean (SD)	15.4 (3.1)	15.3 (3.2)	16.8 (2.5)
Pittsburgh Sleep Quality Index, mean (SD)	12.7 (2.3)	11.5 (3.8)	10.7 (2.5)
Pain Catastrophizing Scale, mean (SD)	20.3 (7.6)	20.7 (5.9)	23.3 (5.9)
Depression Anxiety Stress Scale, mean (SD)	22.6 (13.8)	15.7 (10.5)	22.9 (14.8)

Abbreviations: DLPFC: Dorsolateral prefrontal cortex; M1: Primary motor cortex; rTMS: Repetitive transcranial magnetic stimulation; SD: Standard deviation.

Table 15. Means and standard deviations for patient-reported outcome measures

	Baseline	Post-treatment	Follow-up	Group	Time	Group*Time
Numerical Pain Rating Scale				$F = 5.44$, $\mathbf{p = 0.009}$	$F = 65.95$, $\mathbf{p < 0.001}$	$F = 7.92$, $\mathbf{p < 0.001}$
Sham-rTMS	5.2 (0.6)	4.6 (0.9)	4.3 (1.1)			
M1-rTMS	5.3 (1.1)	2.8 (1.1)	2.8 (1.5)			
DLPFC-rTMS	5.7 (1.3)	2.3 (1.3)	2.5 (1.7)			
Insomnia Severity Index				$F = 3.56$, $\mathbf{p = 0.040}$	$F = 44.26$, $\mathbf{p < 0.001}$	$F = 12.45$, $\mathbf{p < 0.001}$
Sham-rTMS	15.4 (3.1)	14.0 (4.3)	14.7 (4.2)			
M1-rTMS	15.3 (3.2)	13.2 (3.7)	11.3 (3.3)			
DLPFC-rTMS	16.8 (2.5)	9.4 (4.3)	7.8 (3.3)			
Roland Morris Disability Questionnaire				$F = 1.99$, $p = 0.822$	$F = 13.73$, $\mathbf{p < 0.001}$	$F = 2.11$, $p = 0.089$
Sham-rTMS	8.3 (2.7)	7.3 (2.2)	7.9 (2.3)			
M1-rTMS	8.1 (3.6)	6.0 (4.6)	7.8 (5.9)			
DLPFC-rTMS	8.9 (3.5)	5.1 (4.7)	6.7 (5.6)			
Pain Catastrophizing Scale				$F = 0.84$, $p = 0.442$	$F = 28.40$, $\mathbf{p < 0.001}$	$F = 1.35$, $p = 0.263$
Sham-rTMS	20.3 (7.6)	15.8 (10.3)	16.8 (9.6)			
M1-rTMS	20.7 (5.9)	12.4 (7.2)	11.7 (6.6)			
DLPFC-rTMS	23.3 (5.9)	16.1 (8.6)	15.9 (7.1)			
Depression Anxiety Stress Scale				$F = 1.34$, $p = 0.276$	$F = 25.05$, $\mathbf{p < 0.001}$	$F = 1.18$, $p = 0.330$
Sham-rTMS	22.6 (13.8)	15.5 (11.1)	14.8 (12.0)			
M1-rTMS	15.7 (10.5)	10.3 (7.7)	7.8 (9.3)			
DLPFC-rTMS	22.9 (14.8)	10.6 (6.1)	12.6 (9.5)			

Abbreviations: DLPFC: Dorsolateral prefrontal cortex; M1: Primary motor cortex; rTMS: Repetitive transcranial magnetic stimulation.

Footnote: P value was calculated by the two-way repeated-measures ANOVA. The p-value in bold indicates a statistically significant time, group, or interaction effects ($p < 0.05$).

Table 16. Means and standard deviations for sleep parameters and pain perception

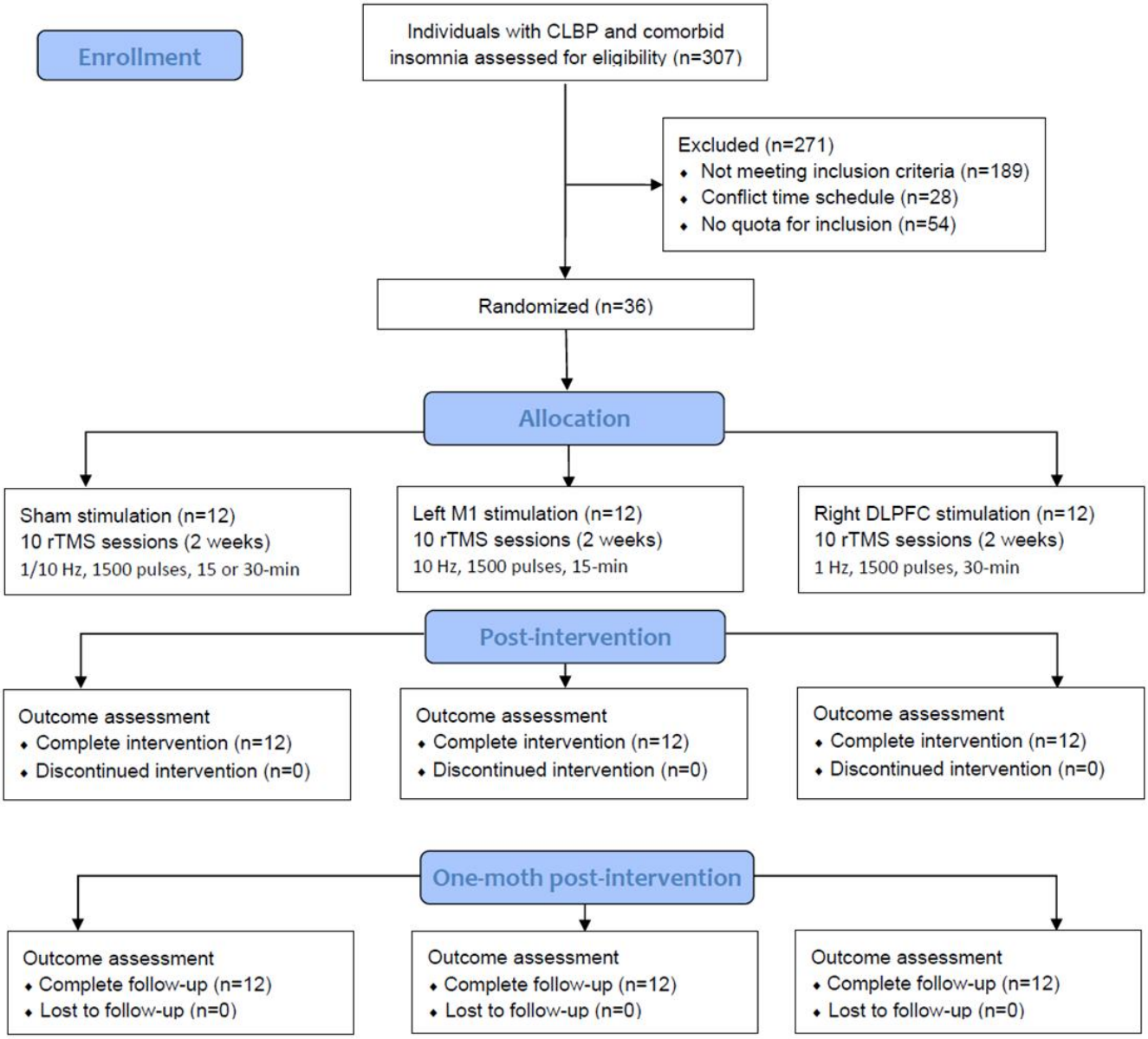
	Sham-rTMS		M1-rTMS		DLPFC-rTMS		*p* value
	Baseline	Post-treatment	Baseline	Post-treatment	Baseline	Post-treatment	
Subjective sleep parameters measured by sleep diary							
Total sleep time (min)	375.13 (32.66)	386.63 (33.74)	378.52 (52.82)	375.51 (47.94)	352.57 (51.17)	375.35 (65.72)	0.652
Sleep onset latency (min)	39.01 (14.56)	36.38 (26.22)	30.14 (29.77)	38.14 (40.32)	32.57 (23.59)	18.92 (21.67)	0.104
Wake after sleep onset (min)	18.89 (18.95)	23.46 (25.46)	27.74 (22.95)	30.15 (27.34)	35.94 (37.27)	14.81 (15.08)	0.082
Sleep efficiency (%)	74.85 (8.08)	76.89 (12.82)	75.67 (8.61)	76.55 (12.52)	73.83 (13.70)	83.07 (10.43)	0.081
Objective sleep parameters measured by Actigraphy							
Total sleep time (min)	434.81 (57.49)	424.58 (50.57)	433.59 (57.42)	437.82 (78.44)	425.78 (36.90)	406.48 (61.35)	0.409
Sleep onset latency (min)	3.89 (3.93)	3.20 (2.40)	5.95 (11.23)	5.14 (4.15)	4.32 (5.72)	3.87 (4.80)	0.600
Wake after sleep onset (min)	67.28 (22.75)	73.38 (29.75)	63.07 (31.93)	67.30 (28.60)	59.51 (27.34)	45.75 (26.90)	**0.010**
Sleep efficiency (%)	85.88 (4.31)	84.74 (4.74)	86.27 (5.06)	85.50 (5.85)	86.82 (6.12)	88.89 (7.61)	0.050
Pain perception							
Cold pain threshold (hand, ˚C)	17.36 (7.31)	18.31 (6.92)	17.10 (8.60)	19.99 (5.40)	18.19 (8.68)	17.01 (8.23)	0.314
Cold pain threshold (back, ˚C)	21.85 (7.14)	20.15 (7.44)	18.62 (8.29)	18.04 (9.06)	23.14 (6.76)	21.02 (9.03)	0.867
Head pain threshold (hand, ˚C)	40.33 (3.28)	40.91 (3.28)	39.68 (4.03)	40.62 (4.05)	40.15 (2.98)	41.21 (3.52)	0.829
Head pain threshold (back, ˚C)	39.56 (2.90)	40.27 (3.24)	39.91 (3.69)	40.01 (3.33)	40.98 (2.91)	41.19 (2.42)	0.613
Mechanical pain threshold (hand, Nm)	57.96 (64.66)	97.61 (73.84)	67.45 (75.10)	91.08 (65.58)	89.09 (75.78)	161.32 (123.66)	0.218
Mechanical pain threshold (back, Nm)	65.61 (84.88)	91.94 (97.71)	50.69 (29.55)	88.86 (77.01)	120.89 (99.70)	165.56 (117.68)	0.714
Pressure pain threshold (hand, Kg/cm^2)	2.46 (0.72)	2.71 (0.87)	2.01 (1.04)	2.74 (1.05)	2.51 (0.96)	3.42 (1.11)	0.081
Pressure pain threshold (back, Kg/cm^2)	3.87 (2.07)	4.57 (2.21)	3.41 (1.92)	4.44 (2.37)	5.59 (2.25)	6.55 (2.71)	0.681
Temporal summation of pain	3.04 (1.75)	2.29 (1.41)	2.67 (1.44)	1.63 (1.09)	2.42 (0.95)	0.92 (0.87)	**0.041**
Conditioned pain modulation	-0.25 (0.34)	-0.38 (0.52)	-0.25 (0.31)	0.18 (0.34)	-0.19 (0.31)	0.49 (0.39)	**<0.001**

Abbreviations: DLPFC: Dorsolateral prefrontal cortex; M1: Primary motor cortex; rTMS: Repetitive transcranial magnetic stimulation.

Footnote: P value was calculated by the one-way ANCOVA. The p-value in bold indicates a statistically significant difference among the three groups ($p < 0.05$).

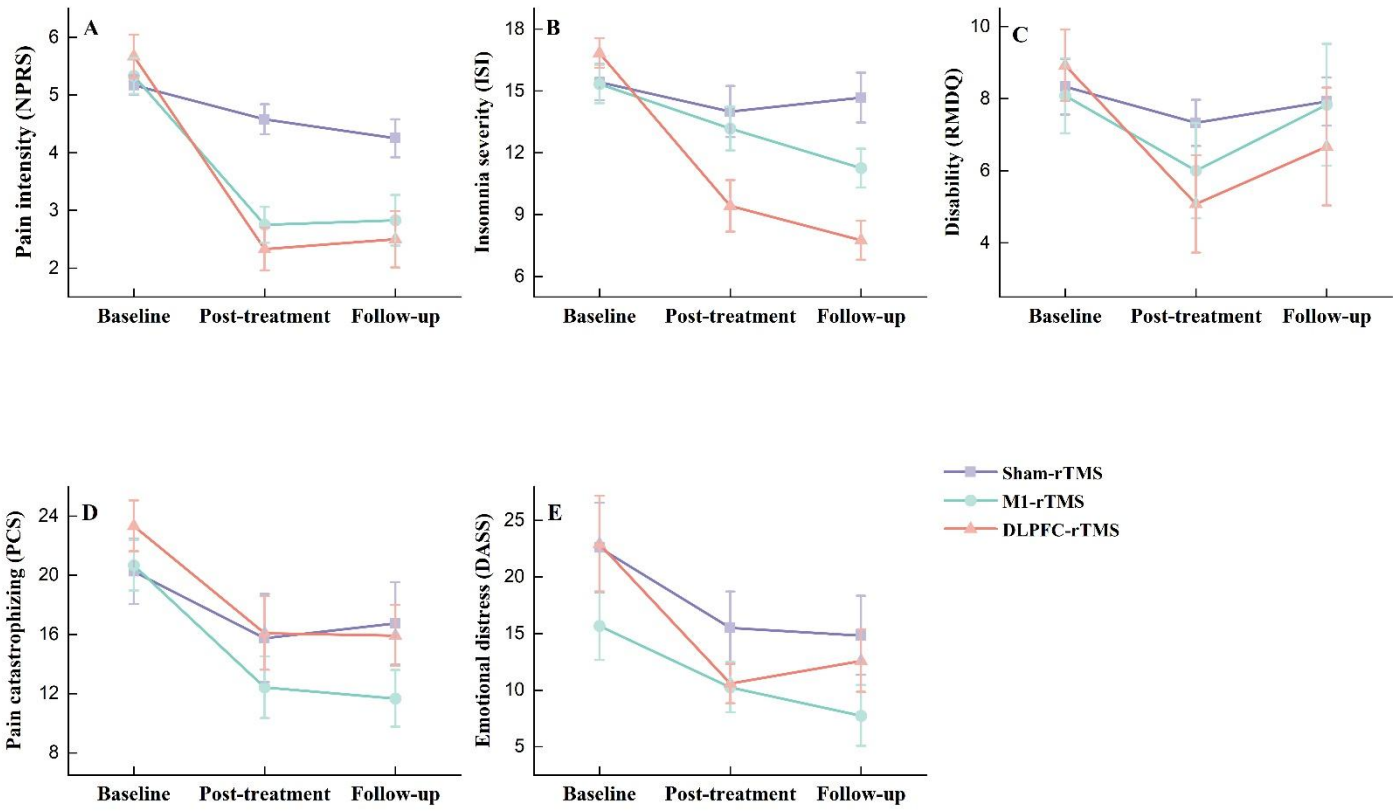
8.8 Figures

Figure 11. CONSORT flow chart of the study procedure



Abbreviations: CLBP: Chronic low back pain; DLPFC: Dorsolateral prefrontal cortex; M1: Primary motor cortex; rTMS: Repetitive transcranial magnetic stimulation.

Figure 12. Patient-reported outcome measures over time



Abbreviations: DASS: Depression Anxiety Stress Scale; DLPFC: Dorsolateral prefrontal cortex; ISI: Insomnia Severity Index; M1: Primary motor cortex; NPRS: Numerical Pain Rating Scale; PCS: Pain Catastrophizing Scale; RMDQ: Roland Morris Disability Questionnaire; rTMS: Repetitive transcranial magnetic stimulation.

Footnote: Values are presented as mean and standard error.

Chapter 9: General Discussion and Conclusion

Sleep disturbance is a prevalent and clinically significant comorbidity with chronic pain [8], resulting in greater functional impairments and worsened prognosis [10, 11]. The aforementioned studies (Chapters 3 to 8) in this thesis investigated: (1) the impact of different sleep deprivation paradigms on pain perception in healthy individuals and those with chronic pain; (2) the characteristics of pain perception and neural activity in individuals with comorbid CLBP and insomnia; (3) the prospective relationship between sleep parameters and clinical variables in individuals with CLBP; (4) the relative efficacy of non-pharmacological treatments for enhancing sleep quality in individuals with chronic musculoskeletal pain; and (5) the feasibility and acceptability of rTMS for individuals with concurrent CLBP and insomnia. This chapter presents a synthesis of the primary findings from these studies and discusses their clinical and research implications.

9.1 Summary of Research Findings

9.1.1 The Differential Effects of Sleep Deprivation on Pain Perception in Individuals with or without Chronic Pain: A Systematic Review and Meta-Analysis (Study 1)

This systematic review and meta-analysis provided an updated and thorough synthesis of the literature examining how different experimental sleep deprivation paradigms influence pain-related outcomes, including spontaneous pain intensity, pain threshold, pain tolerance, CPM, and TSP among individuals with and without chronic pain. This study included 32 studies involving 699 healthy individuals and 47 patients with chronic pain. Evidence ranging from

very limited to moderate indicated that total/partial sleep deprivation or sleep fragmentation led to increased subjective pain intensity, peripheral sensitization, or central sensitization among healthy individuals. Similarly, limited evidence suggested that total or partial sleep deprivation significantly exacerbated spontaneous pain intensity in individuals with chronic pain. Nevertheless, no studies to date have examined how selective sleep deprivation or fragmented sleep affects pain processing in this population. These results suggest that different sleep deprivation paradigms produce distinct effects on pain perception in healthy individuals and those with chronic pain. This emphasizes the necessity for additional investigations into the neurophysiological pathways linking sleep and pain, particularly in chronic pain contexts.

9.1.2 Differential Pain Perception among Females with or without Non-specific Chronic Low Back Pain and Comorbid Insomnia: A Quantitative Sensory Testing Analysis (Study 2)

This cross-sectional study with QST analyses investigated the pain perception characteristics among 100 females with CLBP, insomnia, comorbid conditions, or neither. Our results found that the coexisting of CLBP and insomnia showed significantly lower mechanical and pressure pain threshold across both symptomatic and asymptomatic regions compared to healthy controls. Additionally, the comorbid group exhibited reduced PPT at the back and more substantial dysfunction in descending pain inhibitory mechanisms than those with CLBP alone. In terms of psychological factors, the comorbid group and insomnia group reported elevated levels of pain catastrophizing, fear-avoidance beliefs, or negative moods relative to those with CLBP alone or control groups. Insomnia was independently related to

MPT at both the back and remote sites within the comorbid group, after adjusting for pain-related variables and psychological distress. Our findings indicate a possible interplay between CLBP and insomnia, characterized by diminished PPT and impaired descending pain modulation. Further research is warranted to evaluate targeted treatments aimed at restoring impaired descending inhibitory control in comorbid cases.

9.1.3 Neural Oscillations and Brain Connectivity in Females with Chronic Low Back Pain and Comorbid Insomnia (Study 3)

This cross-sectional study utilized resting-state EEG to quantify unique neural oscillation patterns and brain connectivity among four groups of age-matched females, including healthy controls, those with CLBP, insomnia, and concomitant conditions. The results revealed that females with comorbid CLBP and insomnia showed altered theta-band connectivity across multiple brain networks and enhanced beta-band information processing relative to those with CLBP alone, insomnia alone, or healthy controls. Furthermore, insomnia was independently correlated with aberrant connectivity patterns in the comorbid condition, after accounting for pain-related factors and psychological variables. These neurophysiological characteristics hold promise in facilitating patient phenotyping, enhancing our understanding of the neural basis of the comorbid states, and potentially laying the groundwork for developing biomarkers and informing effective therapeutic interventions for this complex condition.

9.1.4 Are Changes in Sleep Quality/Quantity or Baseline Sleep Parameters Related to Changes in Clinical Outcomes in Individuals with Nonspecific Chronic Low Back Pain? A Systematic Review (Study 4)

Previous chapters have illustrated that sleep deprivation paradigms led to heightened pain sensitivity, while our cross-sectional study also showed that individuals with comorbid chronic pain and insomnia exhibited disrupted pain processing and heightened brain connectivity related to pain and sleep regulation. This systematic review explored the longitudinal relationship between sleep parameters and clinical outcomes in individuals with CLBP. Our review included six studies and synthesized findings narratively through the GRADE classification. The results revealed very low to moderate certainty supporting the temporal associations between improvements in self-reported sleep measures and corresponding improvements in pain intensity, perceived recovery, or functional disability. However, whether baseline sleep characteristics can reliably predict long-term clinical outcomes in people with CLBP remains uncertain. These results highlight a gap in literature, despite the high prevalence of sleep disturbances among individuals with CLBP. These findings also underscore the importance of determining the causal relations between sleep and pain/function in individuals with CLBP, which may improve the assessments and treatments of individuals with CLBP.

9.1.5 Comparative Effectiveness of Non-Pharmacological Interventions on Sleep in Individuals with Chronic Musculoskeletal Pain: A Systematic Review with Network Meta-Analysis (Study 5)

Considering the widespread occurrence of the comorbid condition and the potential influence of sleep disturbance on pain-related clinical outcomes, a network meta-analysis was conducted to evaluate the relative effectiveness of non-pharmacological treatments for sleep quality. This analysis synthesized data from 107 randomized controlled trials involving 8,121 participants with chronic musculoskeletal pain. Eight out of 13 non-pharmacological interventions (e.g., CBT, exercise, mind-body exercise, non-invasive brain stimulation) were significantly more effective than passive control in improving sleep quality, sleep parameters, pain, and disability immediately after treatment. The consistent benefits observed across multiple sleep domains and follow-up periods suggest that CBT could be considered a first-line therapy for sleep disturbances in this population. However, high attrition rates and a greater number of adverse events associated with CBT in the included studies warrant caution [46]. Furthermore, most studies focused primarily on pain and did not include formal sleep diagnoses, which limits the applicability of results to comorbid conditions. While this review provides the most extensive comparative evidence to date for guiding the selection of non-pharmacological interventions for sleep in individuals with chronic musculoskeletal pain, further high-quality RCTs specifically targeting comorbid chronic pain and insomnia are needed to optimize outcomes for this complex population.

9.1.6 The Efficacy and Safety of Repetitive Transcranial Magnetic Stimulation for Comorbid Chronic Low Back Pain and Insomnia: A Randomized, Double-blind, Sham-controlled Pilot Trial (Study 6)

Our cross-sectional study highlights the importance of stratifying individuals according to their distinct sleep and pain characteristics, because those with concomitant chronic pain and

insomnia exhibited more pronounced disruptions in central pain processing and abnormal neural oscillations. While most studies have focused on CBT [46], its clinical implementation is challenged by low adherence, high costs, and a shortage of credentialed clinicians in primary care settings [47, 48]. These challenges point to the potential of targeted brain modulation approaches as promising alternatives to restore neurophysiological imbalances and improve outcomes in comorbid conditions. Our pilot RCT established the feasibility and acceptability of rTMS for treating individuals with comorbid CLBP and insomnia, with a 100% adherence rate and no participant attrition. No serious adverse events were reported. Preliminary efficacy analyses revealed that both M1-rTMS and DLPFC-rTMS significantly reduced pain intensity and enhanced descending pain inhibitory pathways at post-treatment compared to sham stimulation. However, only DLPFC-rTMS significantly improved in insomnia severity, objective WASO, and TSP. Furthermore, DLPFC-rTMS maintained reductions in pain intensity and insomnia severity at the one-month follow-up. Association analyses showed that decreases in pain intensity were significantly associated with improvements in insomnia severity and descending pain inhibition efficiency. These findings offer preliminary evidence supporting the therapeutic potential of rTMS for comorbid conditions, and provide valuable insights to inform the design of future large-scale, definitive RCTs

9.2 Summary of Research Findings

9.2.1 Pain Perception and Brain Activity in the Slee-Pain Interaction

Emerging evidence highlights the critical influence of sleep on pain modulation. While the close correlation between sleep and pain is well-established, the underlying mechanisms remain unclear. Previous narrative reviews proposed several potential contributors to the influence of sleep on pain perception, such as impaired endogenous pain modulation, elevated concentrations of pro-inflammatory cytokines (e.g., IL-6, TNF-α, and C-reactive protein), autonomic system imbalance, emotional distress or mood-related disorders, endogenous substances (e.g., dopamine, orexin, melatonin, vitamin D), altered brain function in pain processing, and other sleep-pain mediators (e.g., fatigue, physical activity, hypothalamus-pituitary-adrenal axis) [15, 16, 501]. However, much of this evidence is based on experimental sleep deprivation studies, animal models, or patient-reported outcomes [15, 16, 501], with limited use of objective measures (e.g., quantitative sensory testing or neuroimaging) in clinical populations. This knowledge gap is further confirmed by our first systematic review (Chapter 3), which indicated the paucity of studies evaluating the impacts of sleep loss in individuals with chronic pain. By directly addressing this gap, we utilized QST and resting-state EEG to examine the neurophysiological characteristics in individuals with different sleep and pain profiles (Chapters 4 and 5). Our findings demonstrated that the comorbidity of CLBP and insomnia exhibited greater sensitivity to painful stimuli, more severe impairments in descending inhibitory pathways, and increased levels of maladaptive psychological traits compared to those with CLBP alone and healthy controls. These findings are consistent with previous cluster analyses that identified a subgroup of patients with CLBP characterized by greater pressure pain sensitivity who had higher likely to report sleep issues [13]. Likewise, *Campbell et al*. reported worsened central sensitization in people with knee

osteoarthritis and insomnia relative to healthy control [190]. Taken together, these findings support the hypothesis that insomnia contributes to increased peripheral and central pain sensitivity in people with chronic pain.

Additionally, our EEG findings suggested that the comorbid conditions exhibited disturbed functional connectivity across key brain networks (i.e., DMN, SN, and FPN) and heightened beta-band activity for information transportation compared to healthy controls. However, such neurophysiological alterations were not observed in individuals with CLBP alone, indicating the potential interactions between pain and sleep in comorbid states through shared neurophysiological pathways, leading to synergistic effects on spontaneous cortical activities [15, 16]. This interpretation is consistent with the dynamic pain connectome model, which showed aberrant connectivity between the SN, DMN, and antinociceptive systems in chronic pain during the resting state [86, 87]. Similarly, increased functional connectivity within the SN, DMN, and FPN has also been observed in individuals with insomnia, contributing to hyperarousal and emotional dysregulation [182]. These patterns may lend support to the notion that, despite subjective sleepiness, those with comorbid conditions exhibit intensified cognitive or attentional engagement associated with persistent pain and disrupted sleep. This may contribute to a prolonged state of cortical hyperarousal, potentially worsening their clinical symptoms. Overall, our neurophysiological results build upon existing hypotheses by providing objective evidence in a clinical population. They suggest that increased peripheral and central pain sensitivity, along with altered large-scale brain network connectivity, may represent key mechanisms linking sleep disturbance and chronic pain.

9.2.2 Therapeutic Potential of Targeting Sleep in Pain Management

It is worth noting that there is limited evidence to investigate the temporal association between sleep and pain. Our second systematic review (Chapter 6) directly addressed this gap and reported that improvements in self-reported sleep parameters were prospectively linked to the corresponding reductions in pain intensity, enhanced self-perceived recovery, or decreased LBP-related disability. These findings are further validated by more recent evidence in individuals with CLBP, suggesting sleep as a prognostic indicator for pain progression and recovery [188]. Given that sleep problems are modifiable, targeting sleep-related issues holds substantial clinical relevance for pain management in individuals with concurrent insomnia and chronic pain. These insights underscore the critical need to integrate sleep assessments into routine clinical evaluations for people with chronic pain. Detecting and addressing sleep disturbances early in this population may help reduce their negative impact on pain and enhance the effectiveness of treatment strategies [12, 46].

9.2.3 Current Evidence for Sleep Management in Pain

Current evidence consistently recommends incorporating sleep management into chronic pain care [12, 27, 38, 46, 502]. However, they offer limited guidance on the relative effectiveness of specific non-pharmacological treatments for improving sleep quality in this population. Our network meta-analysis (Chapter 7) estimated the relative effectiveness of multiple competing non-pharmacological interventions. The results showed found that eight out of 13 non-pharmacological interventions (e.g., CBT, exercise, mind-body exercise, non-invasive

brain stimulation) demonstrated significantly greater improvements in sleep quality compared to true control. While CBT emerged as the most effective first-line treatment, it was also associated with higher attrition rates and a greater incidence of mild adverse events compared to control groups. Therefore, the choice of sleep intervention should be based on patients' preferences, clinicians' expertise, relative effectiveness, acceptability, and adverse events. Although we conducted the first comprehensive network meta-analysis to summarize existing non-pharmacological interventions on sleep quality in individuals with chronic musculoskeletal pain, most included studies did not require the presence of insomnia symptoms for inclusion. There is limited evidence on the effectiveness of these interventions in individuals with comorbid chronic pain and insomnia. Therefore, caution is warranted when applying these findings to populations with comorbid conditions.

9.2.4 Current Evidence for Sleep Management in Pain

Previous research has demonstrated substantial heterogeneity in pain responses and oscillatory patterns among individuals with chronic pain, as assessed through diverse QST [13, 116] and brain activity [32, 503]. Classifying individuals with chronic pain according to their sleep characteristics may reveal more homogeneous subgroups with distinct somatosensory or neural profiles. Our cross-sectional study supports this hypothesis, indicating impaired pain processing and altered brain activity in individuals with comorbid chronic pain and insomnia, but not in those with pain alone. Given that such neurophysiological abnormalities are linked to greater pain intensity and poorer clinical outcomes [101, 504], stratification based on sleep and pain profiles may represent a critical

first step in tailoring chronic pain management. This approach could facilitate more targeted interventions and improve treatment effectiveness by addressing underlying mechanisms that differ across subgroups (**Figures**

Figure 13).

In our study, sleep status was determined using the Brief Insomnia Questionnaire according to the criteria outlined in DSM-5, implemented by a semi-structured interview. To further validate the presence of insomnia or poor sleep quality, we administered the ISI and the PSQI, using established cutoff scores [282, 283]. However, such comprehensive assessment procedures may be impractical in primary care settings due to time constraints. While single-item screening questions have been commonly used in prior studies and may offer greater feasibility in clinical practice, they are associated with unacceptably low accuracy and may risk misclassifying sleep problems due to deviations from validated instruments [505, 506]. One study found that both the ISI and PSQI demonstrate moderate accuracy in detecting insomnia among individuals with LBP [505]. A recent scoping review recommended using the PSQI for a general overview of sleep symptoms, the ISI for assessing insomnia risk, and the STOP-Bang questionnaire for screening obstructive sleep apnea [506]. Collectively, clinicians should begin by asking brief screening questions to identify potential sleep problems (i.e., trouble falling asleep, staying asleep, or early morning awakenings). If such symptoms are reported, validated tools like the ISI and PSQI should be used to assess the type and intensity of the disturbance. When scores exceed established cutoff points (PSQI >

5, ISI > 14, or STOP-Bang > 2), it is appropriate to refer the individual to a sleep medicine specialist for further evaluation and formal diagnosis [447].

Clinicians could differentiate individuals with comorbid chronic pain and insomnia from those with chronic pain alone using the aforementioned screening and assessment procedures. When patients report only pain-related symptoms, treatment should follow existing clinical guidelines for chronic pain [2, 507, 508]. However, if both pain and sleep disturbances are present, additional interventions targeting sleep should be considered. Current evidence supports CBT to be the primary treatment for individuals with comorbid chronic pain and insomnia [41, 46]. A systematic review reported that CBT produced a large effect on sleep outcomes (0.89) but only a small effect size on pain (0.20) in this population [41]. Following CBT, the probabilities of improved sleep and reduced pain were 81% and 58%, respectively [41]. Further comparisons of CBT components revealed that CBT for insomnia was more effective in improving pain intensity, disability, and sleep outcomes than CBT for pain or combined CBT for both insomnia and pain [206]. Despite its clinical utility, CBT faces several barriers in primary care, including low adherence, high costs, a higher incidence of mild adverse events, and a shortage of trained clinicians [47, 48]. These limitations highlight the necessity of developing alternative, accessible, and effective treatment approaches.

Although interventions such as gabapentin, pregabalin, physical therapy, and complementary or alternative medicine have been recommended for treating sleep problems in chronic pain populations, the evidence supporting their efficacy for comorbid conditions remains limited

[17, 46]. Given that comorbid chronic pain and insomnia and chronic pain are associated with dysregulated central pain processing and abnormal neural oscillations [12, 49], our pilot RCT (Chapter 8) investigated the feasibility of a two-week rTMS treatment as a potential neuromodulator treatment in this population. The intervention demonstrated high adherence, no attrition, and no serious adverse events, supporting its feasibility, tolerability, and safety. Preliminary efficacy findings showed that low-frequency rTMS over the DLPFC significantly reduced pain intensity, improved descending pain inhibition, and alleviated insomnia severity and objective WASO compared to sham stimulation.

9.3 Future Research Directions

This thesis lays the foundation for advancing research at the intersection of sleep and pain. Several key research directions have emerged from the current work (**Figure 14**). Our first systematic review highlighted a significant gap in existing research regarding the effects of sleep deprivation paradigms on individuals with chronic pain. Further studies should investigate how sleep loss influences peripheral and central sensitization in this population. Such studies would enhance our understanding of the causal role of sleep disturbances on pain processing among clinical populations.

The relatively small sample size in our cross-sectional study may have constrained statistical power for some parameters, particularly in the oscillatory analyses. The development of future large-scale, international neuroimaging initiatives (e.g., ENGIMA consortium [346]) is needed to confirm these findings by classifying individuals with chronic pain according to

their sleep characteristics. The current findings underscore the critical role of identifying distinct pain-sleep phenotypes, which could enhance the precision and clinical relevance of future research. Moreover, future studies should carefully account for the complex interactions between chronic pain and insomnia in their analyses. Identified neurophysiological characteristics of comorbid conditions were derived from cross-sectional studies, which constricts us to determine causal links among chronic pain, insomnia, pain perception, and neural activity. Therefore, future large-scale, high-quality prospective research is essential to clarify the temporal relationship between these factors.

Our cross-sectional study has identified several neurophysiological markers (e.g., PPT, MPT, CPM, and functional connectivity across DMN, FPN, and SN) that may distinguish individuals with comorbid chronic pain and insomnia from those with chronic pain alone or from asymptomatic individuals. However, it remains unclear which specific components of QST assessments or neuroimaging measures are most sensitive or reliable to be chosen as diagnostic tools or prognostic biomarkers for predicting treatment response in comorbid conditions. Additionally, it may be worth exploring whether integrating data across multiple modalities can improve classification accuracy for distinct pain-sleep phenotypes. As such, future research should apply advanced analytic approaches (e.g., machine learning algorithms) to evaluate the predictive value and clinical utility of these neurophysiological features.

Evidence regarding the evaluation and management of comorbid chronic pain and sleep disturbances remains limited. Although a recent scoping review outlined terminology used in chronic pain research and offered general guidance on sleep assessment in this context [506], there is currently no standardized approach tailored to this population. To enhance consistency across studies and ensure clinical applicability, a systematic evaluation of the measurement properties of various sleep assessment tools in chronic pain and an international, multidisciplinary consensus on such tools are urgently needed. In addition, our network meta-analysis focused exclusively on non-pharmacological interventions, without considering pharmacological treatments that have been recommended in previous research [17]. Future network meta-analyses should estimate the relative effectiveness and safety of pharmacological treatments to address sleep problems in people with chronic pain.

Since current evidence for comorbid chronic pain and insomnia primarily centers on CBT, additional clinical research is needed to investigate alternative interventions (e.g., exercise, mind-body exercise, and non-invasive brain stimulation) aimed at improving sleep in this complex population. Insights from our cross-sectional study suggest that effective interventions should target mechanisms linking central sensitization and abnormal brain activity. Modulating neural activity directly may help restore these imbalances and improve clinical outcomes. Our pilot RCT provided preliminary support for the feasibility, safety, and efficacy of rTMS in individuals with comorbid conditions. These promising findings underscore the need for rigorously designed, larger-scale, definitive RCT to optimize rTMS protocols and examine their therapeutic potential in this complex clinical population.

Notably, the clinical effectiveness of rTMS depends on several stimulation parameters (e.g., stimulation frequency, targeted areas, pulses) [500]. Future research should compare different protocol configurations to identify the most effective treatment strategies for this complex clinical group. If rTMS are proven to be a feasible and effective intervention, head-to-head comparisons with CBT will be essential to inform clinical decision-making and expand treatment options in comorbid conditions.

9.4 Limitations of the Studies

Several limitations should be acknowledged across the studies included in this thesis. First, some findings in the first systematic review were pooled from a limited number of studies with heterogeneous designs. These analyses might introduce heterogeneity or bias, and the findings should be interpreted cautiously. Second, the cross-sectional study accounted for potential confounders such as age, gender, and pain classification. This may restrict the applicability of findings to older population, males, or individuals with different chronic pain conditions. Third, although participants with clinically diagnosed depression or anxiety disorders were excluded, those with comorbid CLBP and insomnia showed significantly higher depression and anxiety levels. The impact of these psychological factors on between-group differences cannot be completely ruled out. Fourth, the EEG source reconstruction was conducted using the standard MNI template, which inherently limits spatial resolution and may not accurately capture individual variations in head anatomy. Fifth, despite initial plans to conduct a meta-analysis in the second systematic review, considerable variability in sleep assessment tools, follow-up periods, and LBP-related outcomes precluded quantitative

synthesis. Finally, while interventions in the third systematic review and network meta-analysis were categorized according to previous guidelines [431] and other NMAs [432, 433], grouping several similar interventions into a single node might introduce potential heterogeneity.

9.5 Conclusions

This project has significantly enhanced our understanding of the interplay between sleep disturbance and chronic pain. The findings consistently demonstrate the detrimental effects of poor sleep on pain sensitivity, central pain regulation, and brain function in healthy individuals and those with chronic pain. Sleep emerged as a modifiable prognostic factor, with CBT, exercise, mind-body exercise, non-invasive brain stimulation as the effective non-pharmacological intervention for improving sleep in individuals with chronic musculoskeletal pain. Importantly, the pilot RCT provided preliminary evidence for the feasibility and efficacy of rTMS in individuals with comorbid CLBP and insomnia. These findings underscore emphasize the critical need for routine assessment and management of sleep problems in chronic pain management. Further research is warranted to validate these findings, optimize intervention strategies, and explore mechanisms underlying the sleep-pain relationship to guide precision treatments for comorbid conditions.

9.6 Figures

Figure 13. Management in chronic pain and sleep

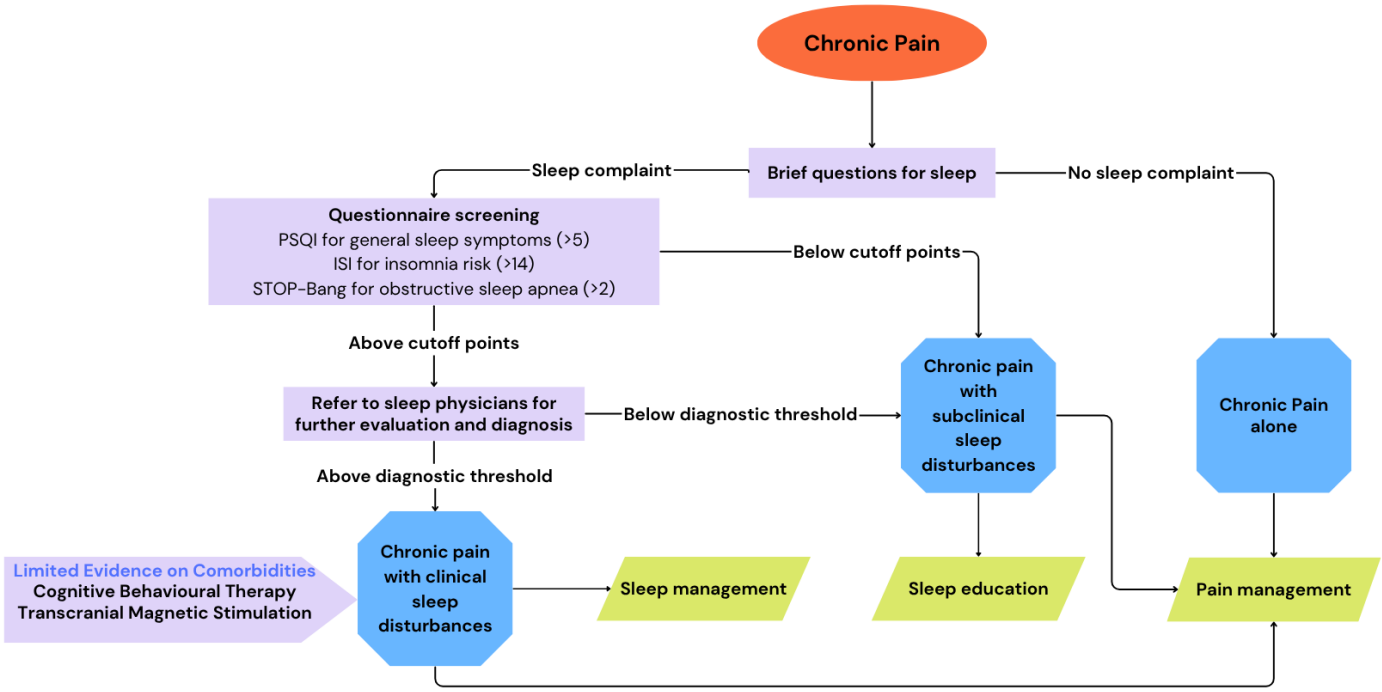
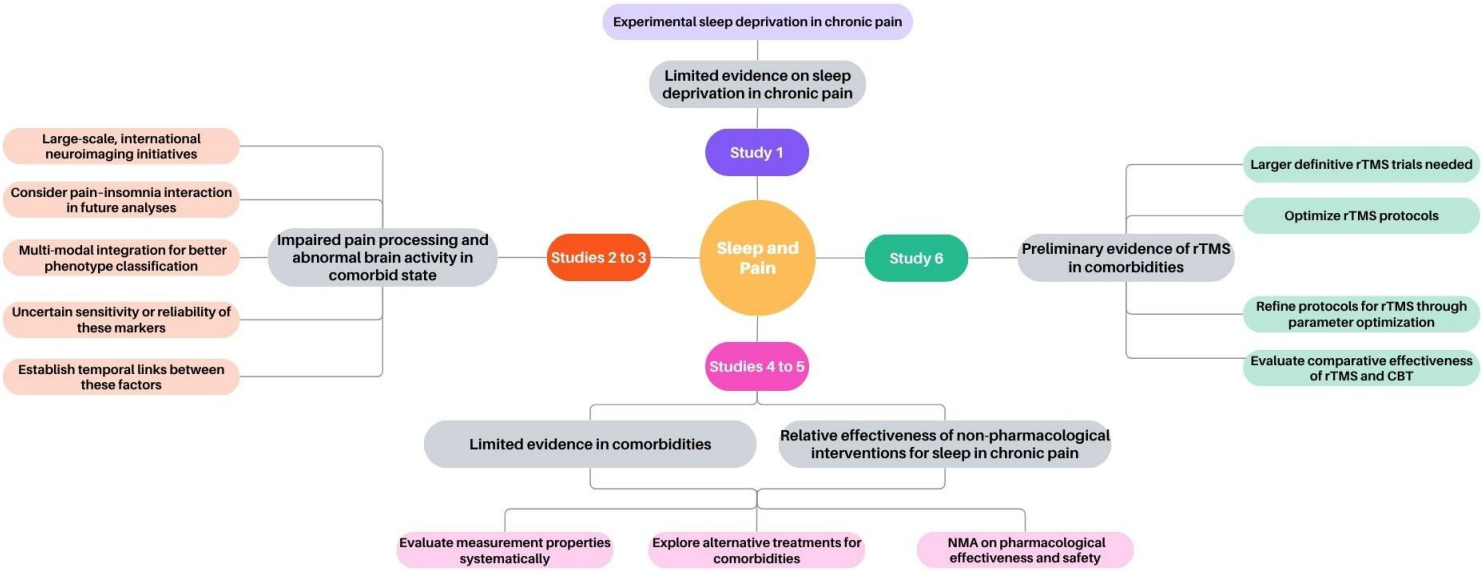


Figure 14. Future research directions



Appendices

Appendix 1. Search strategy in Chapter 3

Table S1.1 Search strategy

1	Pain perception OR pain interference OR pain intensity OR pain threshold OR pain processing OR pain modulation OR pain sensitivity OR pain sensation OR central sensitization OR pain tolerance OR pain severity
2	Pain measurement OR pain assessment OR pain testing OR experimental pain OR nociception test* OR analgesia* test* OR evoked pain OR induced pain OR pain induction OR pain administration OR quantitative sensory testing
3	1 OR 2
4	Pain stimul* OR acute pain response* OR pressure pain threshold OR pressure stimul* OR mechanical pain OR mechanical stimul* OR electric stimul* OR dolorimeter OR algometer OR thermal pain OR thermal stimul* OR heat pain OR heat stimul* OR cold pressor OR cold stimul* OR temporal summation of pain OR spatial summation of pain OR visual analog scale OR VAS OR McGill pain questionnaire OR numeric pain rating scale OR numeric rating scale OR NPRS
5	3 OR 4
6	Sleep restrict* OR sleep depriv* OR sleep loss OR sleep interruption OR sleep fragment* OR sleep insufficiency OR insufficient sleep OR sleep deficiency OR inadequate sleep OR sleepless* OR lack of sleep
7	5 AND 6

Appendix 2. Level of evidence in Chapter 3

Table S1.2. Levels of evidence

	Level	Strength of evidence assessment
1	Strong evidence	Pooled results from three or more studies with a minimum of two high-quality studies that were statically homogenous ($I^2 > 0.05$); may be associated with a statistically significant or non-significant pooled result.
2	Moderate evidence	Statistically significant pooled results from multiple studies that were statistically heterogeneous ($I^2 < 0.05$), including at least one high-quality study, or results from multiple moderate- or low-quality studies that were statistically homogenous ($I^2 > 0.05$).
3	Limited evidence	Pooled results from one high-quality study or multiple moderate- or low-quality studies that were statistically heterogeneous ($I^2 < 0.05$).
4	Very limited evidence	Pooled results from one moderate- or low-quality study.
5	Conflicting evidence	Pooled results that were not significant and derived from multiple studies, regardless of quality, that were statistically heterogeneous ($p < 0.05$, i.e., inconsistent).
6	No evidence	No studies were identified.

Appendix 3. Study characteristics of the included studies in Chapter 3

Table S1.3. Study characteristics of the included studies

Study	Study design	Country	Characteristics of participants	Sleep manipulation	Control	Assessment tool	Testing Site	Pain measure
The effects of SD on pain perception in healthy individuals								
Ablin et al (2013) [35]	RCT	Israel	Healthy participants (n = 46, 27.2 years, and 48% female)	Partial SD (2h for ten days at home)	Habitual sleep (7-9h for ten days at home)	Short VAS from MPQ	Generalized body pain	Pain intensity
Arima et al (2001) [14]	One-way repeated measure design	Denmark	Healthy participants (n = 10, 22.7 years, and 0% female)	Selective slow-wave (NREM stage 3 and 4) SD (Three days at the lab)	Habitual sleep (9h for one night at the lab)	100mm VAS	Headache, jaw muscles, and neck/shoulder.	Pain intensity
						Pressure (Algometer)	Masseter	Pain threshold
Azevedo et al (2011) [41]	RCT	Brazil	Healthy participants (n = 28, 23.5years, and 0% female)	Selective REM SD (Four days at the lab) Total SD (Two days at the lab)	Habitual sleep (9h for four days at the lab)	Heat (Radiant)	Dorsum of hand	Pain threshold
Drews et al (2000) [15]	One-way repeated measure design	Denmark	Healthy participants (n = 20, 22.7 years, and 70% female)	Selective slow-wave (NREM stage 3 and 4) SD (Three days at the lab)	Habitual sleep (9.5h for one day at the lab)	100mm VAS	Generalized body pain, joint pain, headache, neck/shoulder, and lower back	Pain intensity
						Cold (Water)	Forearm	Pain threshold and tolerance
						Heat (Thermode)	Forearm	Pain threshold
						Pressure (Algometer)	lateral epicondyle,	Pain threshold

							trapezius, knee pads, and gluteal muscles	
						Mechanical (Electrical)	Hand	Pain threshold
Eichhorn et al (2018) [42]	Non-randomized balanced crossover study	Germany	Healthy participants (n = 36, 23.6 years, and 50% female)	Total SD (One day at the lab)	Habitual sleep (8h for one day at home)	Cold (Thermode)	Dorsum of hand	Pain threshold and tolerance
						Heat (Thermode)	Dorsum of hand	Pain threshold
						Pressure (Algometer)	Dorsum of hand	Pain threshold
						Mechanical (Electrical)	Dorsum of hand	Pain threshold and temporal summation
						Cold (Ice water) and pressure (Algometer)	Distal forearm	CPM
Faraut et al (2015) [50]	Randomized crossover study	France	Healthy participants (n = 11, 27.0 years, and 0% female)	Partial SD (6h for one day at the lab)	Habitual sleep (8h for one day at the lab)	Cold (Thermode)	Lower back, Supraspinatus, and thigh	Pain threshold
						Heat (Thermode)	Lower back, Supraspinatus, and thigh	Pain threshold
						Pressure (Algometer)	Lower back, Supraspinatus, and thigh	Pain threshold
Haack et al (2009) [43]	RCT	USA	Healthy participants (n = 24, 35.1 years, and 29% female)	Total SD (Three days at the lab)	Habitual sleep (8h for three days at the lab)	100mm VAS	Generalized body pain	Pain intensity
Haack and Mullington (2005) [51]	RCT	USA	Healthy participants (n =	Partial SD (4h for 12 days at the lab)	Habitual sleep (8h for	100mm VAS	Generalized body pain, backache,	Pain intensity

			40, 26.3 years, and 35% female)		12 days at the lab)		headache, joint pain, muscular pain	
Hakkionen et al (2001) [44]	Randomized crossover study	France	Healthy participants (n = 9, 31.0 years, and 0% female)	Total SD (One day at the lab)	Habitual sleep (8h for one day at the lab)	Heat (Thermode)	Thenar eminence	Pain tolerance
						Pressure (Algometer)	Finger	Pain tolerance
Irwin et al (2012) [34]	One-way repeated measure design	USA	Healthy participants (n = 27, 60.4 years, and 78% female)	Partial SD (4h for one day at the lab)	Habitual sleep (8h for one day at the lab)	MPQ	Generalized body pain	Pain intensity
Kamiyama et al (2019) [12]	Randomized crossover study	Japan	Healthy participants (n = 13, 27.6 years, and 46% female)	Total SD (One day at the lab)	Habitual sleep (6.6h for one day)	Pressure (Algometer)	Thumb and tongue tip	Pain threshold
						Mechanical (Electrical)	Thumb and tongue tip	Pain threshold
Krause et al (2019) [10]	Non-randomized balanced crossover study	USA	Healthy participants (n = 25, 20.8 years, and 48% female)	Total SD (One day at the lab)	Habitual sleep (8h for one day at the lab)	Heat (Thermode)	Leg	Pain threshold
Kristiansen et al (2017) [36]	One-way repeated measure design	Denmark	Healthy participants (n = 15, 23.1 years, and 40% female)	Total SD (One day at home)	Habitual sleep (One day at home)	Pressure (Algometer)	Temporal and masseter muscle	Pain threshold
						Pressure and cold	Temporal and masseter muscle	CPM
Kundermann et al (2004) [45]	RCT	Germany	Healthy participants (n = 20, 35.8 years, and 45% female)	Total SD (Two days at the lab)	Habitual sleep (8h for two days at the lab)	Pain questionnaire	Generalized body pain	Pain intensity
						Cold (Thermode)	Volar forearm	Pain threshold
						Heat (Thermode)	Volar forearm	Pain threshold
Lacovides et al (2017) [55]	Randomized crossover study	South Africa	Healthy participants (n = 11, 21 years, and 100% female)	Sleep fragmentation (Two days at the lab)	Habitual sleep (8h for one day at the lab)	PILL	Generalized body pain	Pain intensity
						Mechanical (Electrical)	Hand	Pain threshold

						Pressure (ischemia)	Forearm	Pain tolerance
Larson and Carter (2016) [46]	Randomized crossover study	USA	Healthy participants (n = 27, 22 years, and 48% female)	Total SD (One day at the lab)	Habitual sleep (7.5h for one day at the lab)	Cold (Ice water)	Hand	Pain threshold
Letzen et al (2020) [56]	Non-randomized balanced crossover study	USA	Healthy participants (n = 19, 24.0 years, and 68% female)	Sleep fragmentation (One day at the lab)	Habitual sleep (8h for one day at the lab)	Heat (Thermode)	NA	Pain threshold
Matre et al (2016) [38]	Randomized crossover study	Norway	Healthy participants (n = 22, 23.2 years, and 64% female)	Partial SD (50% habitual sleep for two days at home)	Habitual sleep (7.4h for two days at home)	Heat (Thermode)	Volar forearm	Pain threshold
						Cold (Ice water)	Volar forearm	CPM
Matre et al (2015) [37]	Randomized crossover study	Norway	Healthy participants (n = 21, 23.4 years, and 62% female)	Partial SD (50% habitual sleep for two days at home)	Habitual sleep (7.4h for two days at home)	Pressure (Algometer)	Volar forearm	Pain threshold
						Mechanical (Electrical)	Volar forearm	Pain threshold
Moldofsky and Scarisbrick (1976) [54]	Non-randomized balanced crossover study	Canada	Healthy participants (n = 13, 22.0 years, and 8% female)	Selective NREM stage 4 SD (Two days at the lab) Selective REM SD (Three days at the lab)	Habitual sleep (Two days at the lab) Habitual sleep (Three days at the lab)	Scale for musculoskeletal symptom intensity (0-6)	Generalized body pain	Pain intensity
Neverdahl et al (2021) [52]	Randomized crossover study	Norway	Healthy participants (n = 31, 36.2 years, and 74% female)	Partial SD (4h for two days at the lab)	Habitual sleep (7h for two days at the lab)	Heat (Thermode)	Volar forearm	Heat threshold and tolerance
						Pressure (Algometer)	Trapezius muscles	Pain threshold

Odegard et al (2015) [39]	RCT	Norway	Healthy participants (n = 33, 22.9 years, and 52% female)	Partial SD (4h for one day at home)	Habitual sleep (9h for one day at home)	Cold (Thermode)	Palm and forehead	Pain threshold
						Heat (Thermode)	Palm and forehead	Pain threshold and temporal summation
Roehrs et al (2006) [47]	One-way repeated measure design	USA	Healthy participants (n = 13, 25.2 years, and 31% female)	Total SD (One day at the lab) Partial SD (4h or 2h for one day at the lab) Selective SD (one day at the lab) Selective NREM SD (one day at the lab)	Habitual sleep (8h for one day at the lab)	Heat (Radiant)	Finger	Pain tolerance
Schuh-Hofer et al (2015) [48]	Non-randomized balanced crossover study	Germany	Healthy participants (n = 12, 23.2 years, and 42% female)	Total SD (One day at the lab)	Habitual sleep (7.4h for one day at home)	Heat (Radiant)	Dorsum of hand	Pain threshold
Schuh-Hofer et al (2013) [49]	Randomized crossover study	Germany	Healthy participants (n = 14, 23.5 years, and 43% female)	Total SD (One day at the lab)	Habitual sleep (7.4h for one day at home)	Cold (Ice water)	Dorsum of hand	Pain threshold
						Heat (Thermode)	Dorsum of hand	Pain threshold
						Pressure (Algometer)	Thenar eminence	Pain threshold
						Mechanical (Electrical)	Dorsum of hand	Pain threshold and temporal summation

Simpson et al (2018) [13]	Randomized crossover study	USA	Healthy participants (n = 14, 25.1 years, and 50% female)	Partial SD (4h for five days at the lab)	Habitual sleep (8h for five days at the lab)	100mm VAS	Generalized body pain, headache, and back pain	Pain intensity
						Cold (Ice water)	Thenar eminence	Pain tolerance and temporal summation
						Heat (Thermode)	Thenar eminence	Pain threshold
Smith et al (2019) [16]	Randomized crossover study	USA	Healthy participants (n = 79, 27.2 years, and 58% female)	Sleep fragmentation (Two days at the lab)	Habitual sleep (8h for two days at the lab)	Cold (Water)	Hand	Pain tolerance
						Heat (Thermode)	Volar forearm	Pain threshold
						Pressure (Algometer)	Thumb	Pain threshold
						Mechanical (Electrical)	Volar forearm	Temporal summation
Smith et al (2007) [53]	RCT	USA	Healthy participants (n = 32, 25.3 years, and 100% female)	Sleep fragmentation (3 days at the lab) Partial SD (3 days at the lab)	Habitual sleep (7.5h for three days at the lab)	PILL	Generalized body pain	Pain intensity
						Pressure (Algometer) and cold condition (Ice water)	Volar forearm or Trapezius	Pain threshold and CPM
Staffe et al (2019) [11]	One-way repeated measure design	Denmark	Healthy participants (n = 24, 22.6 years, and 33% female)	Total SD (one day at home)	Habitual sleep (7.3h for one day at home)	Cold (Ice water)	Volar forearm	Pain tolerance
						Heat (Thermode)	Volar forearm	Pain threshold
						Pressure (Algometer)	Gastrocnemius muscle	Pain threshold, tolerance, and CPM
						Mechanical (Electrical)	Gastrocnemius muscle	Temporal summation

Tiede et al (2010) [40]	One-way repeated measure design	Germany	Healthy participants (n = 10, 25.3 years, and 20% female)	Partial SD (3.87h for one day at home)	Habitual sleep (7.2h for one day at home)	Heat (Radiant)	Dorsum of hand	Pain threshold
The effects of SD on pain perception in patients with chronic pain								
Bush et al (2011) [33]	One-way repeated measure design	Germany	Patients with chronic somatoform pain patients (n = 20, 50.1 years, and 70% female)	Total sleep deprivation (one day at the lab)	Habitual sleep (7-9h for one day at home)	10cm VAS	Generalized body pain	Pain intensity
						Cold (Thermode)	Dorsum of hand	Pain threshold
						Heat (Thermode)	Dorsum of hand	Pain threshold
						Pressure (Algometer)	Dorsum of hand	Pain threshold
Irwin et al (2012) [34]	One-way repeated measure design	USA	Patients with chronic rheumatoid arthritis (n = 27, 59.9 years, and 89% females)	Partial sleep deprivation (4h for one day at the lab)	Habitual sleep (8h for one day at the lab)	MPQ	Generalized pain perception	Pain intensity
						A 5-point VAS	Joint pain	Pain intensity

Abbreviation: CPM: Conditioned Pain Modulation; MPQ: Mcgill Pain Questionnaire; NA: Not Available; NREM: Non-Rapid Eye Movement; PILL: Pennebaker Inventory Of Limbic Languidness; RCT: Randomized Controlled Trial; REM: Rapid Eye Movement; SD: Sleep Deprivation; VAS: Visual Analog Scale.

Appendix 4. Risk of bias assessment for the included studies in Chapter 3

Figure S1.1. Methodological assessments of randomized controlled trials by the RoB 2.0 tool.

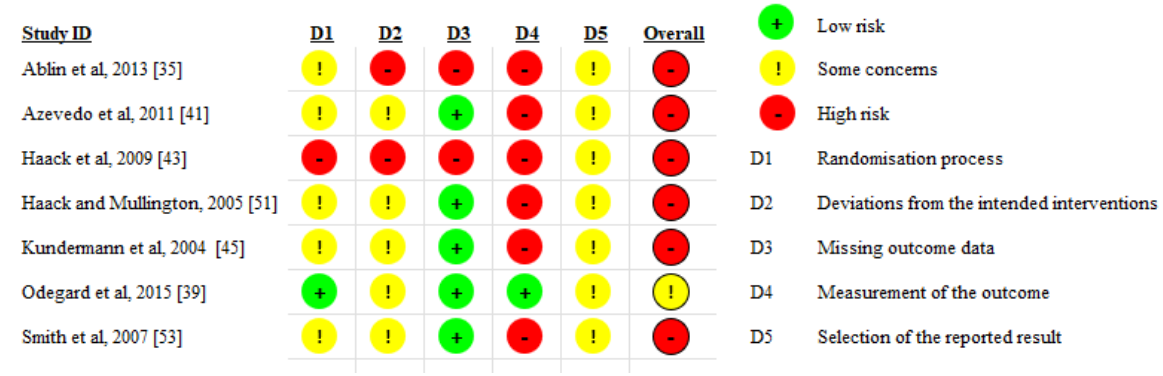


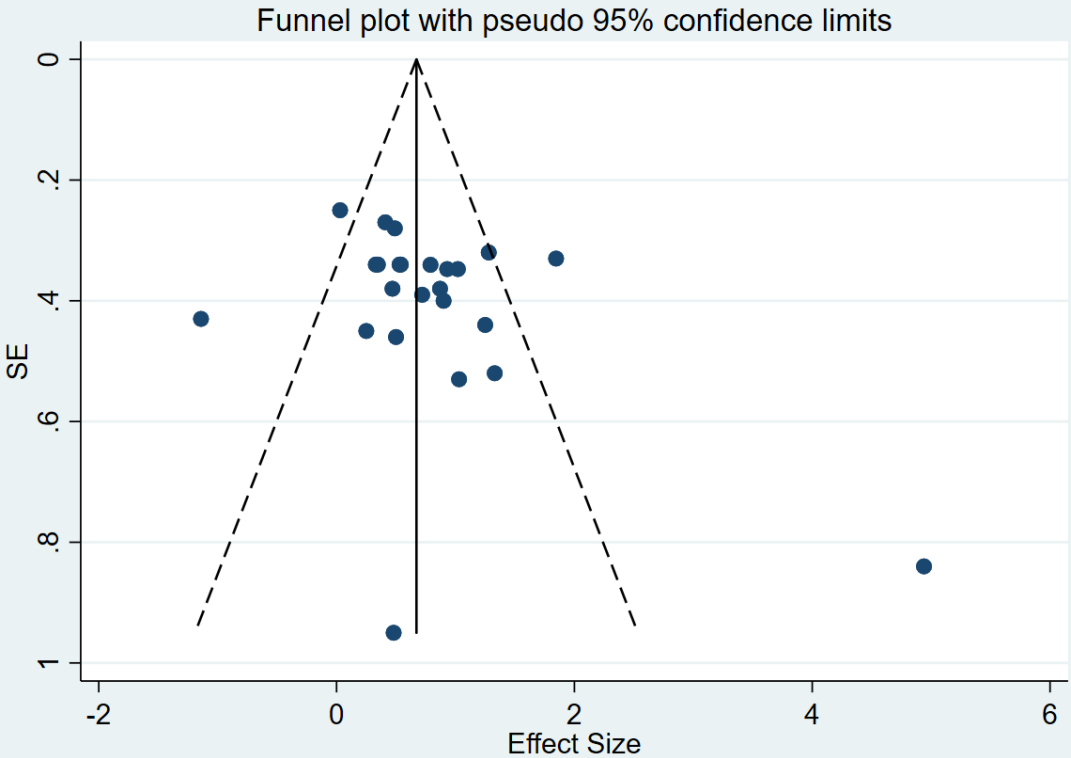
Figure S1.2. Methodological assessments of randomized cross-over trials by the RoB 2.0 tool

Table S1.4. Methodological assessment of non-randomized studies of interventions by the ROBINS-I tool

Study	**Confounding**	**Selection of participants**	**Classification of interventions**	**Deviations from intended interventions**	**Missing data**	**Measurement of outcomes**	**Selection of the reported result**	**Overall**
Arima et al (2001) [23]	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Bush et al (2012) [227]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Drews et al (2000) [24]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Eichhorn et al (2018) [232]	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Irwin et al (2012) [228]	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Krause et al (2019) [19]	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Kristiansen et al (2017) [230]	Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Letzen et al (2020) [191]	Moderate	Low	Low	Low	Low	Serious	Moderate	Serious
Moldofsky and Scarisbrick (1976) [244]	Moderate	Low	Low	Low	Low	Serious	Serious	Serious
Roehrs et al (2006) [237]	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Schuh-Hofer et al (2015) [238]	Low	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Staffe et al (2019) [20]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Tiede et al (2010) [194]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate

Appendix 5. A funnel plot of the publication bias for articles in Chapter 3

Figure S1.3. A funnel plot of the effects of total sleep deprivation on pain threshold in healthy individuals.



Appendix 6. Meta-analysis results in Chapter 3

Figure S1.4. The effects of total sleep deprivation on spontaneous pain intensity in healthy individuals

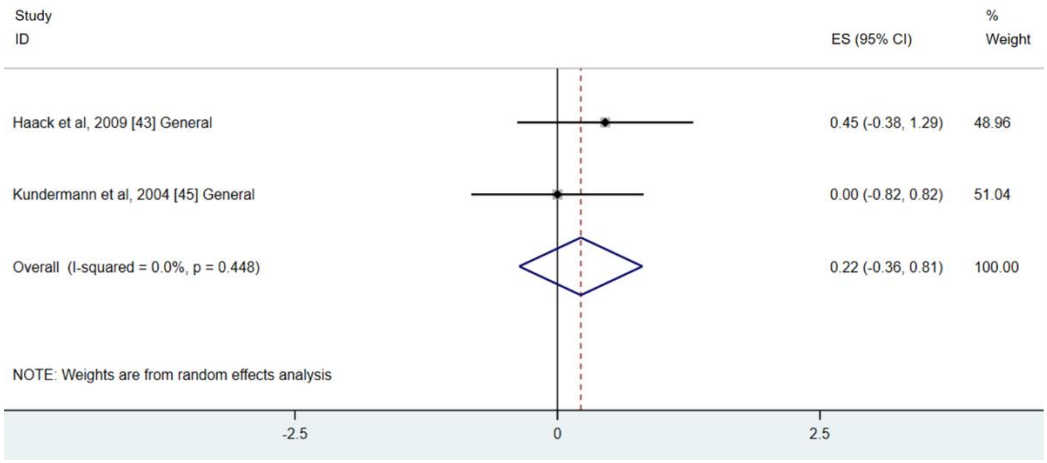


Figure S1.5. The effects of total sleep deprivation on conditioned pain modulation in healthy individuals

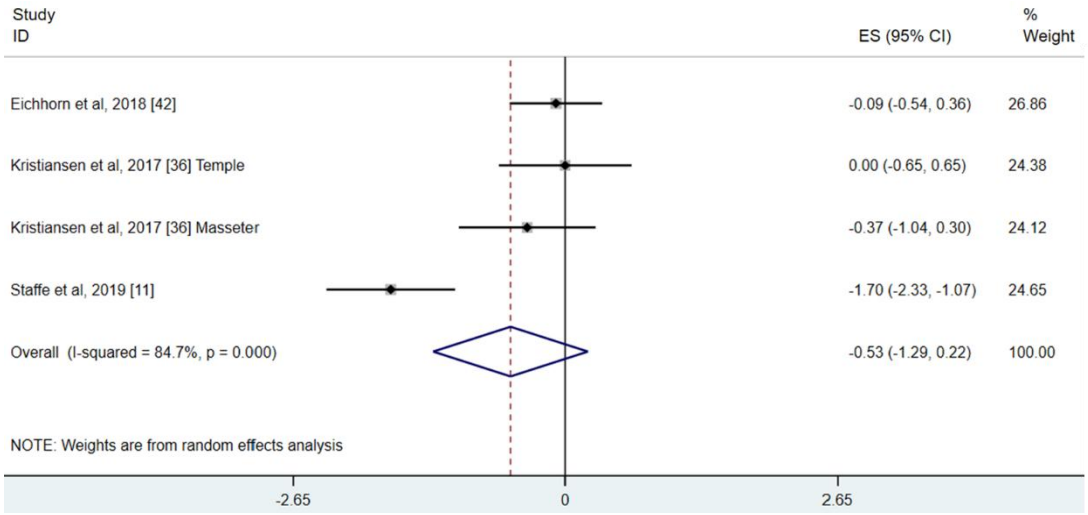


Figure S1.6. The effects of total sleep deprivation on temporal summation of pain in healthy individuals

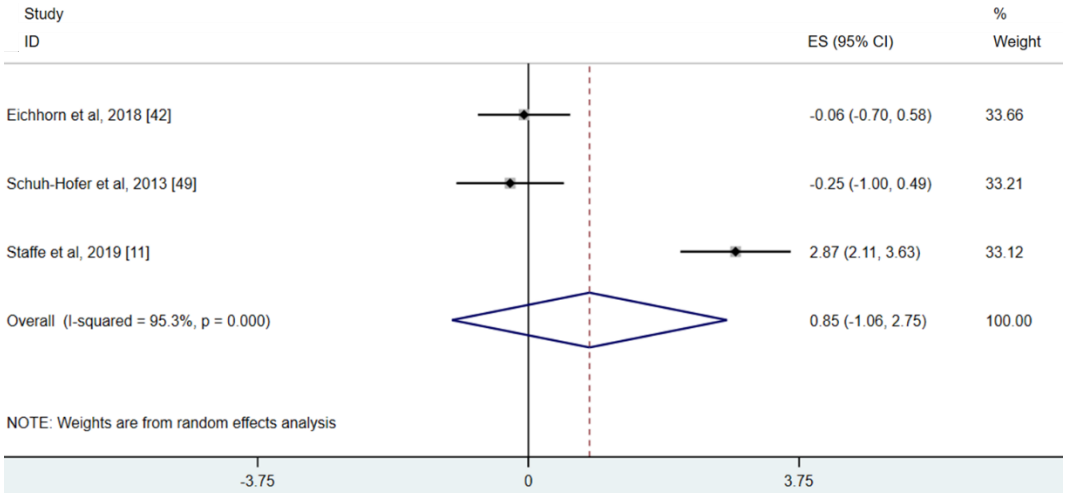


Figure S1.7. The effects of partial sleep deprivation on spontaneous pain intensity in healthy individuals.

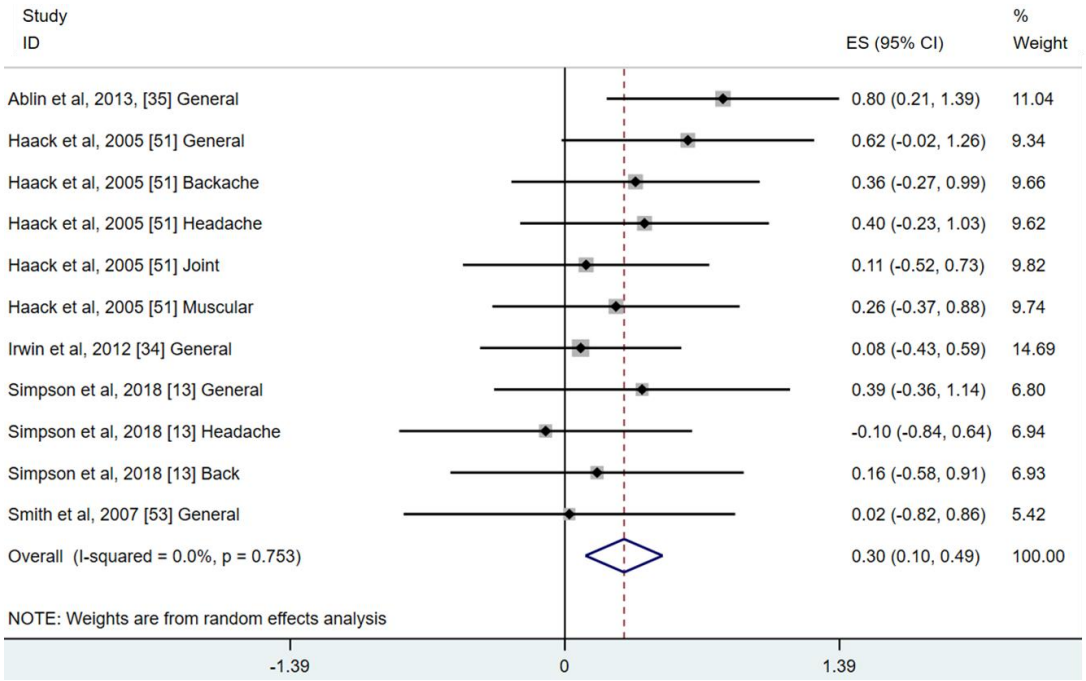
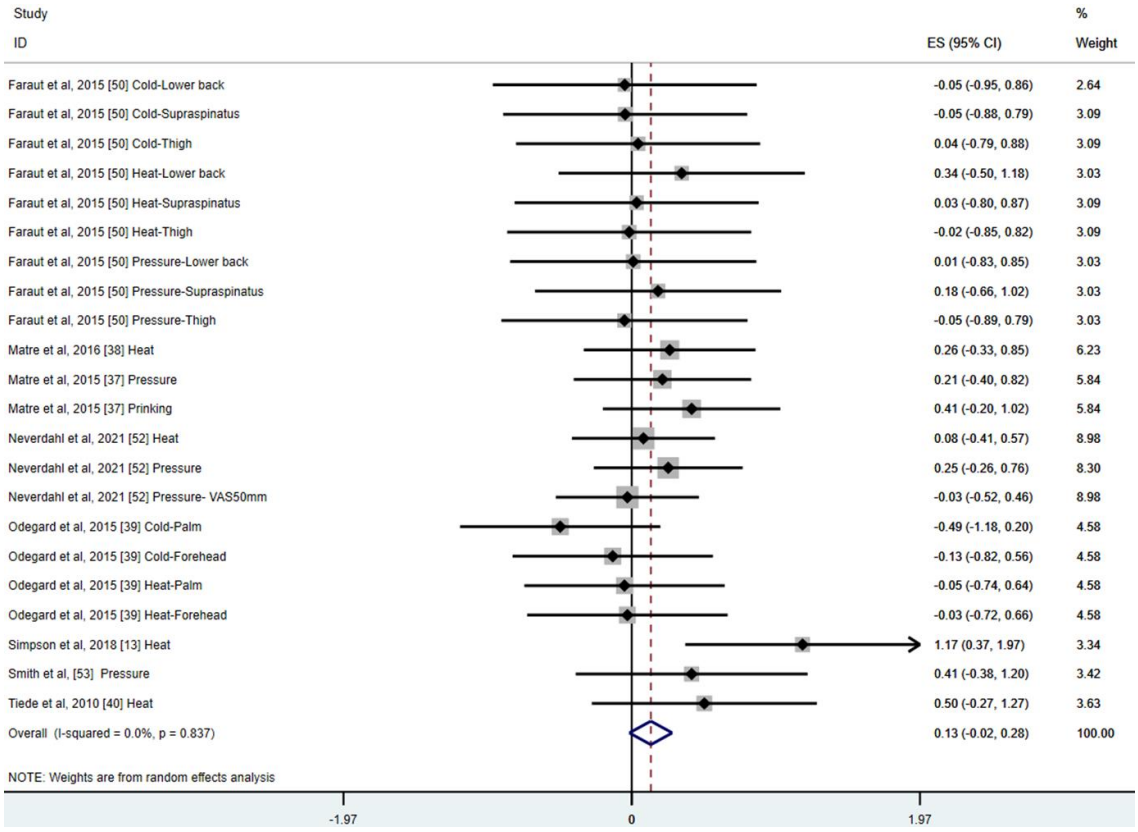


Figure S1.8. The effects of partial sleep deprivation on pain threshold in healthy individuals



Abbreviation: VAS: Visual Analog Scale.

Figure S1.9. The effects of partial sleep deprivation on pain tolerance in healthy individuals

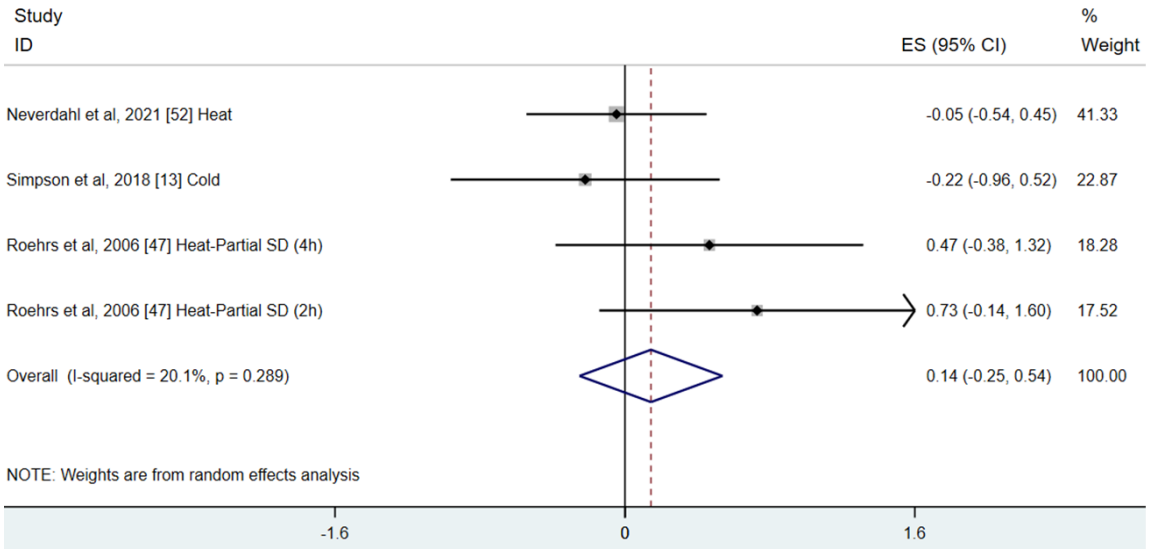


Figure S1.10. The effects of partial sleep deprivation on conditioned pain modulation in healthy individuals

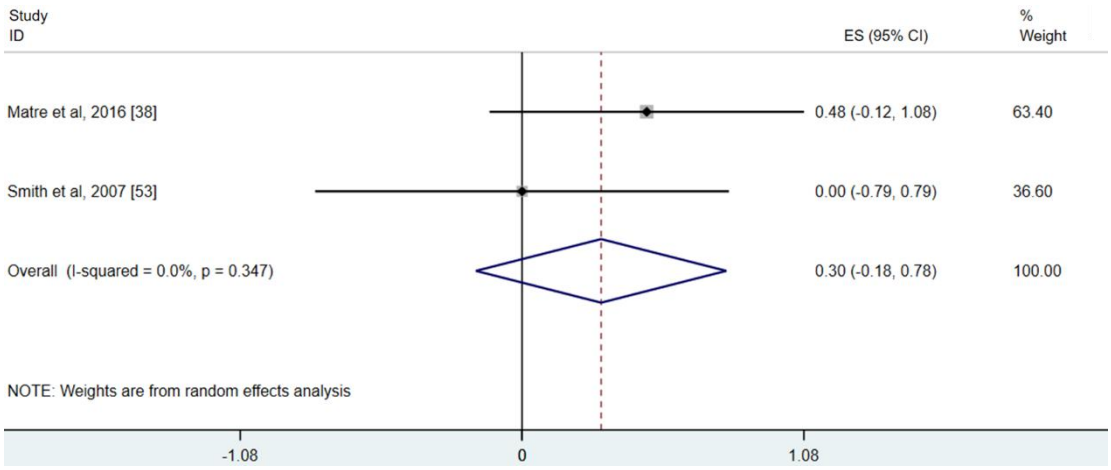


Figure S1.11. The effects of partial sleep deprivation on temporal summation of pain in healthy individuals

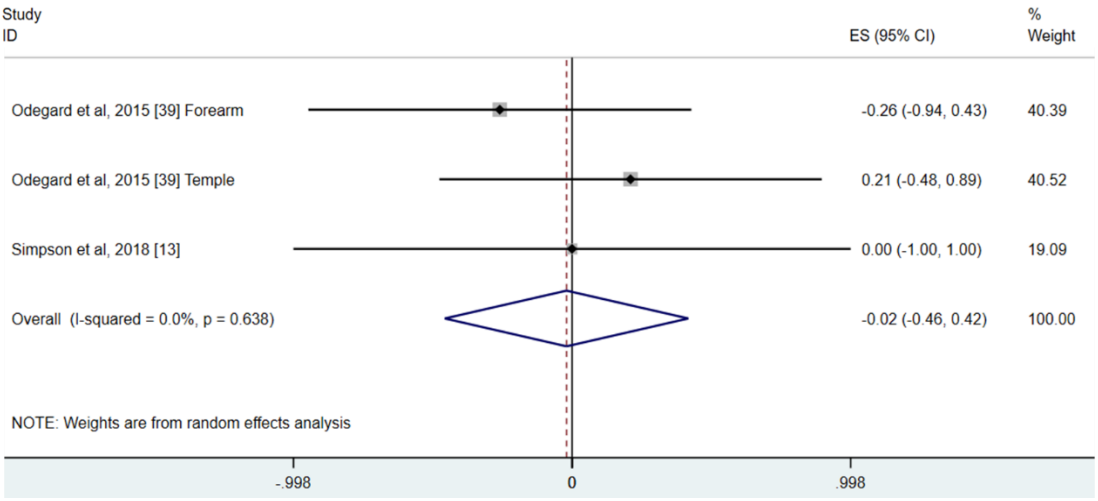
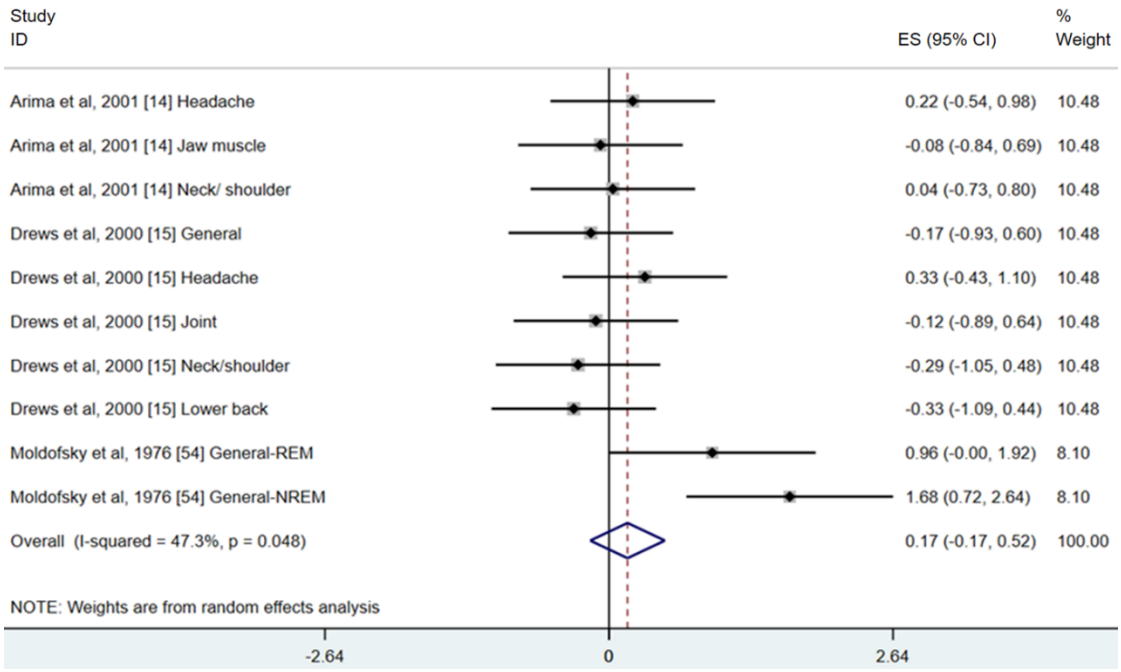


Figure S1.12. The effects of selective sleep deprivation on spontaneous pain intensity in healthy individuals



Abbreviation: NREM: Non-Rapid Eye Movement.REM: Rapid Eye Movement.

Figure S1.13. The effects of selective sleep deprivation on pain threshold in healthy individuals

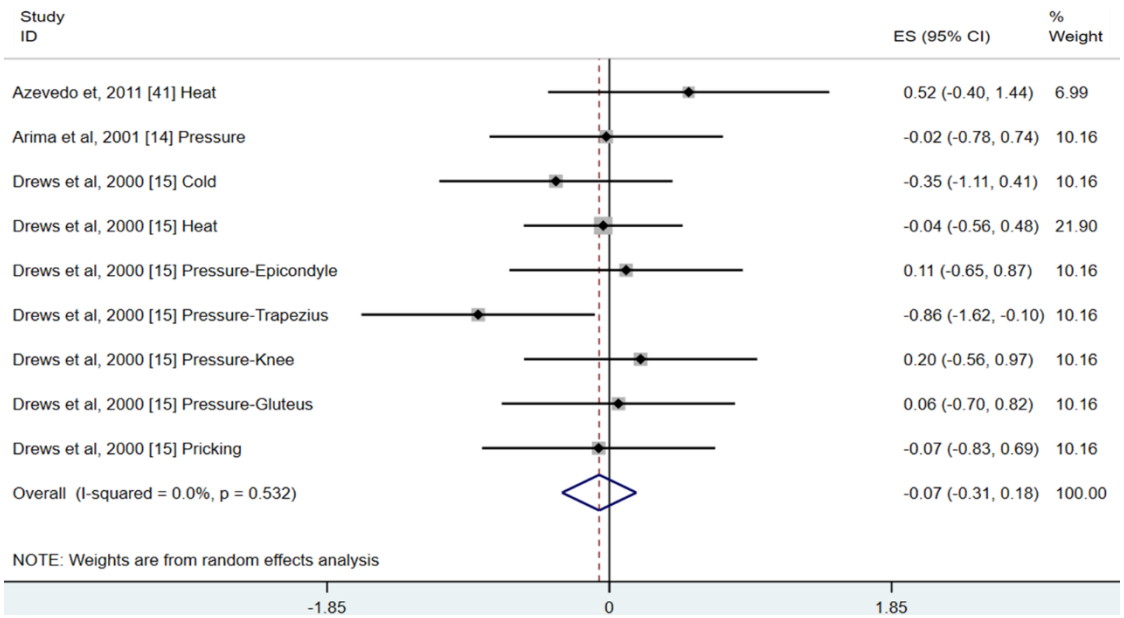
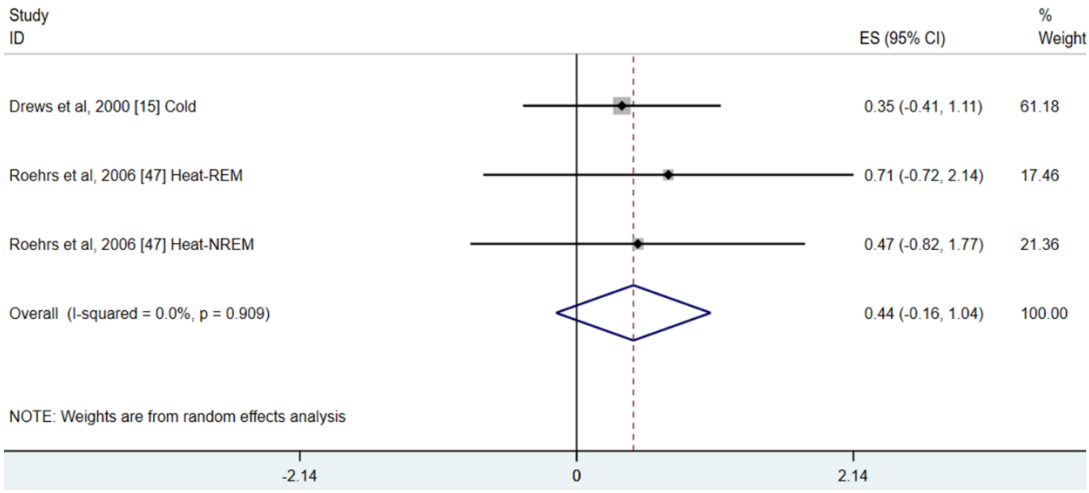


Figure S1.14. The effects of selective sleep deprivation on pain tolerance in healthy individuals



Abbreviation: NREM: Non-Rapid Eye Movement.REM: Rapid Eye Movement.

Figure S1.15. The effects of sleep fragmentation on pain threshold in healthy individuals

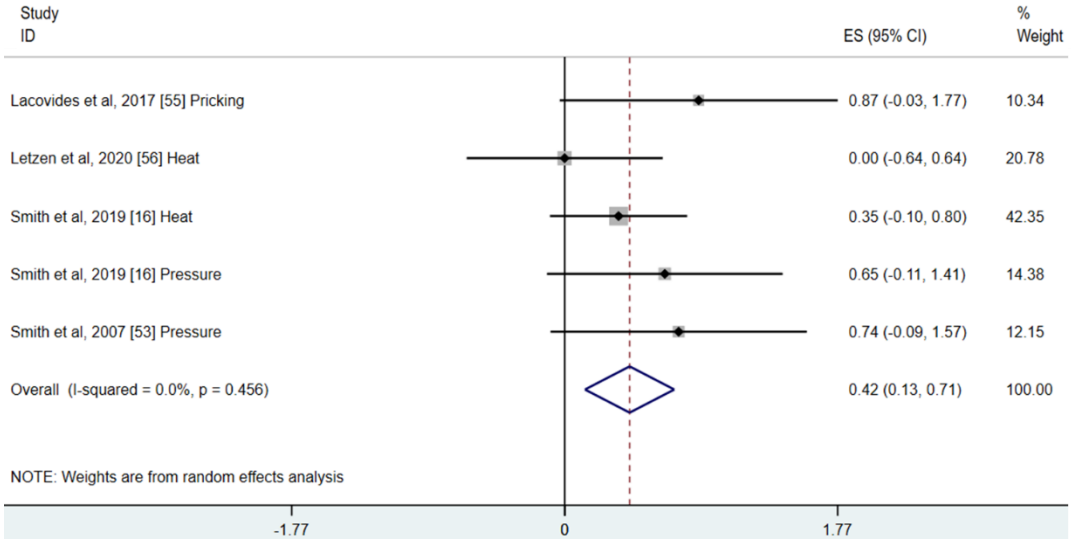


Figure S1.16. The effects of sleep fragmentation on pain tolerance in healthy individuals

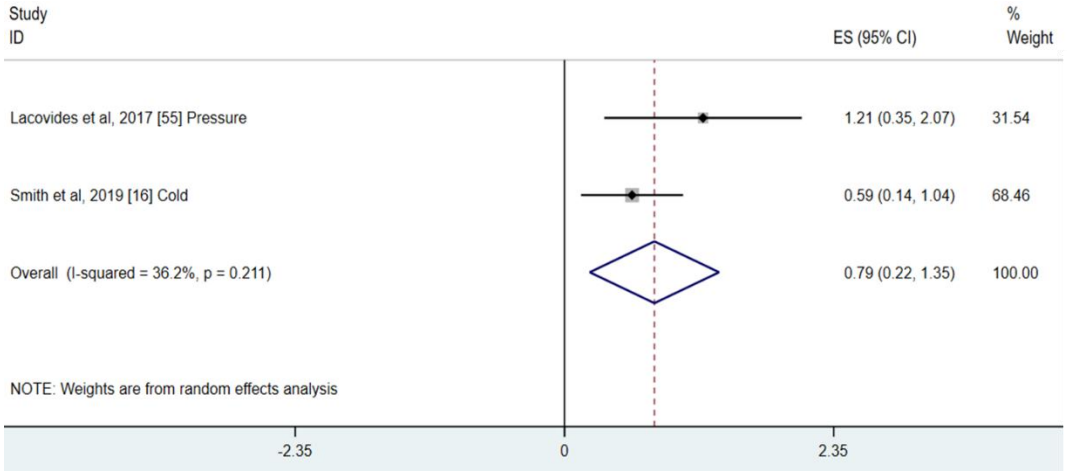
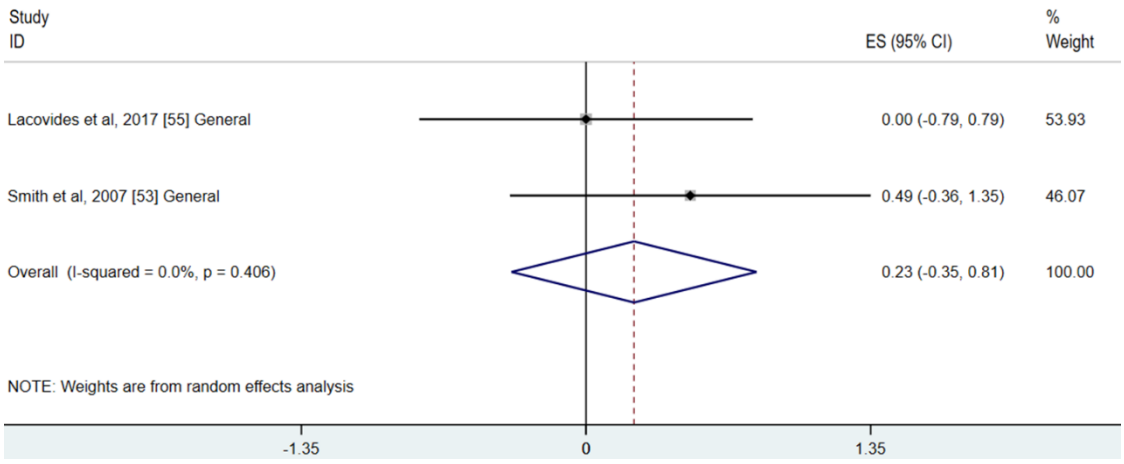


Figure S1.17. The effects of sleep fragmentation on spontaneous pain intensity in healthy individual



Appendix 7. Intra-rater reliability of QST in Chapter 4

Table S2.1. Measure of intra-rater reliability of QST

	$Mean_{1st}$ (SD)	**$Mean_{2se}$ (SD)**	**$ICC_{3,1}$ (95%CI)**
Cold pain threshold (back, ˚C)	15.18 (9.82)	17.74 (10.21)	0.90 (0.65 to 0.98)
Cold pain threshold (hand, ˚C)	13.47 (6.57)	12.96 (6.73)	0.97 (0.88 to 0.99)
Head pain threshold (back, ˚C)	41.54 (2.68)	41.53 (2.14)	0.90 (0.66 to 0.98)
Head pain threshold (hand, ˚C)	42.20 (2.13)	42.41 (2.31)	0.91 (0.67 to 0.98)
Mechanical pain threshold (back, Nm)	1.95 (0.35)	1.90 (0.32)	0.91 (0.69 to 0.98)
Mechanical pain threshold (hand, Nm)	2.04 (0.24)	2.01 (0.23)	0.91 (0.72 to 0.98)
Pressure pain threshold (back, Kg/cm^2)	4.73 (1.54)	4.80 (1.26)	0.91 (0.68 to 0.98)
Pressure pain threshold (hand, Kg/cm^2)	2.45 (0.76)	2.61 (0.63)	0.90 (0.66 to 0.98)
Temporal summation of pain (Mechanical)	2.95 (1.61)	2.55 (1.28)	0.86 (0.53 to 0.96)
Temporal summation of pain (46 ˚C)	-0.05 (1.40)	-0.85 (1.38)	0.78 (0.39 to 0.94)
Temporal summation of pain (48 ˚C)	0.38 (0.99)	-0.45 (1.09)	0.85 (0.51 to 0.96)
Conditioned pain modulation	0.11 (0.43)	0.03 (0.35)	0.76 (0.29 to 0.93)

Abbreviations: ICC: Intraclass correlation coefficient; QST: Quantitative sensory testing; SD: Standard deviation.
Footnote: Values are presented as mean and standard error. The intra-rater reliability of the QST protocol was conducted on ten healthy individuals, with a 5-day interval between two occasions.

Appendix 8. Sensitivity analyese of QST in Chapter 4

Table S2.2. Sensitivity analyses of QST by removing extreme values

	Healthy controls	**Insomnia+**	**CLBP+**	**CLBP+I**	***p* value**
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
Mechanical pain threshold (mN)					
Remote site	2.11 (1.95 to 2.37)	1.96 (1.79 to 2.19)	1.96 (1.75 to 2.22)	1.85 (1.50 to 2.07)	**0.009**
	n=25	n=24	n=25	n=25	
Pressure pain threshold (Kg)					
Remote site	0.49 (0.39 to 0.57)	0.46 (0.33 to 0.55)	0.40 (0.32 to 0.53)	0.33 (0.22 to 0.41)	**0.003**
	n=25	n=25	n=25	n=23	
Back	0.74 (0.64 to 0.82)	0.68 (0.54 to 0.79)	0.70 (0.57 to 0.76)	0.43 (0.32 to 0.54)	**< 0.001**
	n=25	n=25	n=23	n=24	
Temporal summation of heat pain (46°C)	-1.00 (-3.00 to 0.00)	-1.25 (-2.75 to 0.00)	-2.00 (-2.00 to 1.00)	-1.00 (-1.50 to 0.00)	0.661
	n=25	n=24	n=23	n=23	
Temporal summation of heat pain (48°C)	0.00 (-2.00 to 0.00)	-1.00 (-1.25 to 0.00)	0.00 (-1.00 to 0.00)	-0.50 (-1.00 to 0.00)	0.653
	n=25	n=21	n=23	n=22	
Conditioned pain modulation	-0.20 (-0.40 to 0.25)	-0.20 (-0.35 to 0.30)	-0.10 (-0.30 to 0.20)	0.20 (0.10 to 0.30)	**0.009**
	n=25	n=25	n=25	n=22	

Abbreviations: CLBP+: Individuals with non-specific chronic low back pain; CLBP+I: Individuals with concomitant non-specific chronic low back pain and insomnia; Insomnia+: Individuals with insomnia; IQR: Interquartile range; QST: Quantitative sensory testing.
Footnote: Values are presented as median and interquartile range. P value was calculated by the Kruskal-Wallis test with removing participants outside 1.5 times IQR being ranked as outliers. The p-value in bold indicates a statistically significant difference among the four groups ($p < 0.05$).

Table S2.3. Sensitivity analyses of QST by removing individuals with underweight or overweight

	Healthy control (n=19) Median (IQR)	**Insomnia+ (n=17)** Median (IQR)	**CLBP+ (n=21)** Median (IQR)	**CLBP+I (n=19)** Median (IQR)	***p* value**
Cold pain threshold (°C)					
Back	11.04 (0.00 to 21.84)	19.96 (5.84 to 26.66)	24.10 (15.35 to 27.21)	14.30 (8.08 to 27.18)	**0.027**
Remote site	8.56 (5.24 to 14.34)	14.30 (6.25 to 22.88)	18.15 (9.50 to 21.10)	12.76 (10.76 to 22.12)	**0.030**
Heat pain threshold (°C)					
Back	42.30 (40.81 to 43.50)	41.37 (38.35 to 42.95)	39.78 (38.53 to 41.80)	41.20 (37.46 to 42.14)	0.055
Remote site	43.74 (41.60 to 44.99)	42.38 (38.81 to 44.28)	41.58 (39.92 to 43.36)	41.48 (38.94 to 43.32)	**0.011**
Mechanical pain threshold (mN)					
Back	2.28 (1.98 to 2.54)	2.19 (1.69 to 2.42)	1.87 (1.68 to 2.31)	1.84 (1.41 to 2.08)	**0.005**
Remote site	2.07 (1.92 to 2.47)	2.02 (1.86 to 2.25)	1.96 (1.72 to 2.14)	1.87 (1.60 to 2.11)	**0.078**
Pressure pain threshold (Kg)					
Back	0.74 (0.64 to 0.82)	0.75 (0.59 to 0.82)	0.70 (0.55 to 0.76)	0.44 (0.26 to 0.55)	**< 0.001**
Remote site	0.49 (0.38 to 0.59)	0.50 (0.38 to 0.60)	0.40 (0.31 to 0.52)	0.34 (0.22 to 0.44)	**0.020**
Temporal summation of mechanical pain	0.75 (0.00 to 2.00)	1.50 (0.50 to 2.50)	1.50 (0.00 to 2.25)	2.00 (0.50 to 2.50)	0.164
Temporal summation of heat pain (46°C)	-1.50 (-3.25 to 0.00)	-1.50 (-3.00 to 0.00)	-2.00 (-2.50 to 0.50)	-1.00 (-2.00 to -0.05)	0.719
Temporal summation of heat pain (48°C)	0.00 (-2.00 to 0.13)	-1.00 (-1.00 to 0.00)	0.00 (-1.00 to 0.00)	-0.50 (-2.00 to 0.00)	0.408
Conditioned pain modulation	-0.15 (-0.45 to 0.20)	-0.20 (0.30 to -0.30)	-0.10 (-0.25 to 0.20)	0.20 (0.00 to 0.30)	**0.047**

Abbreviations: CLBP+: Individuals with non-specific chronic low back pain; CLBP+I: Individuals with concomitant non-specific chronic low back pain and insomnia; Insomnia+: Individuals with insomnia; IQR: Interquartile range; QST: Quantitative sensory testing.

Footnote: Values are presented as median and interquartile range. P value was calculated by the Kruskal-Wallis test with removing participants with underweight (BMI under 18.5 kg/m^2) or overweight (BMI over 25.0 kg/m^2). The p-value in bold indicates a statistically significant difference among the four groups ($p < 0.05$).

Appendix 9. One-way ANOVA of functional connectivity with post-hoc analyses in Chaper 5

Table S3.1. One-way ANOVA of amplitude-based functional connectivity (AEC) with post-hoc analyses

a. *F* and *P* values for theta band

Salience network	NA		
Default mode network	**F=3.454, P = 0.007, $P_{corrected}$ = 0.028**	NA	
Frontoparietal network	**F=3.134, P=0.012, $P_{corrected}$ = 0.048**	**F=3.835, P=0.003, $P_{corrected}$ = 0.012**	NA
	Salience network	Default mode network	Frontoparietal network

CLBP+I showed increased functional connectivity between the salience network and default mode network compared to Insomnia+ ($p_{corrected}$= 0.007) and health controls ($p_{corrected}$ = 0.022)

CLBP+I showed increased functional connectivity between the salience network and frontoparietal network compared to Insomnia+ ($p_{corrected}$ = 0.011) and health controls ($p_{corrected}$ = 0.019)

CLBP+I showed increased functional connectivity between default mode network and frontoparietal network compared to CLBP+ ($p_{corrected}$ = 0.030), Insomnia+ ($p_{corrected}$ = 0.004) and health controls ($p_{corrected}$ =0.006)

b. *F* and *P* values for alpha band

Salience network	NA		
Default mode network	F=0.355, P=0.878	NA	
Frontoparietal network	F=0.387, P=0.857	F=0.345, P=0.884	NA
	Salience network	Default mode network	Frontoparietal network

c. *F* and *P* values for beta band

Salience network	NA		
Default mode network	F=2.081, P=0.075	NA	
Frontoparietal network	F=2.161, P=0.065	F=2.490, P=0.037, $P_{corrected}$ = 0.112	NA
	Salience network	Default mode network	Frontoparietal network

d. *F* and *P* values for gamma band

Salience network	NA		
Default mode network	F=0.719, P=0.611	NA	
Frontoparietal network	F=0.799, P=0.553	F=0.837, P=0.527	NA
	Salience network	Default mode network	Frontoparietal network

Table S3.2. One-way ANOVA of phase-based functional connectivity (dwpli) with post-hoc analyses

a. *F* and *P* values for theta band

Salience network	NA		
Default mode network	F=0.672, P=0.646	NA	
Frontoparietal network	F=0.673, P=0.645	F=0.409, P=0.842	NA
	Salience network	Default mode network	Frontoparietal network

b. *F* and *P* values for alpha band

Salience network	NA		
Default mode network	F=1.364, P=0.245	NA	
Frontoparietal network	F=1.443, P=0.216	F=1.089, P=0.371	NA
	Salience network	Default mode network	Frontoparietal network

c. *F* and *P* values for beta band

Salience network	NA		
Default mode network	F=1.197, P=0.317	NA	
Frontoparietal network	F=0.667, P=0.642	F=0.748, P=0.590	NA
	Salience network	Default mode network	Frontoparietal network

d. *F* and *P* values for gamma band

Salience network	NA		
Default mode network	F=0.570, P=0.723	NA	
Frontoparietal network	F=0.422, P=0.832	F=0.386, P=0.857	NA
	Salience network	Default mode network	Frontoparietal network

Appendix 10. One-way ANOVA of brain network measures with post-hoc analyses in Chaper 5

Table S3.3. Significance of the local graph theory at 10% thresholds of the strongest connections

	Local clustering coefficient	**Local degree**	**Post-hoc analyses**
Theta frequency band			
Salience network	AEC ($F = 2.11$, $P = 0.071$)	AEC ($F = 2.68$, $P = 0.026$, $P_{corrected} = 0.104$)	
	dwPLI ($F = 1.05$, $P = 0.396$)	dwPLI ($F = 1.55$, $P = 0.182$)	
Fronto-parietal network	AEC ($F = 0.80$, $P = 0.554$)	AEC ($F = 1.25$, $P = 0.294$)	
	dwPLI ($F = 0.34$, $P = 0.885$)	dwPLI ($F = 0.56$, $P = 0.731$)	
Default mode network	AEC ($F = 1.84$, $P = 0.112$)	AEC ($F = 1.06$, $P = 0.389$)	
	dwPLI ($F = 0.39$, $P = 0.855$)	dwPLI ($F = 1.35$, $P = 0.250$)	
Alpha frequency band			
Salience network	AEC ($F = 0.38$, $P = 0.864$)	AEC ($F = 0.28$, $P = 0.926$)	
	dwPLI ($F = 0.71$, $P = 0.615$)	dwPLI ($F = 0.21$, $P = 0.958$)	
Fronto-parietal network	AEC ($F = 0.80$, $P = 0.553$)	**AEC ($F = 4.10$, $P = 0.002$, $P_{corrected} = 0.008$)**	No post-hoc significant differences
	dwPLI ($F = 1.13.$, $P = 0.351$)	dwPLI ($F = 1.45$, $P = 0.215$)	
Default mode network	AEC ($F = 0.45$, $P = 0.809$)	AEC ($F = 1.25$, $P = 0.291$)	
	dwPLI ($F = 0.83$, $P = 0.533$)	dwPLI ($F = 1.12$, $P = 0.356$)	
Beta frequency band			
Salience network	AEC ($F = 3.08$, $P = 0.013$, $P_{corrected} = 0.052$)	AEC ($F = 1.74$, $P = 0.132$)	
	dwPLI ($F = 0.75$, $P = 0.590$)	dwPLI ($F = 0.28$, $P = 0.923$)	
Fronto-parietal network	AEC ($F = 1.74$, $P = 0.134$)	AEC ($F = 0.82$, $P = 0.536$)	
	dwPLI ($F = 0.88$, $P = 0.500$)	dwPLI ($F = 2.33$, $P = 0.049$, $P_{corrected} = 0.196$)	
Default mode network	**AEC ($F = 3.71$, $P = 0.004$, $P_{corrected} = 0.016$)**	AEC ($F = 0.61$, $P = 0.694$)	**CLBP+I > Controls* ($P_{corrected} = 0.015$)**
	dwPLI ($F = 0.55$, $P = 0.739$)	dwPLI ($F = 0.21$, $P = 0.959$)	
Gamma frequency band			
Salience network	AEC ($F = 0.31$, $P = 0.907$)	AEC ($F = 1.19$, $P = 0.320$)	
	dwPLI ($F = 1.06$, $P = 0.389$)	dwPLI ($F = 0.72$, $P = 0.608$)	
Fronto-parietal network	AEC ($F = 0.69$, $P = 0.632$)	AEC ($F = 3.33$, $P = 0.566$)	

	dwPLI ($F = 0.49$, $P = 0.783$)	dwPLI ($F = 0.539$, $P = 0.709$)
Default mode network	AEC ($F = 1.48$, $P = 0.204$)	AEC ($F = 1.66$, $P = 0.151$)
	dwPLI ($F = 0.43$, $P = 0.829$)	dwPLI ($F = 2.10$, $P = 0.072$)

The bolded p-value indicates a statistically significant difference among the four groups with the Holm–Bonferroni correction ($p < 0.05$). Significance levels with Bonferroni corrections for post-hoc analyses are denoted as * ($p < 0.05$) and ** ($p < 0.01$). AEC: Amplitude envelope correlation; CLBP+: Individuals with non-specific chronic low back pain; CLBP+I: Individuals with concomitant non-specific chronic low back pain and insomnia; Controls: Individuals without non-specific chronic low back pain nor insomnia; dwPLI: Debiased weighted phase lag index; Insomnia+: Individuals with insomnia.

Table S3.4. Global graph theory-based network measures

	AEC	dwPLI	Post-hoc analyses
Theta frequency band			
Global cluster coefficient	$F = 1.15$, $P = 0.340$	$F = 0.43$, $P = 0.830$	
Global efficiency	$F = 1.34$, $P = 0.255$	$F = 1.32$, $P = 0.264$	
Small-world networks	$F = 1.08$, $P = 0.374$	$F = 0.47$, $P = 0.799$	
Alpha frequency band			
Global cluster coefficient	$F = 0.49$, $P = 0.781$	$F = 1.40$, $P = 0.233$	
Global efficiency	$F = 0.66$, $P = 0.656$	$F = 1.23$, $P = 0.303$	
Small-world networks	$F = 0.58$, $P = 0.715$	$F = 0.91$, $P = 0.478$	
Beta frequency band			
Global cluster coefficient	$F = 2.68$, $P = 0.026$, $P_{corrected} = 0.104$	$F = 0.41$, $P = 0.842$	
Global efficiency	$F = 1.08$, $P = 0.379$	$F = 1.89$, $P = 0.104$	
Small-world networks	$\mathbf{F = 3.23, P = 0.010, P_{corrected} = 0.040}$	$F = 0.33$, $P = 0.893$	CLBP+I > Controls* ($\mathbf{P_{corrected} = 0.017}$)
Gamma frequency band			
Global cluster coefficient	$F = 1.04$, $P = 0.401$	$F = 1.36$, $P = 0.246$	
Global efficiency	$F = 0.77$, $P = 0.575$	$F = 0.89$, $P = 0.491$	
Small-world networks	$F = 1.10$, $P = 0.366$	$F = 1.55$, $P = 0.181$	

The bolded p-value indicates a statistically significant difference among the four groups with the Holm–Bonferroni correction ($p < 0.05$). Significance levels with Bonferroni corrections for post-hoc analyses are denoted as * ($p < 0.05$) and ** ($p < 0.01$). AEC: Amplitude envelope correlation; CLBP+: Individuals with non-specific chronic low back pain; CLBP+I: Individuals with concomitant non-specific chronic low back pain and insomnia; Controls: Individuals without non-specific chronic low back pain nor insomnia; dwPLI: Debiased weighted phase lag index; Insomnia+: Individuals with insomnia.

Appendix 11. Search strategy in Chapter 6

Table S4.4. Search strategy

1	Pain OR ache OR agony
2	Back OR low* back OR lumba* OR lumbosacr* OR lumbopelv* OR spine OR spinal
3	1 AND 2
4	Backache* OR back ache OR back-ache OR low backache OR lumbago OR sciatica
5	3 OR 4
6	low back pain OR LBP OR lower back pain OR NSLBP OR ((lumbar or lumbo* or low* back) adj3 pain)
7	5 OR 6
8	Persist* OR chronic OR prolong*
9	7 AND 8
10	Insomnia OR sleep quality OR sleepless* OR sleep disturb* OR poor sleep OR sleep problem* OR sleep disorder* OR disturb* sleep* OR (sleep adj3 problem*) OR (sleep adj3 disturb*) OR (sleep adj3 disorder*)
11	9 AND 10
12	Associat* OR predict* OR relat* OR correlate*
13	11 AND 12

Appendix 12. Outcome measures of included studies in Chapter 6

Table S4.5. Measurements of sleep variables

Study	Sleep parameters	Measurement methods	Clinically meaningful changes
Roseen et al (2020) [384]	Sleep quality	PSQI	A global score > 5 indicates clinically significant sleep problems, MCIC ≥3 points.
Pakpour et al (2018) [367]	Sleep quality	PSQI	A global score ≥ 5 indicates clinically significant sleep problems.
Nordeman et al (2017) [394]	1) Sleep quantity 2) sleep quality	Two questions 1) Do you think you get enough sleep? (range 1-4) 2) On the whole, how do you think you sleep? (range 1-4)	Higher score indicates better sleep quantity and quality.
Rabey et al (2017) [395]	Sleep quality	PSQI	A global score ≥ 5 indicates clinically significant sleep problems.
Goforth et al (2014) [201]	1) Total sleep time (TST) 2) Sleep onset latency (SOL) 2) Wake time after sleep onset (WASO) 3) Number of awakenings (NUAK) 4) Sleep efficiency (SE%) 5) Sleep quality 6) Restedness	All sleep variables were extracted from self-rated sleep diaries, which included the time of light out, the time for falling asleep, the duration of each period awaking, the time of final awakening, the time of lights on when they got out of bed, 10-point rating for sleep quality, and 10-point scale for restedness. TST= (times from lights out to light on) - (the time for falling sleep + all times for awakening)	Not reported
Sherman et al (2013) [383]	Sleep quality	The sleep question in RMDQ: I sleep less well because of my back pain (Yes or No).	Not reported

Abbreviation: MCIC = Minimum Clinically Important Change; PSQI = Pittsburgh Sleep Quality Index; RMDQ = Roland-Morris Disability Questionnaire

Table S4.6. Measurements of LBP-related outcomes

Study	LBP-related outcomes	Measurement methods	Clinically meaningful changes
Roseen et al (2020) [384]	1) Pain intensity 2) Back-related disability	1) An 11-point NPRS 2) RMDQ with 24 items	The MCICs of NPRS and RMDQ are ≥ 30% improvements from baseline.
Pakpour et al (2018) [367]	1) Recovery 2) Pain intensity and recovery	1) Self-report global rating of change (GRC) with 6 categories 2) 100mm VAS with 0 indicating no pain and 100mm indicating the worst imaginable pain	1) The recovered group with answering 'completely recovered', 'much better', and 'better'. The nonrecovery group with answering 'no changes', 'worse', and 'much worse'. 2) The cutoff of 0 to 10mm as an indication of patient recovery from pain.
Nordeman et al (2017) [394]	Back-related disability	RMDQ with 24 items	Higher scores indicate greater activity limitation
Rabey et al (2017) [395]	1) Pain intensity 2) Back-related disability 3) GRC 4) Bothersomeness	1) An 11-point NPRS with 0 indicating no pain and 10 indicating the worst imaginable pain 2) RMDQ with 24 items 3) A 7-point global rating of change scale 4) A 7-pont scale for Bothersomeness	1) Not reported 2) Not reported 3) The administration with 'much' or 'very much improved' indicates a positive outcome of recovery [36]. 4) The answer with 'very much' or 'extremely' is classified as clinically important bothersomess [15].
Goforth et al (2014) [201]	Pain intensity	1) 100mm VAS 2) A global impression of pain rating (PGI) with 1 to 5 rating	Not reported
Sherman et al (2013) [383]	Back-related dysfunction	The modified RMDQ with 23 items	Not reported

Abbreviation: GRC = Global Rating Of Change; MCIC= Minimum Clinically Important Change; NPRS = 11-Point Numerical Pain Rating Scale; PGI = Global Impression Of Pain; RMDQ = Roland-Morris Disability Questionnaire; VAS = 100mm Visual Analog Scale.

Appendix 13. Risk of bias assessment for the included studies in Chapter 6

Figure S4.1. Methodological assessment of randomized controlled trials by the RoB 2.0 tool

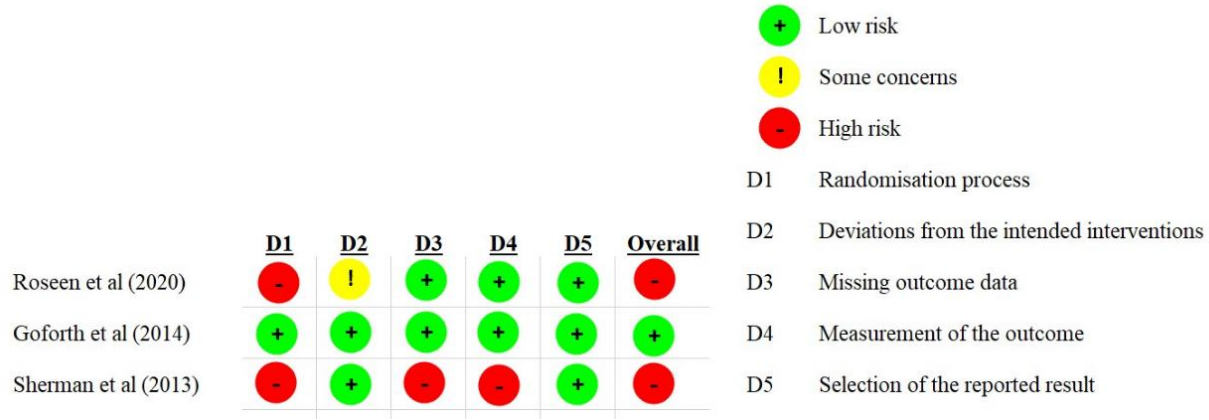


Table S4.7. Methodological assessment of prospective study (QUIPS)

Quality of Prognosis Studies Risk of Bias Assessment Instrument for Prognostic Factor Studies (QUIPS)																																								
Study	**Study participation**								**Study attrition**						**Prognostic factor measurements**						**Outcome measurements**				**Study confounding**								**Statistical analysis and reporting**					**Overall risk**
	1	**2**	**3**	**4**	**5**	**6**	**7**	**S**	**1**	**2**	**3**	**4**	**5**	**S**	**1**	**2**	**3**	**4**	**5**	**S**	**1**	**2**	**3**	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**S**	**1**	**2**	**3**	**4**	**S**	
(Pakpour et al., 2018)	Y	Y	Y	Y	Y	Y	Y	**L**	Y	N	N	N	U	**H**	Y	Y	Y	Y	N	**M**	Y	Y	Y	**L**	Y	Y	Y	Y	N	Y	Y	**M**	Y	Y	Y	Y	**L**	**Moderate**
(Normdeman et al., 2017)	Y	Y	Y	Y	Y	Y	Y	**L**	Y	Y	Y	N	U	**M**	Y	N	Y	Y	N	**H**	Y	Y	Y	**L**	Y	N	Y	Y	N	Y	Y	**H**	Y	Y	Y	Y	**L**	**High**
(Rabey et al., 2017)	Y	Y	N	Y	Y	Y	Y	**M**	Y	N	N	Y	N	**H**	Y	Y	Y	Y	Y	**L**	Y	Y	Y	**L**	Y	N	Y	Y	N	Y	P	**H**	Y	Y	Y	Y	**L**	**High**

Appendix 14. Search strategy in Chapter 7

1. Chronic Pain [Mesh] or widespread pain [Title/Abstract]
2. Musculoskeletal Pain [Mesh] or musculoskeletal disorder* [Title/Abstract]
3. Shoulder Pain [Mesh] or (elbow pain or hip pain or knee pain or ankle pain or leg pain) [Title/Abstract]
4. Neck Pain [Mesh] or (cervical pain or cervicalgia* or cevicodynia*) [Title/Abstract]
5. Low Back Pain [Mesh] or (backache* or back pain or dorsalgia or lumbago or sciatica or coccyx or coccydynia or (lumb* adj pain) or (back adj pain)) [Title/Abstract]
6. Fibromyalgia [Mesh] or (myofascial pain syndrome or muscular rheumatism or fibrositis syndrome) [Title/Abstract]
7. Arthritis [Mesh] or (arthritides or arthrosis or arthroses) [Title/Abstract]
8. Osteoarthritis [Mesh] or (osteoarthritides or osteoarthro* or coxarthriti* or coxarthro* or gonarthriti* or gonarthro*) [Title/Abstract]
9. Spondylarthritis [Mesh] or (spondylarthritides or spondylosis or spondylitis or spondylolisthesis) [Title/Abstract]
10. Arthritis, Rheumatoid [Mesh] or (chronic articular rheumatism or rheumarthritis or rheumatism) [Title/Abstract]
11. or 1-10
12. Sleep Initiation and Maintenance Disorders [Mesh] or Sleep Wake Disorders [Mesh] or Sleep Disorders, Intrinsic [Mesh] or (early awakening or sleep initiation dysfunction or insomnia* or dyssomnia* or agrypnia or hyposomnia* or sleepless* or sleep wake disorder* or sleep disorder* or sleep perturbation or disturb* sleep* or sleep disturb* or sleep problem* or poor sleep) [Title/Abstract]
13. Sleep Quality [Mesh] or Sleep Latency [Mesh] or (sleep parameter* or bedtime or time in bed or sleep* duration or sleep efficiency or rising time or sleep pattern* or sleep* time or total sleep time or total wake time or wake after sleep onset or wake time after sleep onset or wake up time or sleep depth or sleep* quantit*) [Title/Abstract]
14. or 12-13
15. Randomized Controlled Trials as Topic [Mesh] or Randomized Controlled Trial [Publication Type] or Controlled Clinical Trials as Topic [Mesh]
16. (((randomi?ed or randomi?ation or randomi?ing) and trial) or RCT or (random* and (assign* or allocat*))) [Title/Abstract]
17. 15 or 16
18. 11 and 14 and 17
19. Animal Experimentation [Mesh] or (animal experiment* or animal stud* or animal physical conditioning or animal research) [Title/Abstract]
20. 18 NOT 19

TIAB=(((chronic pain or widespread pain or musculoskeletal pain or musculoskeletal disorder* or shoulder pain or elbow pain or hip pain or knee pain or ankle pain or leg pain or neck pain or cervical pain or cervicalgia* or cevicodynia*) or (low back pain or backache* or back pain or dorsalgia or lumbago or sciatica or coccyx or coccydynia or (lumb* adj pain) or (back adj pain)) or (fibromyalgia or myofascial pain syndrome or fibrositis syndrome or muscular rheumatism) or (arthritis or arthritides or arthrosis or arthroses) or (osteoarthritis or osteoarthritides or osteoarthro* or coxarthriti* or coxarthro* or gonarthriti* or gonarthro*) or (spondylarthr* or spondylosis or spondylitis or spondylolisthesis) or (rheumatoid arthritis or chronic articular rheumatism or rheumarthritis or rheumatism)) and ((sleep initiation and maintenance disorder*) or (disorder* of initiating and maintaining sleep) or early awakening or sleep initiation dysfunction or insomnia* or dyssomnia* or agrypnia or hyposomnia* or sleepless* or sleep wake disorder* or sleep disorder* or long sleep* syndrome* or sleep perturbation or disturb* sleep* or sleep disturb* or sleep problem* or poor sleep or sleep* quality* or sleep* onset latenc* or sleep* latenc* or sleep parameter* or bedtime or time in bed or sleep* duration or sleep efficiency or rising time or sleep pattern* or sleep* time or total sleep time or total wake time or wake after sleep onset or wake time after sleep onset or wake up time or sleep depth or sleep* quantit*) and (randomized controlled trial or controlled clinical trial or ((randomi?ed or randomi?ation or randomi?ing) and trial) or RCT or (random* and (assign* or allocat*))) not (animal experiment* or animal stud* or animal physical conditioning or animal research))

Appendix 15. Additional details on Methods in Chapter 7

PCIOS framework

Types of participants

The population of interest was individuals aged 18 years or older with chronic musculoskeletal pain (a duration ≥ 3 months) according to the multidimensional diagnostic criteria [430] and the ICD-11 for chronic pain [58]. Studies involved participants with other types of pain (cancer pain, post-surgical pain, post-traumatic pain, primary headache, orofacial pain, neuropathic pain, or visceral pain) [58] or mixed chronic pain conditions without separate results were excluded.

Type of intervention and comparators

Any nonpharmacological treatments (e.g., acupuncture, physical, psychological therapy) were eligible for inclusion regardless of frequency, duration, or intensity. The comparators had at least one inactive (placebo, sham treatment, waiting list, usual care, or no treatment) or eligible active interventions. The classification of interventions was determined based on the clinical practice guideline [431] and other network meta-analyses [432, 433] (Table 1). The intervention or control arm with multiple co-interventions (e.g., physical modalities combined exercise) was excluded to avoid divergences across trials [434]. Studies only with the comparison of different dosages across multiple arms within one study were excluded. Whereas if there were additional arms with different intervention regimens, the data from identical interventions would be merged as a single node according to the guidelines of the Cochrane Handbook [437].

Type of outcome

The primary outcome was subjective sleep quality assessed by any valid instruments (e.g., the Insomnia Severity Index, the Pittsburgh Sleep Quality Index, or the Numeric Rating Scale for sleep quality). The secondary outcomes were subjective (sleep diary) and objective (actigraphy or polysomnography) sleep parameters (sleep efficiency, sleep onset latency, total sleep time, or wake after sleep onset), pain intensity, disability, the acceptability of interventions (assessed by the proportion of participants who withdrew from studies for any reason during the intervention period) [435], and the safety of interventions (assessed by the proportion of participants who experienced any treatment-related adverse events during the intervention period) [436]. The primary endpoint for existing outcomes was immediate post-intervention. The follow-up points were only extracted for sleep, pain intensity, and disability. The time points were classified as short-term treatment sustainability (closest to 3 months post-intervention), mid-term treatment sustainability (closest to 6 months post-intervention), and long-term treatment sustainability (closest to 12 months post-intervention). If two follow-up assessments were equidistant within pre-defined follow-up periods, data were analyzed as the lower limit of the category.

Type of study

This review included English-language randomized controlled trials (RCTs) with a parallel-group or cluster design published or accepted by peer-reviewed journals. Narrative or systematic reviews, cross-over studies, secondary analyses, observational studies, quasi-experimental studies, case reports, animal studies, letters to the editor, or conference abstracts were excluded. Studies were ineligible for inclusion if they had no full-text articles or sufficient data to calculate effect size even after contacting the corresponding authors.

Data extraction

If multiple publications reported data from the same cohort, only the study with the informative and complete data would be included. Data were extracted from the assessment used most frequently across studies to reduce heterogeneity for studies involving multiple measures on the same outcomes. The results from the intention-to-treat analysis were extracted whenever available. Otherwise, the reported results for participants who completed the study were extracted. If continuous data were not available for mean difference and standard deviation, they were estimated by conversion from other values (e.g., standard error, p-values, t-values) [437]. When included cluster RCTs did not adjust clustering effects, "design effects" were estimated by $1 + (M - 1)$ ICC, where M was the average cluster size and intracluster correlation coefficient (ICC) was set as 0.02 [437]. When data were only presented on the figures rather than numerical data within the text, OriginPro software (OriginThe lab, 2021) was used to extract data from the figures [437]. If there were missing or unclear data in the published report, the corresponding author would be contacted at least three times with a one-week interval via emails to request relevant information.

Appendix 16. Study characteristics of the included studies in Chapter 7

Table S5.1. Study characteristics of the included studies

Study	Country	Design	Condition (type, setting, diagnosis, medication)	Sample size	Age (years)	Female (%)	Treatment	Node	Treatment duration (weeks)	Follow-up duration (months)	Sleep outcomes	Pain or disability outcomes	Adverse events
Akodu et al (2021) [509]	Nigeria	Three-arm RCT	CNP Healthcare Nonspecific neck pain for > 3 mon, NPRS > 5/10 Stable pain medications	14	47.4 ± 9.2	64.3	Pilate exercise	Mind-body exercise	8	NA	ISI	NPRS NDI	NI
				17	47.7 ± 10.0	58.8	Neck stabilization	Exercise					4
				14	44.9 ± 6.3	50	Dynamic isometric exercise	Exercise					NI
Almeida et al (2003) [510]	Brazil	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM and self-reported sleep difficulties No medications	9	56.0 ± 6.0	100	Ultrasound and interferential current	Physical agents	4	NA	VAS-sleep PSG (WASO)	VAS	NI
				7	57.0 ± 5.0	100	Sham control	Inert treatment					
Alves et al (2013) [511]	Brazil	Two-arm pilot RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	16	48.7 ± 8.	100	Creatine supplementation	Nutritional therapy	16	NA	PSI	VAS FIQ	0
				16	49.0 ± 10.1	100	The same dose of dextrose	Inert treatment					0
Amirova et al (2017) [512]	United Kingdom	Three-arm RCT	FM General population Meet the American College of Rheumatology criteria for FM NI	67	48.1± 11.1	94	The Mitchell Method Relaxation Technique	Relaxation	4	NA	MOS	VAS FIQR	0
				66	50.5 ± 10.8	96	Attention control	Inert treatment					0

				58	48.9 ± 10.1	91	Usual care	Passive control					0
Amutio et al (2018) [513]	United Kingdom	Two-arm RCT	FM General population Prove FM diagnosis from medical records Stable medications	20	51.8 ± 10.2	100	Flow Meditation	Mindful psychotherapy	7	3	PSQI	NA	NI
				19		100	A waiting-list control	Passive control					
Bakir et al (2018)[514]	Turkey	Two-arm RCT	RA Healthcare Diagnosed with RA > 1 year, VAS > 4/10, PSQI > 6 scores Stable medications	34	50.8 ± 12.1	80	Foot reflexology	Manual therapy	6	NA	PSQI	VAS	1
				34	49.5 ± 16.4	73.3	Usual care	Passive control					1
Basler (1991) et al [515]	Germany	Two-arm RCT	AS General population Prove AS diagnosis from medical records Anti-inflammatory medications	25	42.2 ± 12.7	45.5	CBT	CBT	12	6	Six-point scale for sleep	VAS Six-point scale for functional limitation	NI
				20	47.5 ± 12.4	41.2	A waiting-list control	Passive control					
Bestas et al (2022) [516]	Turkey	Three-arm RCT	AS General population Meet the New York diagnostic criteria for AS Stable medications	20	42.3 ± 9.0	35	Balneotherapy	Physical agents	4	2	PSQI	BASDAI BASFI	0
				20	42.0 ± 12.3	50	Water-based exercise	Exercise					0
				20	38.6 ± 12.2	40	Multimodal exercise	Exercise					0
Blodt et al (2015) [517]	Germany	Two-arm RCT	CLBP Healthcare Nonspecific low back pain for > 3 mon, VAS > 4/10 Stable pain medications	64	45.7 ± 10.0	90.6	Qigong	Mind-body exercise	12	3 and 9	VAS-sleep	VAS RMDQ	10
				64	47.7 ± 10.8	69.8	Multimodal exercise	Exercise					10
Bongi et al (2010) [518]	Italy	Two-arm RCT	FM General population	22	44.4 ± 13.1	90.9	Rességuier method	Mind-body exercise	8	NI	NPRS-sleep	NPRS FIQ	0

			Meet the American College of Rheumatology criteria for FM Stable medications	22	46.6 ± 10.5	94.7	Maintain lifestyle	Passive control					0
Brattberg (1999) [519]	Sweden	Two-arm RCT	FM General population Meet the American College of Rheumatology criteria for FM Stable medications	27	48.0 ± 12.4	97.9	Connective tissue massage	Manual therapy	10	NA	10-item scale for sleep	VAS FIQ	NI
				25			A waiting-list control	Passive control					
Brietzke et al (2020) [520]	Brazil	Two-arm RCT	FM General population and healthcare Meet the American College of Rheumatology criteria for FM Stable medications	10	48.6 ± 35.7	100	tDCS	Non-invasive brain stimulation	12	NA	PSQI	VAS	NI
				10	49.7 ± 8.4	100	Sham tDCS	Inert treatment					
Burns et al (2022) [521]	USA	Four-arm RCT	CLBP General population and healthcare Low back pain for > 6 mon, NPRS > 4/10 Stable pain medications	120	53.4 ± 12.3	58	Behaviour therapy	CBT	8	6	Six-item scale for sleep	NPRS Physical functioning scale	NI
				129	52.7 ± 12.9	55.8	Cognitive therapy	CBT					
				143	52.7 ± 11.7	58	Mindfulness-based stress reduction	Mindful psychotherapy					
				129	52.8 ± 12.0	59.7	Usual care	Passive control					
Calandre et al (2009) [522]	Spain	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	42	49.0 ± 8.4	92.9	Pool-based Taichi	Mind-body exercise	6	3	PSQI	VAS FIQ	3
				39	52.8 ± 12.0	87.2	Pool-based stretching	Exercise					0
Canovas et al	Spain	Three-	KOA Healthcare	53	36.9 ± 12.8	47.0	Eggshell membrane	Nutritional therapy	8	NA	PSQI	VAS WOMAC	0

(2022) [523]		arm RCT	Meet the American College of Rheumatology criteria for KOA No medications	27	41.3 ±14.4	61.5	Placebo control	Inert treatment					0
Carson et al (2010) [524]	USA	Two-arm pilot RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	25	51.4 ± 13.7	100	Yoga of Awareness	Mind-body exercise	8	NA	VAS-sleep	VAS FIQR	NI
				28	55.8 ± 8.9	100	A waiting-list control	Passive control					
Cash et al (2015) [525]	USA	Two-arm RCT	FM General population Prove FM diagnosis from physicians NI	51	NI	100	Mindfulness-based stress reduction	Mindful psychotherapy	8	2	SSQ	VAS FIQ	NI
				40	NI	100	A waiting-list control	Passive control					
Castel et al (2012) [526]	Spain	Three-arm RCT *	FM General population and healthcare Meet the American College of Rheumatology criteria for FM Stable medications	34	50.0 ± 7.6	94	CBT	CBT	14	3 and 6	MOS	NPRS FIQ	NI
				30	48.7 ± 6.5	100	Standard care control	Passive control					
Castro Sanchez et al (2014) [527]	Spain	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	45	54.0 ± 8.0	53.3	Myofascial release	Manual therapy	5	NA	PSQI	VAS FIQ	NI
				44	53.0 ± 7.0	54.5	Activities as usual	Passive control					
Caumo et al (2022) [528]	Brazil	Two-arm RCT	FM General population and healthcare Meet the American College of Rheumatology criteria for FM Stable medications	32	49.6 ± 9.0	100	tDCS	Non-invasive brain stimulation	4	NA	PSQI	NPRS Pain disability	3.2
				16	48.0 ± 6.7	100	Sham tDCS	Inert treatment					0.64

Cheung et al (2014) [529]	USA	Two-arm pilot RCT	KOA General population Meet the American College of Rheumatology criteria for KOA No restrictions on medications	18	71.9 ± 5.7	100	Yoga	Mind-body exercise	8	NA	PSQI	WOMAC-pain	0
				18	71.9 ± 6.5	100	A waiting-list control	Passive control				WOMAC-physical function	0
Colbert et al (1999) [530]	USA	Two-arm pilot RCT	FM General population and healthcare Meet the American College of Rheumatology criteria for FM Stable medications	16	51.2 ± 13.5	100	Magnetized mattres	Assistive technique	16	NA	VAS-sleep	VAS FIQ	0
				14	48.2 ± 11.1	100	Sham mattres	Inert treatment					0
Currie et al (2000) [531]	Canada	Two-arm RCT	Mixed conditions Healthcare Prove musculoskeletal pain from physicians and self-reported sleep difficulties No restrictions on medications	32	45.0 ± 8.0	55	CBT for insomnia	CBT	7	3	PSQI Sleep diary (TST, SE, SOL, and WASO)	MPI	NI
				28			A waiting-list control	Passive control					
Dall'Agnol et al (2014) [532]	Brazil	Two-arm RCT	Chronic MPS NI Regional pain several times a week during the last 3 months and prove diagnosis from physicians No restrictions on medications	12	45.8 ± 9.6	100	rTMS	Non-invasive brain stimulation	12	NA	VAS-sleep	VAS	0
				12	44.8 ± 14.1	100	Sham rTMS	Inert treatment					0
Darnall et al (2021) [533]	USA	Three-arm RCT *	CLBP General population Meet the National Institutes of Health Task Force on	88	45.9 ± 13.1	45.5	CBT for pain	CBT	NA	3	PROMIS-sleep	VAS PROMIS-physical function	0
				88	48.0 ± 13.2	53.4	Health education	Education					0

			Research Standards for CLBP No restrictions on medications										
De Medeiros et al (2020) [534]	Brazil	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM NI	21	45.5 ± 10.6	100	Mat Pilates	Mind-body exercise	12	NA	PSQI	VAS FIQ	1
				21	50.7 ± 9.7	100	Aquatic aerobic exercise	Exercise					NI
Deluze et al (1992) [535]	Switzerland	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	36	46.8 ± 3.8	91.7	Electroacupuncture	Acupuncture	3	NA	VAS-sleep	VAS	6
				34	49.0 ± 11.7	61.8	Sham control	Inert treatment					5
Durcan et al (2014) [536]	Ireland	Two-arm RCT	RA Healthcare Meet the American College of Rheumatology criteria for RA Stable medications	42	61.0 ± 8.0	75	Multimodal exercise	Exercise	12	NA	PSQI	VAS HAQ	NI
				38	59.0 ± 12.0	52.6	Advice on the benefits of exercise	Education					
Edinger et al (2005) [537]	USA	Three-arm RCT	FM General population Meet the American College of Rheumatology criteria for FM and structured interview criteria for insomnia based on DSM-III No restrictions on medications	18	50.1 ± 6.9	94	CBT	CBT	6	6	ISQ Sleep diary and Actigraphy (TST, SE, SOL, and WASO)	MPQ	NI
				18	46.5 ± 9.0	94	Sleep hygiene	Education					
				11	48.3 ± 9.1	100	Usual care	Passive control					
Ekici et al (2017) [538]	Turkey	Two-arm pilot RCT	FM Healthcare Meet the American College of	21	37.1 ± 6.4	100	Pilates	Mind-body exercise	4	NI	NHP-sleep	VAS FIQ	NI
				22	36.9 ± 7.7	100	Connective tissue massage	Manual therapy					

			Rheumatology criteria for FM No medications										
Ericsson et al (2016) [539]	Sweden	Two-arm RCT	FM General population Meet the American College of Rheumatology criteria for FM No restrictions on medications	67	50.8 ± 9.1	100	Resistance exercise	Exercise	15	NA	PSQI	NA	5
				63	52.1 ± 9.8	100	Autogenic training	Relaxation					NI
Fernández García et al (2011) [540]	Spain	Two-arm RCT	FM NI Prove FM diagnosis No restrictions on medications	16	51.6 ± 6.2	100	Laser therapy	Physical agents	4	NA	VAS-sleep	VAS FIQ	NI
				15	52.4 ± 5.9	100	Placebo control	Inert treatment					
Field et al (2015) [541]	USA	Two-arm RCT	KOA General population Prove FM diagnosis from physicians NI	24	47	100	Moderate pressure massage	Manual therapy	4	NA	PSQI	WOMAC-pain WOMAC-physical function	NI
				24		100	A waiting-list control	Passive control					
Field et al (2007) [542]	USA	Two-arm RCT	CLBP NI Nonspecific low back pain > 6 mon NI	15	41	46.7	Massage therapy	Manual therapy	5	NA	VAS-sleep	VAS	NI
				15			Progressive muscle relaxation	Relaxation					
Fonseca et al (2021) [543]	Brazil	Two-arm RCT	FM General population Meet the American College of Rheumatology criteria for FM Stable medications	27	53.8 ± 10.4	100	Aquatic exercise	Exercise	11	NA	PSQI	MPQ FIQ	NI
				19	54.5 ± 11.2	100	Health education program	Education					
Franco et al (2022) [544]	Brazil	Two-arm RCT	FM General population Meet the American College of Rheumatology criteria for FM	49	48.5 ± 10.0	100	Aerobic exercise	Exercise	8	4 and 10	PSQI	NPRS FIQ	1
				48	51.4 ± 10.1	97.9	Pilates	Mind-body exercise					1

			No restrictions on medications										
Gillis et al (2006) [545]	USA	Two-arm RCT	FM General population and healthcare Meet the American College of Rheumatology criteria for FM No restrictions on medications	45 38	50.3	97.2	Exposure therapy Neutral time management	CBT Inert treatment	NA	3	Seven-point ordinal scale for sleep	AIMS2-pain FIQ	NI
Goldway et al (2019) [546]	Israel	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	31 12	35.5 ± 12.6 35.9 ± 10.6	96 77.8	Neurofeedback training Sham control	Relaxation Inert treatment	5	NA	PSQI Actigraphy (SE and SOL)	VAS	NI
Gur et al (2002) [547]	Turkey	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM No medications	20 20	NI	100 100	Laser therapy Placebo control	Physical agents Inert treatment	2	NA	Four-point ordinal scale for sleep	Four-point ordinal scale for pain	0 0
Haak et al (2008) [548]	Sweden	Two-arm RCT	FM General population and healthcare Meet the American College of Rheumatology criteria for FM No restrictions on medications	29 28	54.0 ± 9.4 53.4 ± 8.0	100 100	Qigong A waiting-list control	Mind-body exercise Passive control	7	NA	Seven-point ordinal scale for sleep	Seven-point ordinal scale for pain	NI
Hagiwara et al (2017) [549]	Japan	Two-arm RCT	CLBP General population and healthcare Low back pain for > 6 mon, NPRS > 3/10 NI	61 60	44.7 ± 10.0 44.7 ± 9.6	96.3 98.11	Lumbosacral support A waiting-list control	Assistive technique Passive control	12	NA	AIS	VAS RMDQ	2 NI

Hargrove et al (2012) [550]	USA	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	45	51.3 ± 10.3	94.9	Noninvasive cortical electrostimulation	Non-invasive brain stimulation	11	NA	VAS-sleep	FIQ-pain FIQ	5
				46	54.0 ± 9.1	89.5	Sham stimulation	Inert treatment					3
Harvey et al (2017) [551]	Canada	Two-arm pilot RCT	Mixed conditions General population Stable musculoskeletal pain > 3 mon and ISI > 7 scores Stable medications	6	72.0 ± 6.0	83.3	tDCS	Non-invasive brain stimulation	1	0.25	PSQI	MPQ	NI
				8	71.0 ± 8.0	75	Sham tDCS	Inert treatment					
Hedman-Lagerlöf et al (2018) [552]	Sweden	Two-arm RCT	FM General population Prove FM diagnosis Stable medications	70	51.8 ± 10.7	97	Exposure therapy	CBT	10	NA	ISI	FIQ-pain FIQ	24
				70	49.3 ± 10.0	99	A waiting-list control	Passive control					4
Heffner et al (2018) [553]	USA	Two-arm pilot RCT	KOA General population and healthcare Prove KOA diagnosis from physicians and meet research diagnostic criteria for insomnia disorder No medications	16	60.8 ±6.64	60	CBT for insomnia	CBT	6	NA	ISI	WOMAC-pain WOMAC-physical function	NI
				17			A waiting-list control	Passive control					
Hernandez-Reif et al (2001) [554]	USA	Two-arm RCT	CLBP Healthcare Nonspecific low back pain > 6 mon NI	12	43.8 ± 13.7	58.3	Massage therapy	Manual therapy	5	NA	VAS-sleep	VAS	NI
				12	36.7 ± 16.1	50	Progressive relaxation therapy	Relaxation					
Innes et al (2018) [555]	USA	Two-arm pilot RCT	KOA General population and healthcare	11	58.1 ± 5.3	81.8	Mantra Meditation	Mindful psychotherapy	8	NA	PSQI	NPRS KOOS-function	0
				11	58.8 ± 7.4	54.5	Music Listening	Relaxation					0

			Prove KOA diagnosis from physicians Stable medications										
Jones et al (2012) [556]	USA	Two-arm RCT	FM General population Meet the American College of Rheumatology criteria for FM Stable medications	51	53.3	92.1	Taichi	Mind-body exercise	12	NA	PSQI	NPRS FIQ	0
				50	54.8	93.6	Education about FM	Education					0
Jungquist et al (2010) [557]	USA	Two-arm RCT	Mixed conditions General population and healthcare Non-malignant pain in the spine > 6 mon, SOL > 30 min and/or WASO > 30 min for > 3 day/week for > 6 mon Stable pain medications	19	52.0 ± 9.9	83.3	CBT for insomnia	CBT	8	NA	ISI Sleep diary (TST, SE, SOL, and WASO)	MPI PDI	NI
				9	43.0 ± 10.7	88.9	Health discussion	Inert treatment					
Kilic et al (2021) [558]	Turkey	Two-arm RCT	RA General population Prove RA diagnosis > 6 mon Stable pain medications	37	46.3 ± 13.4	77.1	Progressive muscle relaxation	Relaxation	6	NA	PSQI	NA	1
				37	56.6 ± 11.2	78.4	Contact control	Passive control					NI
Lai (2014) [559]	China	Two-arm pilot RCT	Chronic MPS NI Meet the diagnostic criteria for MPS in the neck and upper back NI	24	53.9 ± 11.2	33.3	Far-infrared irradiation	Physical agents	1	NA	ESS	VAS	0
				24	56.9 ± 9.2	33.3	Sham control	Inert treatment					0
Lami et al (2018) [560]	Spain	Three-arm RCT	FM General population and healthcare Meet the American College of	42	49.4 ± 6.4	100	CBT for pain	CBT	9	3	PSQI	VAS FIQ	NI
				42	49.7 ± 8.4	100	CBT for insomnia and pain	CBT					

			Rheumatology criteria for FM and DSM-IV for insomnia Stable medications	42	51.4 ± 9.4	100	Usual medical care	Passive control					
Latocha et al (2022) [561]	Denmark	Two-arm RCT	RA General population and healthcare Meet the American College of Rheumatology criteria for RA and ICD-3 for insomnia Stable medications	31	60.0 ± 10.0	90	CBT for insomnia	CBT	6	5	PSQI PSG (TST, SE, SOL, and WASO)	VAS HAQ	1
				31	57.0 ± 11.0	87	Usual care	Passive control					1
Lauche et al (2016) [562]	Germany	Three-arm RCT	FM General population Meet the American College of Rheumatology criteria for FM Stable medications	47	54.4 ± 10.6	97.9	Cupping therapy	Physical agents	2.5	6	PSQI	VAS FIQ	7
				48	56.3 ± 8.7	97.9	Sham cupping	Inert treatment					1
				46	56.8 ± 7.7	100	A waiting-list control	Passive control					0
Lee et al (2022) [563]	South Korea	Two-arm RCT	OA Healthcare Prove OA diagnosis, VAS > 3/10, and PSQI > 5 scores Stable pain medications	29	78.4 ± 4.6	57.7	Auricular acupressure	Acupuncture	8	NA	PSQI PSG (TST, SE, and SOL)	VAS	NI
				29	79.3 ± 4.5	57.7	Placebo control	Inert treatment					1
Lin et al (2022) [564]	Taiwan, China	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	19	48.3 ± 13.6	68	tACS	Non-invasive brain stimulation	2	NA	PSQI	VAS FIQ	13
				19	48.9 ± 12.3	89	Sham tACS	Inert treatment					10
Liu et al (2012) [565]	USA	Two-arm pilot RCT	FM General population and healthcare Meet the American College of	8	55.6	100	Qigong	Mind-body exercise	6	NA	PSQI	MPQ FIQ	0
				6	57.7	100	Sham Qigong	Inert treatment					0

			Rheumatology criteria for FM Stable medications										
Loeppenthin et al (2022) [566]	Denmark	Two-arm RCT	RA Healthcare Prove RA diagnosis from physicians and PSQI > 5 scores Stable medications	17	57.8 ± 9.8	76	Aerobic exercise	Exercise	6	NA	ESS Sleep diary and PSG (TST, SE, SOL, and WASO)	VAS HAQ	0
				21	54.8 ± 9.6	95	Usual care	Passive control					0
Lu et al (2017) [567]	China	Two-arm RCT	KOA General population Meet the American College of Rheumatology criteria for KOA Stable medications	23	64.6 ± 3.4	100	Tai Ji Quan training	Mind-body exercise	24	NA	PSQI	WOMAC-pain WOMAC-function	0
				23	64.5 ± 3.4	100	Health education	Education					0
Lumley (2017) [568]	USA	Three-arm cluster RCT *	FM General population and healthcare Meet the American College of Rheumatology criteria for FM Stable medications	67	48.1 ± 13.5	90.7	CBT	CBT	8	6	PSQI	BPI SF12-physical function	0
				68	50.3 ± 13.5	98.7	Fibromyalgia education	Education					0
Lynch et al (2012) [569]	Canada	Two-arm RCT	FM General population Meet the American College of Rheumatology criteria for FM Stable medications	53	52.8 ± 8.9	94	Qigong	Mind-body exercise	8	4 and 6	PSQI	NRS FIQ	2
				47	52.1 ± 8.6	98	A waiting-list control	Passive control					0
Macian et al (2022) [570]	France	Two-arm RCT	FM General population Meet the American College of Rheumatology criteria for FM No restrictions on medications	38	54.0 ± 11.5	NI	Magnesium supplementation	Nutritional therapy	4	2	PSQI	NRS FIQ	NI
				38	51.8 ± 10.9		Placebo control	Inert treatment					

Maddali Bongi et al (2016) [571]	Italy	Two-arm RCT	FM NI Meet the American College of Rheumatology criteria for FM No restrictions on medications	22	50.4 ± 13.7	NI	Tai Ji Quan training	Mind-body exercise	16	NA	PSQI	WPI FIQ	0
				22	54.3 ± 10.7		Health education	Education					0
Maestu et al (2013) [572]	Spain	Two-arm RCT	FM General population Meet the American College of Rheumatology criteria for FM Stable medications	34	40.7 ± 6.7	100	Low-intensity TMS	Non-invasive brain stimulation	8	NA	VAS-sleep	VAS VAS-function	0
				33		100	Sham TMS	Inert treatment					0
Martinez et al (2014) [573]	Spain	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM and DSM IV for insomnia Stable medications	32	46.5 ± 6.3	100	CBT for insomnia	CBT	6	3 and 6	PSQI	MPQ FIQ	NI
				32	48.7 ± 7.3	100	Sleep hygiene	Education					
McCrae et al (2019) [483]	USA	Three-arm RCT	FM General population and healthcare Meet the American College of Rheumatology criteria for FM and SOL > 30 min or WASO > 30 min for > 3 day/week for > 6 mon Stable medications	39	54.1 ± 11.0	100	CBT for insomnia	CBT	8	6	Five-point ordinal scale for sleep Sleep diary and PSG (TST, SE, SOL, and WASO)	VAS PDI	NI
				37	51.5 ± 10.6	91.89	CBT for pain	CBT					
				37	52.3 ± 11.2	100	A waiting-list control	Passive control					
McCurry et al (2022) [479]	USA	Two-arm RCT	OA Healthcare Prove RA diagnosis from	163	70.1 ± 7.1	76.1	CBT for insomnia	CBT	8	12	ISI	BPI	37
				164	70.4 ± 6.5	73.2	Education related to OA	Education					31

			medical records and ISI > 11scores Stable medications										
McKenna et al (2021) [574]	Ireland	Two-arm pilot RCT	RA General population and healthcare Meet the American College of Rheumatology criteria for FM and PSQI > 5 scores No restrictions on medications	10	58.0 ± 7.4	100	A walking-based exercise	Exercise	8	NA	PSQI	VAS HAQ	3
				10	56.0 ± 7.9	100	Exercise education	Education					0
Mhalla et al (2011) [474]	France	Two-arm RCT	FM NI Meet the American College of Rheumatology criteria for FM Stable medications	20	51.8 ± 11.6	100	rTMS	Non-invasive brain stimulation	9	NA	NPRS-sleep	NPRS FIQ	7
				20	49.6 ± 10.0	100	Sham rTMS	Inert treatment					6
Miro et al (2011) [575]	Spain	Two-arm pilot RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM and DSM IV criteria for insomnia Stable medications	22	43.9 ± 6.1	100	CBT for insomnia	CBT	6	NA	PSQI	MPQ FIQ	NI
				22	50.2 ± 6.1	100	Sleep hygiene	Education					
Munguia-Izquierdo et al (2008) [576]	Spain	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	35	50.0 ± 7.0	100	Aquatic exercise	Exercise	16	NA	PSQI	FIQ	NI
				25	46.0 ± 8.0	100	Usual care	Passive control					NI
Murphy et al (2019) [577]	USA	Three-arm pilot RCT	CLBP General population and healthcare Prove non-specific CLBP diagnosis	22	51.1 ± 13.6	68.2	Relaxing acupressure	Acupuncture	6	NA	PSQI	BPI RMDQ	4
				22	48.6 ± 13.8	59.1	Stimulating acupressure	Acupuncture					

			from medical records Stable medications	23	50.3 ± 13.6	60.9	Usual care	Passive control					0
Nadal-Nicolás et al (2020) [578]	Spain	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	15	53.0 ± 6.0	100	Massage therapy	Manual therapy	4	NA	PSQI	VAS	NI
				15		100	Placebo control	Inert treatment					
Nelson et al (2010) [579]	USA	Two-arm RCT	FM General population and healthcare Meet the American College of Rheumatology criteria for FM Stable medications	21	51.6 ± 8.6	100	EEG-Driven Stimulation	Non-invasive brain stimulation	NI	3 and 6	MOS	FIQ	0
				21	52.0 ± 11.4	94.1	Sham control	Inert treatment					0
Nia et al (2019) [580]	Iran	Three-arm RCT *	RA Healthcare Prove RA diagnosis from physicians and ISI > 15 scores NI	25	45.4 ± 11.3	85.3	Guided imagery	Relaxation	2	NA	ISI	NA	NI
				25			No intervention	Passive control					
Norregaard et al (1997) [581]	Denmark	Three-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	15	44.0 ± 8.0	NI	Aerobic dance training	Exercise	12	NA	VAS-sleep	VAS FIQ	NI
				15	51.0 ± 14.0		Steady exercise	Exercise					
				8	55.0 ± 10.0		Hot packs	Physical agents					
Passard et al (2007) [582]	France	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	15	52.6 ± 7.9	100	rTMS	Non-invasive brain stimulation	2	1.5	VAS-sleep	VAS FIQ	5
				15	55.3 ± 8.9	93.3	Sham rTMS	Inert treatment					8

Peng et al (2022) [583]	China	Two-arm RCT	CLBP Healthcare Nonspecific low back pain for > 3 mon, NPRS > 3/10 Stable medications	56	31.7 ± 11.3	46.4	Aquatic exercise	Exercise	12	3 and 9	PSQI	NPRS RMDQ	2
				57	30.4 ± 11.8	57.9	Physical therapy modalities	Physical agents					4
Pigeon et al (2012) [584]	USA	Four-arm pilot RCT	Mixed conditions General population and healthcare Pain >6 mon from spine, shoulders, hips and SOL > 30 min or WASO > 30 min for > 3 day/week for > 6 mon Stable medications	6	50.7 ± 8.3	66.7	CBT for insomnia	CBT	10	NA	ISI Sleep diary (TST and SE)	MPI PDI	NI
				5			CBT for pain	CBT					
				6			CBT for insomnia and pain	CBT					
				4			A waiting-list control	Passive control					
Racine et al (2019) [585]	Canada	Three-arm pilot RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM NI	54	Age > 18	NI	CBT- operant learning	CBT	10	NA	MOS	BPI SF-36 physical function	NI
				53			CBT- energy conservation	CBT					
				71			A waiting-list control	Passive control					
Redondo et al (2004) [586]	Spain	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM No restrictions on medications	19	NI	100	Multimodal exercise	Exercise	8	6 and 12	VAS-sleep	VAS FIQ	1
				21		100	CBT	CBT					NI
Ribeiro et al (2021) [587]	Brazil	Two-arm RCT	FM Healthcare Prove FM diagnosis from a physician Stable medications	17	56.0 ± 5.8	100	Whole-body vibration training	Exercise	6	NA	PSQI	VAS FIQ	NI
				15	54.0 ± 7.2	100	No intervention	Passive control					
Roizenblatt et al (2007) [588]	Brazil	Three-arm RCT	FM Healthcare Meet the American College of	11	54.2 ± 7.4	100	tDCS on DLPFC	Non-invasive brain stimulation	1	NA	PSG (TST, SE, and SOL)	VAS SF-36 physical function	2

			Rheumatology criteria for FM No medications	11	54.8 ± 9.3	100	tDCS on M1	Non-invasive brain stimulation					6
				10	50.8 ± 10.2	100	Sham tDCS	Inert treatment					3
Samartin-Veiga et al (2022) [589]	Spain	Four-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM Stable medications	34	49.4 ± 8.8	100	tDCS on M1	Non-invasive brain stimulation	3	6	PSQI	FIQ-pain	1
				33	50.6 ± 8.9	100	tDCS on DLPFC	Non-invasive brain stimulation					2
				33	50.2 ± 8.2	100	tDCS on OIC	Non-invasive brain stimulation					3
				30	50.7 ± 8.9	100	Sham tDCS	Inert treatment					3
Sanchez et al (2012) [590]	Spain	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM and DSM IV criteria for insomnia Stable medications	13	44.8 ± 5.3	100	CBT for insomnia	CBT	6	NA	PSG (TST, SE, SOL, and WASO)	NA	NI
				13	48.8 ± 4.4	100	Sleep hygiene	Education					
Sanudo et al (2015) [591]	Spain	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM NI	16	55.0 ± 8.0	100	Aerobic exercise	Exercise	24	NA	VAS-sleep	VAS	NI
				16	58.0 ± 6.9	100	Normal daily activities	Passive control					
Sarmento et al	USA	Two-arm	FM Healthcare	14	42.6 ± 10.7	100	Qigong exercise	Mind-body exercise	10	NA	PSQI	VAS FIQR	0

(2020) [592]		pilot RCT	Meet the American College of Rheumatology criteria for FM Stable medications	14	56.1 ± 12.3	100	Sham Qigong control	Inert treatment					0
Schmidt et al (2011) [593]	Germany	Three-arm RCT *	FM General population and healthcare Meet the American College of Rheumatology criteria for FM Stable medications	59	53.4 ± 8.7	100	Mindfulness-based stress reduction	Mindful psychotherapy	8	2	PSQI	PPS FIQ	NI
				59	52.3 ± 10.9	100	A waiting-list control	Passive control					
Silva et al (2022) [594]	Egypt	Two-arm RCT	FM General population and healthcare Meet the American College of Rheumatology criteria for FM Stable medications	32	60.0 ± 6.0	100	Anti-inflammatory diet	Nutritional therapy	3	NA	PSQI	VAS FIQR	NI
				29	56.0 ± 8.0	100	Health dietary education	Education					
Smith et al (2015) [595]	USA	Two-arm RCT	KOA NI Prove KOA diagnosis from physicians and meet research diagnostic criteria for insomnia disorder Stable pain medications	50	59.2 ± 9.9	76	CBT for insomnia	CBT	8	3 and 6	ISI Sleep diary and PSG (SE, SL, TST, WASO)	VAS	3
				50	59.6 ± 9.1	82	Desensitization intervention	Inert treatment					
Soares et al (2002) [596]	Sweden	Three-arm RCT *	FM Healthcare Meet the American College of Rheumatology criteria for FM No restrictions on medications	20	45.0 ± 7.0	100	Behavioral intervention	CBT	10	6	KSQ	MPQ FIQ	NI
				20	47.0 ± 8.0	100	Education	Education					
				20	43.0 ± 12.0	100	A waiting-list control	Passive control		NA			
	China		KOA	20	64.2 ± 8.6	100	Tai chi	Mind-body exercise	12	3 and 6	PSQI	WOMAC-pain	0

Song et al (2022) [597]		Two-arm RCT	General population and healthcare Meet radiographic diagnosis for KOA No medications	20	64.2 ± 8.6	100	Health education	Education				WOMAC-fuction	0
Stegner et al (2021) [598]	USA	Two-arm RCT	Mixed conditions General population and healthcare Nonspecific muscle pain > 3 mon No medications	28	49.7 ± 7.2	NI	Resistance exercise training	Exercise	16	6 and 12	PSQI	VAS	0
				26	50.2 ± 5.6		A waiting-list control	Passive control					0
Tang et al (2021) [599]	USA	Two-arm pilot RCT	OA Healthcare Prove OA diagnosis from medical records, sleep disturbance > 3 day/week for > 6 mon, and ISI > 8 scores NI	16	66.7 ± 5.2	87	Open-loop Audio-Visual Stimulation	Relaxation	2	NA	PSQI Sleep diary (TST, SE, SOL, and WASO)	BPI	NI
				15	68.9 ± 5.0	93	Placebo control	Inert treatment					
Udina-Cortes et al (2020) [600]	Spain	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM NI	23	52.0 ± 9.0	100	Neuro-adaptive electrostimulation	Physical agents	4	3	JSS	VAS FIQ	NI
				19	52.9 ± 8.0	100	Sham control	Inert treatment					
Van Gordon et al (2017) [601]	United Kingdom	Two-arm RCT	FM General population and healthcare Prove FM diagnosis from medical records or physicians Stable medications	74	46.4 ± 9.1	82.4	Meditation awareness training	Mindful psychotherapy	8	6	PSQI	MPQ FIQR	NI
				74	47.3 ± 9.8	83.8	CBT for groups	CBT					
Vitiello et al (2013) [602]	USA	Three-arm clust	OA Healthcare Prove OA diagnosis and meet research diagnostic	104	73.0 ± 9.1	80.3	CBT for pain	CBT	6	9	ISI Actigraphy (SE)	VAS	NI
				104	73.2 ± 8.8	79.5	CBT for insomnia and pain	CBT					

		er RCT	criteria for insomnia No restrictions on medications	105	73.1 ± 8.7	75.6	Education related to pain and sleep	Education					
Vitiello et al (2009) [603]	USA	Two-arm RCT	OA General population and healthcare Prove OA diagnosis from and sleep disturbance > 3 day/week for > 6 mon (SOL 30 min or longer, WASO 60 min or longer, total sleep time < 6.5h per night) No restrictions on medications	23	69.2 ± 8.9	78.3	CBT for insomnia	CBT	8	NA	Sleep diary (TST, SE, SOL, and WASO)	MPQ	NI
				28	66.5 ± 7.7	96.4	Stress management	Mindful psychotherapy					
Wang et al (2018) [604]	USA	Two-arm RCT	FM General population and healthcare Meet the American College of Rheumatology criteria for FM Stable medications	151	52.0 ± 12.0	90.7	Tai chi	Mind-body exercise	24	7	PSQI	VAS FIQR	8
				75	50.9 ± 12.5	96	Aerobic exercise	Exercise					4
Ward et al (2018) [605]	New Zealand	Two-arm pilot RCT	RA Healthcare Meet the American College of Rheumatology/European League Against criteria for RA and self-reported sleep disturbance > 30 min per night in the last month No restrictions on medications	13	50.0 ± 12.0	100	Yoga	Mind-body exercise	8	1	ISI	VAS HAQ	6
				13	59.0 ± 8.0	92	Usual care	Passive control					0
	Norway	Three-	FM Healthcare	20	43.0 ± 9.0	90	Aerobic exercise	Exercise	12	48	VAS-sleep	VAS	NI

Wiger et al (1996) [606]		arm RCT	Meet the American College of Rheumatology criteria for FM Stable medications	20	44.0 ± 12.0	90	Stress management	Mindful psychotherapy					
				20	46.0 ± 9.0	95	Usual care	Passive control					
Wiklund et al (2018) [607]	Sweden	Three-arm RCT	Mixed conditions General population and healthcare Neck, back, and generalized pain > 3 mon No restrictions on medications	100	54.2 ± 10.3	NI	Multimodal exercise	Exercise	8	6 and 12	ISI	NPRS	NI
				99			Acceptance and Commitment Therapy	Mindful psychotherapy	7				
				100			Discussion control	Inert treatment					
Wong et al (2018) [608]	Korea	Two-arm RCT	FM General population Meet the American College of Rheumatology criteria for FM Stable medications	18	51.0 ± 8.3	100	Tai chi	Mind-body exercise	12	NA	VAS-sleep	VAS	0
				19	51.0 ± 7.5	100	Usual care	Passive control					1
Wu et al (2021) [609]	China	Two-arm RCT	FM Healthcare Meet the American College of Rheumatology criteria for FM No restrictions on medications	60	48.6 ± 13.5	95	Neurofeedback for sensorimotor rhythm	Relaxation	8	NA	PSQI	BPI FIQR	NI
				20	42.2 ± 10.9	70	Education related to FM	Education					
Yao et al (2020) [610]	China	Two-arm RCT	CLBP General population and healthcare Nonspecific low back pain > 3mon No medications	36	53.0 ± 16.0	83	Wu qinxi	Mind-body exercise	24	NA	PSQI	VAS	NI
				36	54.0 ± 14.0	78	Muscle activity and strength training	Exercise					
Yeh et al (2016) [611]	USA	Two-arm RCT	CLBP General population and healthcare Low back pain > 3mon, BPI > 4/10 No restrictions on medications	30	60.9 ± 17.4	66.7	Auricular point acupressure	Acupuncture	4	1	PSQI	BPI	NI
				31	65.6 ± 16.0	67.7	Sham control	Inert treatment					

Yousefi et al (2022) [612]	Iran	Three-arm RCT	RA Healthcare Meet the American College of Rheumatology criteria for RA Stable medications	22	51.3 ± 5.7	84.2	Mindfulness-based stress reduction	Mindful psychotherapy	8	3	PSQI	NA	NI
				21	48.7 ± 7.3	84.2	CBT	CBT					
				21	50.9 ± 6.8	84.2	Usual care	Passive control					

Abbreviations: AIS: Athens Insomnia Scale, AIMS-2: Arthritis Impact Measurement Scale–2, AS: Ankylosing Spondylitis, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Function Index, BPI: Brief Pain Inventory, CBT: Cognitive Behavioral Therapy, CLBP: Chronic Low Back Pain, CNP: Chronic Neck Pain, DLPFC: Dorsolateral Prefrontal cortex, DSM: Diagnostic and Statistical Manual of Mental Disorders, ESS: Epworth Sleepiness Scale, FIQ: Fibromyalgia Impact Questionnaire, FIQR: Revised Fibromyalgia Impact Questionnaire, FM: Fibromyalgia, HAQ: Health Assessment Questionnaire Disability Index, ISI: Insomnia Severity Index, JSS: Jenkins Sleep Scale, KSQ: Karolinska Sleep Questionnaire, KOA: Knee Osteoarthritis, KOOS: Knee Injury and Osteoarthritis Outcome Score, M1: Primary Motor Cortex, MOS: Medical Outcome Sleep Scale, MPI: Multidimensional Pain Inventory, MPQ: McGill Pain Questionnaire, MPS: Myofascial Pain Syndrome, NA: Not Available, NDI: Neck Disability Index Scale, NHP: Nottingham Health Profile, NI: No Information, NPRS: Numerical Pain Rating Scale, OA: Osteoarthritis, OIC: Operculo-insular Cortex, PDI: Pain Disability Index, PPS: Pain Perception Scale, PROMIS, Patient Reported Outcomes Measurement Information System, PSG: Polysomnography, PSI: Post-Sleep Inventory, RA: Rheumatoid Arthritis, RCT: Randomized Controlled Trial, RMDQ: Roland Morris Questionnaire, r-TMS: repetitive Transcranial Magnetic Stimulation, SE: Sleep Efficiency, SF-36/12: Short Form 36/12, SOL : Sleep Onset Latency, SSQ: Stanford Sleep Questionnaire, t-ACS: transcranial Alternating Current Stimulation, t-DCS: transcranial Direct Current Stimulation, TST: Total Sleep Time, WASO: Wake Time After Sleep Onset, WOMAC: Western Ontario and McMaster University Osteoarthritis Index, WPI: Widespread Pain Index.
Footnote: *Not all treatment arms were included for data analysis due to combined interventions, pharmacological interventions, or no predefined intervention.

Appendix 17. Risk of bias assessment for the included studies in Chapter 7

Table S5.2. Risk of bias assessment for the included studies

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall quality
Akodu et al (2021) [509]	Some concerns	Some concerns	High	Some concerns	Some concerns	High
Almeida et al (2003) [510]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Alves et al (2013) [511]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Amirova et al (2017) [512]	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Amutio et al (2018) [513]	Low	Some concerns	Low	Low	Low	Some concerns
Bakir et al (2018) [514]	Some concerns	High	Some concerns	Some concerns	Some concerns	High
Basler et al (1991) [515]	Some concerns	High	Some concerns	Low	Some concerns	High
Bestas et al (2022) [516]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Blodt et al (2015) [517]	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Bongi et al (2010) [518]	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Brattberg (1999) [519]	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Brietzke et al (2020) [520]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Burns et al (2022) [521]	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
Calandre et al (2009) [522]	High	Some concerns	High	Some concerns	Some concerns	High
Canovas et al (2022) [523]	Some concerns	Some concerns	High	Some concerns	Some concerns	High
Carson et al (2010) [524]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Cash et al (2015) [525]	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Castel et al (2012) [526]	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Castro Sanchez et al (2014) [527]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Caumo et al (2022) [528]	Low	Low	Low	Low	Some concerns	Some concerns
Cheung et al (2014) [529]	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Colbert et al (1999) [530]	Low	High	Some concerns	Low	Some concerns	High
Currie et al (2000) [531]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Dall'Agnol et al (2014) [532]	Low	Some concerns	Low	Low	Some concerns	Some concerns

Darnall et al (2021) [533]	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
De Medeiroset al (2020) [534]	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Deluze et al (1992) [535]	Low	High	Some concerns	Low	Some concerns	High
Durcan et al (2014) [536]	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Edinger et al (2005) [537]	Some concerns	Some concerns	High	Some concerns	Some concerns	High
Ekici et al (2017) [538]	Low	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Ericsson et al (2016) [539]	Low	Some concerns	High	Low	Some concerns	High
Fernández García et al (2011) [540]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Field et al (2015) [541]	Some concerns	High	High	Some concerns	Some concerns	High
Field et al (2007) [542]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Fonseca et al (2021) [543]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Franco et al (2022) [544]	Low	Some concerns	Low	Low	Low	Some concerns
Gillis et al (2006) [545]	Low	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Goldway et al (2019) [546]	Low	Low	Low	Low	Some concerns	Some concerns
Gur et al (2002) [547]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Haak et al (2008) [548]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Hagiwara et al (2017) [549]	Some concerns	Some concerns	High	Some concerns	Some concerns	High
Hargrove et al (2012) [550]	Some concerns	High	High	Low	Some concerns	High
Harvey et al (2017) [551]	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Hedman-Lagerlöf et al(2018) [552]	Low	Some concerns	Low	Some concerns	Low	Some concerns
Heffner et al (2018) [553]	Some concerns	High	High	Some concerns	Some concerns	High
Hernandez-Reif et al (2001) [554]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Innes et al (2018) [555]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Jones et al (2012) [556]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Jungquist et al (2010) [557]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Kilic et al (2021) [558]	High	Some concerns	Low	Some concerns	Some concerns	High
Lai (2014) [559]	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Lami et al (2018) [560]	Low	High	Some concerns	Low	Low	High

Latocha et al (2022) [561]	Low	Some concerns	Low	Low	Low	Some concerns
Lauche et al (2016) [562]	Low	Some concerns	Some concerns	Low	Low	Some concerns
Lee et al (2022) [563]	Some concerns	Some concerns	High	High	Some concerns	High
Lin et al (2022) [564]	Low	Some concerns	Some concerns	Low	Low	Some concerns
Liu et al (2012) [565]	Some concerns	High	Low	Low	Some concerns	High
Loeppenthin et al (2022) [566]	Some concerns	Some concerns	Low	Low	Low	Some concerns
Lu et al (2017) [567]	Low	Some concerns	Some concerns	Low	Low	Some concerns
Lumley (2017) [568]	Low	Some concerns	Low	Low	Low	Some concerns
Lynch et al (2012) [569]	Low	High	High	Some concerns	Low	High
Macian et al (2022) [570]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Maddali Bongi et al (2016) [571]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Maestu et al (2013) [572]	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Martinez et al (2014) [573]	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
McCrae et al (2019) [483]	Low	Some concerns	Low	Low	Low	Some concerns
McCurry et al (2022) [479]	Low	Some concerns	Low	Low	Low	Some concerns
McKenna et al (2021) [574]	Low	Some concerns	Low	Low	Low	Some concerns
Mhalla et al (2011) [474]	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Miro et al (2011) [575]	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Munguia-Izquierdo et al (2008) [576]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Murphy et al (2019) [577]	Low	Low	Some concerns	Low	Some concerns	Some concerns
Nadal-Nicolás et al (2020) [578]	Low	High	Some concerns	Some concerns	Some concerns	High
Nelson et al (2010) [579]	Low	High	Some concerns	Low	Some concerns	High
Nia et al (2019) [580]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Norregaard et al (1997) [581]	Some concerns	High	Some concerns	Some concerns	Some concerns	High
Passard et al (2007) [582]	Low	Low	Low	Low	Some concerns	Some concerns
Peng et al (2022) [583]	Low	Some concerns	Low	Low	Low	Some concerns
Pigeon et al (2012) [584]	Some concerns	Some concerns	Low	Low	High	High
Racine et al (2019) [585]	Some concerns	High	Some concerns	Some concerns	Low	High

Redondo et al (2004) [586]	Some concerns	Some concerns	High	Low	Some concerns	High
Ribeiro et al (2021) [587]	Low	Some concerns	Low	Low	Low	Some concerns
Roizenblatt et al (2007) [588]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Samartin-Veiga et al (2022) [589]	Low	Low	Low	Low	Low	Low
Sanchez et al (2012) [590]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Sanudo et al (2015) [591]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Sarmento et al (2020) [592]	Some concerns	High	Some concerns	Low	Some concerns	High
Schmidt et al (2011) [593]	Low	Low	Some concerns	Low	Some concerns	Some concerns
Silva et al (2022) [594]	Low	High	Some concerns	Some concerns	Low	High
Smith et al (2015) [595]	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Soares et al (2002) [596]	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Song et al (2022) [597]	Low	Some concerns	Some concerns	Low	Low	Some concerns
Stegner et al (2021) [598]	Low	High	Some concerns	Some concerns	Low	High
Tang et al (2021) [599]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Udina-Cortes et al (2020) [600]	Some concerns	High	Some concerns	Low	Low	High
Van Gordon et al (2017) [601]	Low	Some concerns	Some concerns	Low	Low	Some concerns
Vitiello et al (2013) [602]	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
Vitiello et al (2009) [603]	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Wang et al (2018) [604]	Low	Some concerns	Low	Low	Low	Some concerns
Ward et al (2018) [605]	Low	Some concerns	Low	Low	Low	Some concerns
Wiger et al (1996) [606]	Some concerns	Some concerns	Some concerns	Some concerns	Low	Some concerns
Wiklund et al (2018) [607]	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Wong et al (2018) [608]	Some concerns	High	Some concerns	Some concerns	Some concerns	High
Wu et al (2021) [609]	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Yao et al (2020) [610]	Low	High	Some concerns	Low	Some concerns	High
Yeh et al (2016) [611]	Some concerns	Some concerns	High	Low	Some concerns	High
Yousefi et al (2022) [612]	Some concerns	High	Some concerns	Some concerns	Some concerns	High

Footnote: The methodological quality of eligible studies was assessed using the Cochrane Collaboration risk of bias (RoB) 2.0 tool by two independent reviewers. A third reviewer (AW) was consulted if disagreements persisted. The RoB 2.0 tool comprises six domains: randomization process, deviation from intended interventions, missing outcomes data, measurement

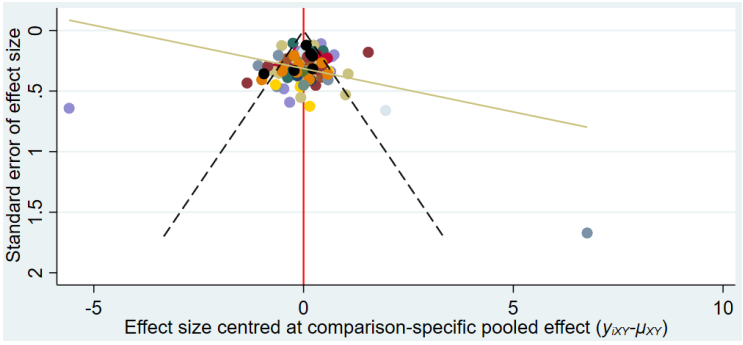
of the outcome, selection of the reported result, and overall bias [218]. The overall risk of bias was rated as low, some concerns, or high according to the results of each domain [219].

Appendix 18. Comparison-adjusted funnel plots in Chapter 7

Because sleep quality, pain, or disability at long-term follow-ups and other sleep parameters at all follow-ups were reported by less than 10 articles, it was not feasible to assess small study effects. There was no small-study effect based on the comparison-adjusted funnel plots and the Egger test results for other outcomes.

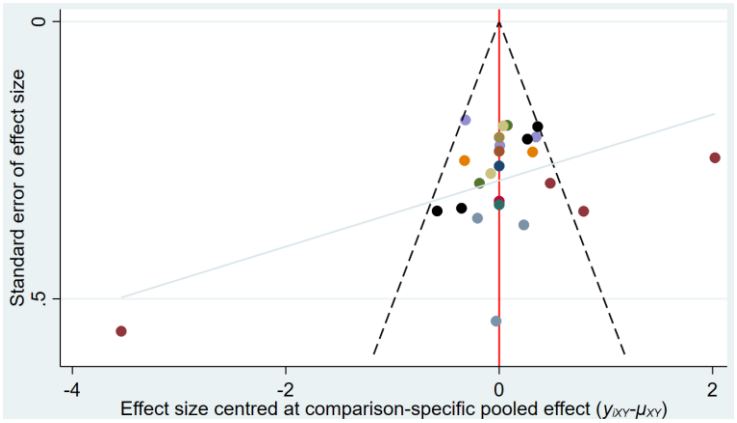
Figure S5.1. The funnel plots for sleep quality

a) At immediate post-intervention



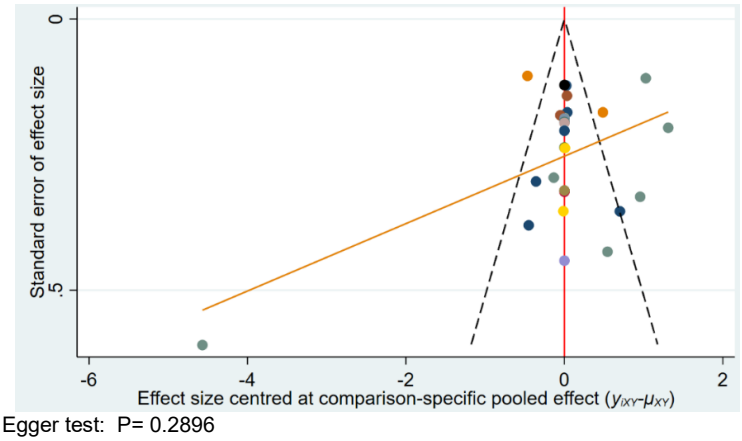
Egger test: P= 0.3618

b) At short-term follow-up



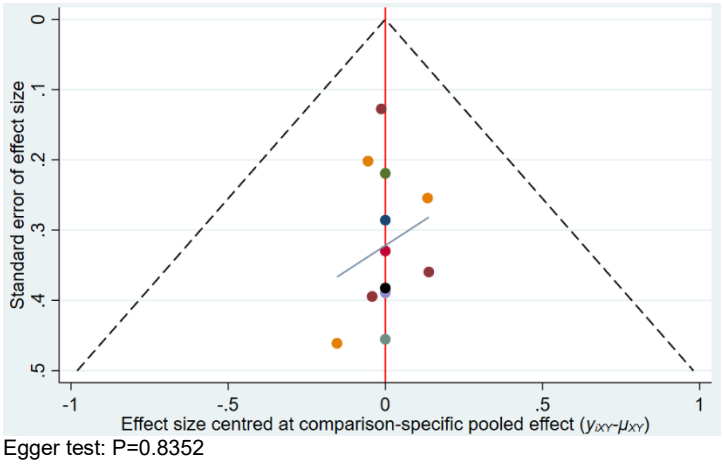
Egger test: P= 0.1067

c) At mid-term follow-up



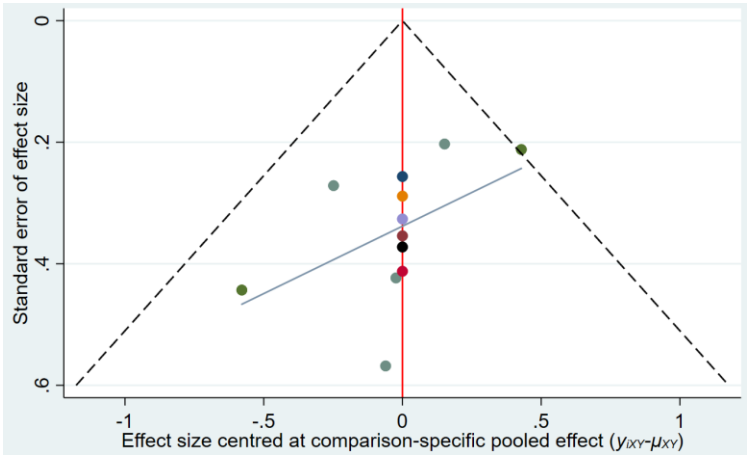
Egger test: P= 0.2896

Figure S5.2. The funnel plot for objective sleep efficiency at immediate post-intervention



Egger test: P=0.8352

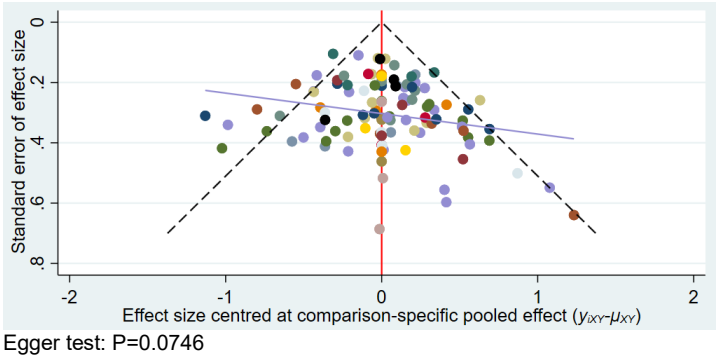
Figure S5.3. The funnel plot for subjective sleep efficiency at immediate post-intervention



Egger test: P=0.0847

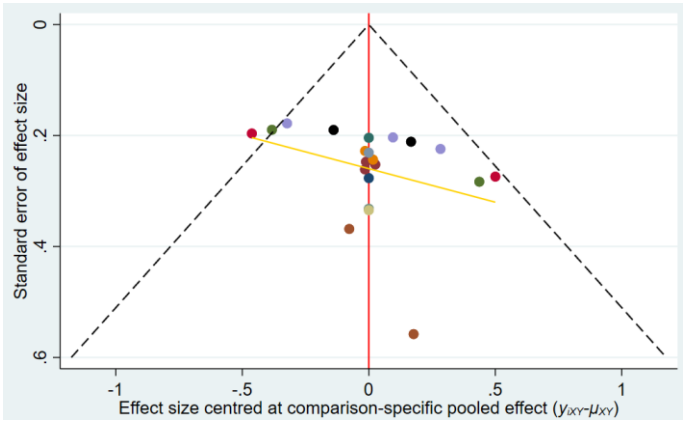
Figure S5.4. The funnel plots for pain

a) At immediate post-intervention



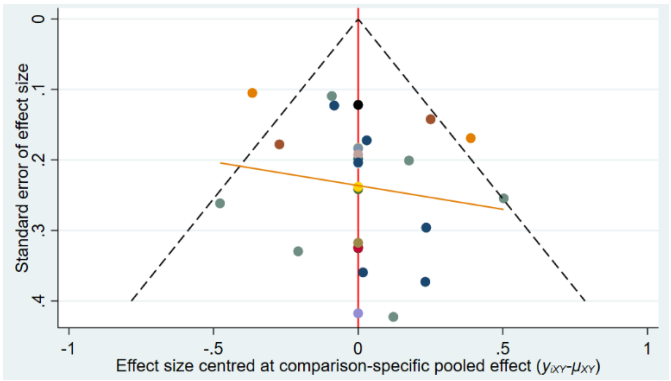
Egger test: P=0.0746

b) At short-term follow-up



Egger test: P=0.0579

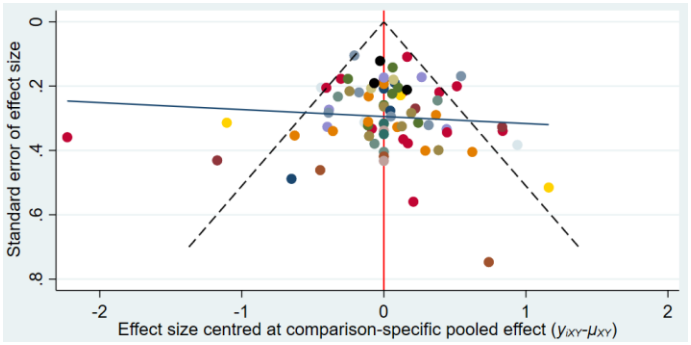
c) At mid-term follow-up



Egger test: P=0.1585

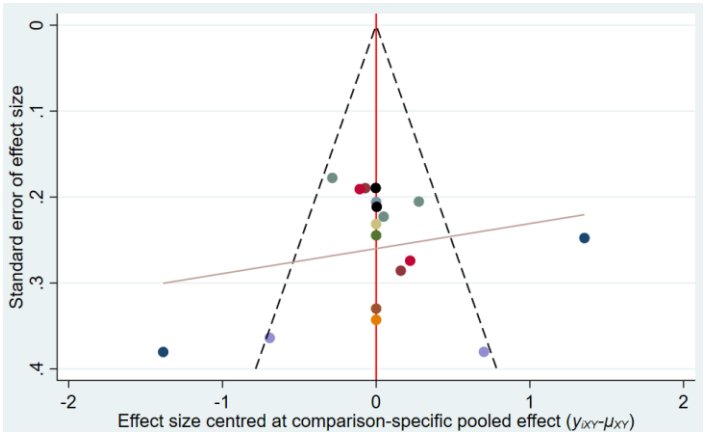
Figure S5.5. The funnel plots for disability

a) At immediate post-intervention



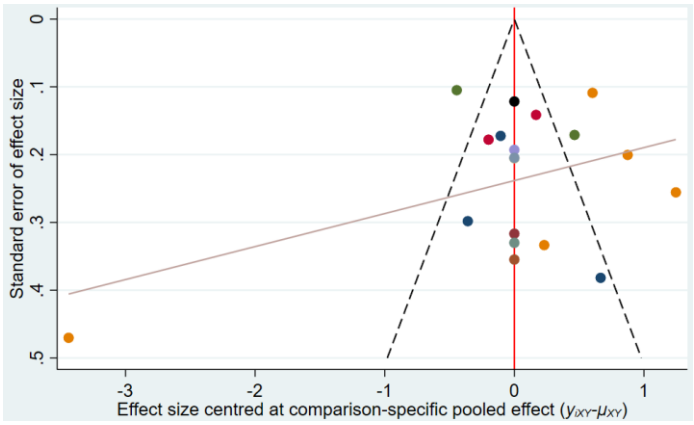
Egger test: P=0.9251

b) At short-term follow-up



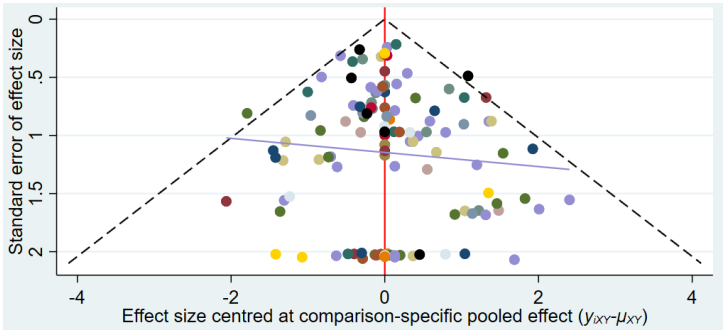
Egger test: P=0.8426

c) At mid-term follow-up



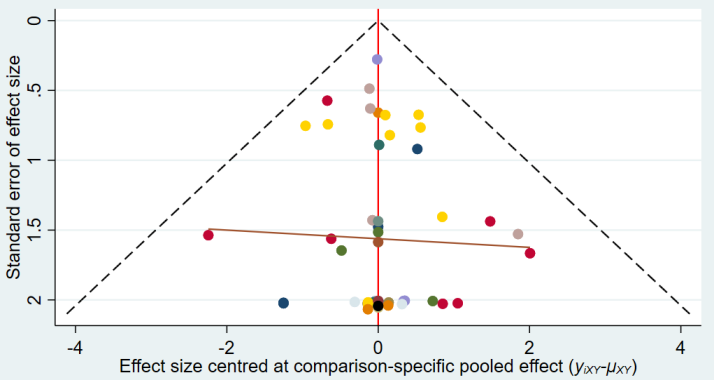
Egger test: P=0.6322

Figure S5.6. The funnel plot for acceptability



Egger test: P=0.1345

Figure S5.7. The funnel plot for safety



Egger test: P=0.2793

Appendix 19. Pairwise meta-analyses in Chapter 7

Table S5.3. Pairwise meta-analyses for sleep quality

At immediate post-intervention					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
Acupuncture	Inert treatment	3	**0.77 (0.46, 1.09)**	**0.00**	0.0
Acupuncture	Passive control	1	0.09 (-0.42, 0.59)	0.73	NA
Assistive technique	Inert treatment	1	0.28 (-0.51, 1.06)	0.50	NA
Assistive technique	Passive control	1	-0.35 (-0.73, 0.03)	0.07	NA
CBT	Education	7	**0.41 (0.07, 0.76)**	**0.02**	**77.7**
CBT	Exercise	1	0.00 (-0.62, 0.62)	1.00	NA
CBT	Inert treatment	2	0.91 (-0.19, 2.00)	0.11	**79.7**
CBT	Mindful psychotherapy	3	-0.15 (-0.64, 0.38)	0.60	**81.6**
CBT	Passive control	13	**0.88 (0.42, 1.33)**	**0.00**	**88.2**
Education	Passive control	2	0.79 (-0.47, 2.06)	0.22	**61.4**
Exercise	Education	3	0.74 (-0.35, 1.83)	0.18	**86.9**
Exercise	Inert treatment	1	0.29 (-0.18, 0.77)	0.23	NA
Exercise	Mindful psychotherapy	2	0.16 (-0.26, 0.57)	0.47	0.0
Exercise	Physical agents	3	0.29 (0.00, 0.58)	0.05	0.0
Exercise	Relaxation	1	0.34 (-0.05, 0.73)	0.09	NA
Exercise	Passive control	6	**0.50 (0.04, 0.96)**	**0.04**	**62.9**
Inert treatment	Passive control	2	-0.11 (-0.49, 0.27)	0.56	0.0
Manual therapy	Inert treatment	1	0.20 (-0.61, 1.02)	0.63	NA
Manual therapy	Mind-body exercise	1	-0.28 (0.95, 0.38)	0.41	NA
Manual therapy	Relaxation	2	0.41 (-0.12, 0.95)	0.13	0.0
Manual therapy	Passive control	4	**0.64 (0.10, 1.18)**	**0.02**	**74.7**
Mind-body exercise	Education	4	**0.49 (0.22, 0.75)**	**0.00**	0.0
Mind-body exercise	Exercise	7	0.06 (-0.20, 0.32)	0.64	**59.9**
Mind-body exercise	Inert treatment	2	**0.78 (0.05, 1.51)**	**0.04**	0.0
Mind-body exercise	Passive control	7	**0.52 (0.24, 0.80)**	**0.00**	35.4
Mindful psychotherapy	Inert treatment	1	0.08 (-0.41, 0.58)	0.75	NA
Mindful psychotherapy	Relaxation	1	0.88 (-0.01, 1.77)	0.05	NA
Mindful psychotherapy	Passive control	6	**0.38 (0.09, 0.66)**	**0.01**	45.2
Non-invasive brain stimulation	Inert treatment	11	**0.58 (0.33, 0.83)**	**0.00**	35.9
Nutritional therapy	Education	1	0.44 (-0.14, 1.03)	0.14	NA
Nutritional therapy	Inert treatment	3	0.04 (-0.43, 0.51)	0.87	**54.7**
Physical agents	Inert treatment	6	**0.86 (0.08, 1.65)**	**0.03**	**84.9**
Physical agents	Passive control	1	0.18 (-0.39, 0.75)	0.54	NA
Relaxation	Education	1	0.13 (-0.38, 0.64)	0.61	NA
Relaxation	Inert treatment	3	0.17 (-0.19, 0.53)	0.35	0.0
Relaxation	Passive control	3	**1.79 (0.15, 3.43)**	**0.00**	**95.2**
At short-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
Acupuncture	Inert treatment	1	0.50 (-0.01, 1.01)	0.05	NA
CBT	Education	2	**0.50 (0.19, 0.81)**	**0.00**	0.0
CBT	Inert treatment	2	0.37 (-0.26, 0.99)	0.25	**71.0**
CBT	Mindful psychotherapy	1	0.02 (-0.86, 0.89)	0.97	NA
CBT	Passive control	4	1.89 (0.00, 3.79)	0.05	**96.6**
Exercise	Physical agents	2	0.02 (-0.28, 0.33)	0.88	0.0
Mind-body exercise	Education	1	0.59 (-0.05, 1.22)	0.07	NA
Mind-body exercise	Exercise	3	0.28 (-0.12, 0.57)	0.17	**66.0**
Mind-body exercise	Passive control	1	**0.81 (0.40, 1.22)**	**0.00**	NA
Mindful psychotherapy	Passive control	4	**0.42 (0.05, 0.79)**	**0.03**	46.6

Non-invasive brain stimulation	Inert treatment	3	0.01 (-0.44, 0.46)	0.97	0.0
Nutritional therapy	Inert treatment	1	-0.44 (-0.89, 0.02)	0.06	NA
Physical agents	Inert treatment	1	0.12 (-0.53, 0.77)	0.72	NA
At mid-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	5	0.15 (-0.06, 0.36)	0.17	15.80
CBT	Exercise	1	-0.08 (-0.70, 0.54)	0.80	NA
CBT	Inert treatment	1	**0.49 (0.03, 0.96)**	**0.04**	NA
CBT	Mindful psychotherapy	2	-0.39 (-1.32, 0.54)	0.42	**94.40**
CBT	Passive control	6	**1.45 (0.44, 2.46)**	**0.01**	**94.90**
Education	Passive control	1	**1.44 (0.18, 2.70)**	**0.03**	NA
Exercise	Inert treatment	1	0.34 (-0.05, 0.73)	0.90	NA
Exercise	Mindful psychotherapy	1	0.13 (-0.47, 0.54)	0.62	NA
Exercise	Physical agents	1	**0.39 (0.02, 0.76)**	**0.04**	NA
Exercise	Passive control	1	0.02 (-0.60, 0.64)	0.95	NA
Mind-body exercise	Education	1	0.32 (-0.30, 0.94)	0.32	NA
Mind-body exercise	Exercise	2	0.13 (-0.09, 0.35)	0.24	0.00
Mind-body exercise	Passive control	1	**0.66 (0.26, 1.01)**	**0.00**	NA
Mindful psychotherapy	Inert treatment	1	-0.09 (-0.62, 0.44)	0.74	NA
Mindful psychotherapy	Passive control	1	**0.35 (0.02, 0.69)**	**0.04**	NA
Non-invasive brain stimulation	Inert treatment	2	0.19 (-0.19, 0.58)	0.34	0.00
Physical agents	Inert treatment	1	-0.10 (-0.51, 0.30)	0.61	NA
At long-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	1	**0.72 (0.48, 0.96)**	**0.00**	NA
CBT	Exercise	1	0.04 (-0.58, 0.66)	0.90	NA
Exercise	Inert treatment	1	0.23 (-0.29, 0.74)	0.38	NA
Exercise	Mindful psychotherapy	2	0.15 (-0.30, 0.59)	0.52	0.0
Exercise	Passive control	2	0.12 (-0.41, 0.64)	0.67	0.0
Mind-body exercise	Exercise	1	0.20 (-0.20, 0.60)	0.32	NA
Mindful psychotherapy	Inert treatment	1	0.10 (-0.43, 0.63)	0.70	NA
Mindful psychotherapy	Passive control	1	-0.06 (-0.94, 0.81)	0.89	NA

Table S5.4. Pairwise meta-analyses for objective sleep efficiency

At immediate post-intervention					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
Acupuncture	Inert treatment	1	**0.68 (0.12, 1.24)**	**0.02**	NA
CBT	Education	3	0.23 (0.00, 0.45)	0.05	0.0
CBT	Inert treatment	1	0.07 (-0.36, 0.50)	0.76	NA
CBT	Passive control	3	0.29 (-0.00, 0.58)	0.05	0.0
Education	Passive control	1	0.31 (-0.59, 1.20)	0.50	NA
Exercise	Passive control	1	0.39 (-0.26, 1.04)	0.24	NA
Non-invasive brain stimulation	Inert treatment	1	-0.20 (-0.95, 0.55)	0.60	NA
Relaxation	Inert treatment	1	0.15 (-0.61, 0.91)	0.70	NA
At short-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Inert treatment	1	-0.14 (-0.62, 0.34)	0.58	NA
At mid-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	2	0.21 (-0.03, 0.45)	0.09	0.0
CBT	Inert treatment	1	0.00 (-0.48, 0.48)	1.00	NA
CBT	Passive control	3	0.02 (-0.43, 0.47)	0.94	49.7

Education	Passive control	1	0.03 (-0.86, 0.92)	0.95	NA

Table S5.5. Pairwise meta-analyses for objective sleep onset latency at immediate post-intervention

At immediate post-intervention					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
Acupuncture	Inert treatment	1	0.18 (-0.36, 0.73)	0.52	NA
CBT	Education	2	-0.06 (-0.58, 0.46)	0.81	0.0
CBT	Inert treatment	1	-0.36 (-0.80, 0.07)	0.10	NA
CBT	Passive control	2	0.44 (-0.34, 1.21)	0.27	**59.3**
Education	Passive control	1	0.61 (-0.30, 1.52)	0.19	NA
Exercise	Passive control	1	-0.63 (-1.29, 0.03)	0.06	NA
Non-invasive brain stimulation	Inert treatment	1	-0.30 (-1.06, 0.45)	0.43	NA
Relaxation	Inert treatment	1	1.18 (0.36, 2.00)	0.01	NA
At short-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Inert treatment	1	0.09 (-0.39, 0.57)	0.71	NA
At mid-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	1	0.04 (-0.67, 0.74)	0.92	NA
CBT	Inert treatment	1	-0.06 (-0.53, 0.42)	0.82	NA
CBT	Passive control	3	0.16 (-0.31, 0.62)	0.51	**52.2**
Education	Passive control	1	0.37 (-0.53, 1.26)	0.42	NA

Table S5.6. Pairwise meta-analyses for objective total sleep time

At immediate post-intervention					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
Acupuncture	Inert treatment	1	0.47 (-0.08, 1.03)	0.09	NA
CBT	Education	2	-0.05 (-0.57, 0.47)	0.86	0.0
CBT	Inert treatment	1	-0.36 (-0.80, 0.08)	0.11	NA
CBT	Passive control	2	0.16 (-0.20, 0.52)	0.38	0.0
Education	Passive control	1	0.07 (-0.82, 0.96)	0.88	NA
Exercise	Passive control	1	0.29 (-0.35, 0.94)	0.37	NA
Non-invasive brain stimulation	Inert treatment	1	0.05 (-0.70, 0.80)	0.90	NA
At short-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Inert treatment	1	-0.05 (-0.51, 0.42)	0.85	NA
At mid-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I2 (%)**
CBT	Education	1	-0.27 (-0.97, 0.44)	0.47	NA
CBT	Inert treatment	1	-0.24 (-0.80, 0.32)	0.40	NA
CBT	Passive control	3	-0.10 (-0.39, 0.19)	0.50	0.0
Education	Passive control	1	-0.25 (-1.14, 0.65)	0.59	NA

Table S5.7. Pairwise meta-analyses for objective wake time after sleep onset

At immediate post-intervention					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	2	0.23 (-0.29, 0.75)	0.39	0.0

CBT	Inert treatment	1	0.34 (-0.09, 0.78)	0.12	NA
CBT	Passive control	2	0.20 (-0.16, 0.56)	0.27	0.0
Education	Passive control	1	-0.11 (-1.00, 0.78)	0.81	NA
Exercise	Passive control	1	0.39 (-0.26, 1.03)	0.24	NA
Physical agents	Inert treatment	1	0.94 (-0.11, 2.00)	0.08	NA
At short-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Inert treatment	1	-0.38 (-0.86, 0.10)	0.12	NA
At mid-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	1	0.06 (-0.64, 0.77)	0.86	NA
CBT	Inert treatment	1	-0.00 (-0.47, 0.48)	0.99	NA
CBT	Passive control	3	-0.04 (-0.43, 0.36)	0.86	37.1
Education	Passive control	1	-0.22 (-1.12, 0.67)	0.62	NA

Table S5.8. Pairwise meta-analyses for subjective sleep efficiency

At immediate post-intervention					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
Acupuncture	Inert treatment	1	0.14 (-0.37, 0.64)	0.60	NA
CBT	Education	1	0.53 (-0.17, 1.22)	0.14	NA
CBT	Inert treatment	2	0.66 (-0.32, 1.63)	0.19	**76.4**
CBT	Mindful psychotherapy	1	0.62 (0.05, 1.19)	0.03	NA
CBT	Passive control	4	**0.61 (0.33, 0.90)**	**0.00**	0.0
Education	Passive control	1	0.10 (-0.71, 0.91)	0.81	NA
Exercise	Passive control	1	-0.06 (-0.70, 0.58)	0.84	NA
Relaxation	Inert treatment	1	0.52 (-0.21, 1.25)	0.16	NA
At short-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
Acupuncture	Inert treatment	1	0.25 (-0.26, 0.75)	0.34	NA
CBT	Inert treatment	1	**0.52 (0.06, 0.99)**	**0.03**	NA
CBT	Passive control	1	**0.77 (0.25, 1.30)**	**0.04**	NA
At mid-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	1	0.57 (-0.13, 1.27)	0.11	NA
CBT	Inert treatment	1	0.23 (-0.24, 0.70)	0.34	NA
CBT	Passive control	2	**0.54 (0.16, 0.91)**	**0.01**	3.0
Education	Passive control	1	0.38 (-0.44, 1.20)	0.36	NA

Table S5.9. Pairwise meta-analyses for subjective sleep onset latency

At immediate post-intervention					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	1	0.11 (-0.58, 0.79)	0.76	NA
CBT	Inert treatment	2	0.59 (-0.72, 1.90)	0.38	**86.5**
CBT	Mindful psychotherapy	1	0.51 (-0.06, 1.01)	0.08	NA
CBT	Passive control	3	**0.65 (0.28, 1.03)**	**0.00**	29.3
Education	Passive control	1	0.75 (-0.09, 1.59)	0.08	NA
Exercise	Passive control	1	0.20 (-0.44, 0.84)	0.54	NA
Relaxation	Inert treatment	1	0.60 (-0.14, 1.33)	0.11	NA
At short-term follow-up					

Treatment 1	Treatment 2	N of studies	SMD (95% CI)	P value	I^2 (%)
CBT	Inert treatment	1	0.22 (-0.24, 0.68)	0.35	NA
CBT	Passive control	1	**0.83 (0.30, 1.36)**	**0.00**	NA
At mid-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	1	0.25 (-0.44, 0.93)	0.11	NA
CBT	Inert treatment	1	-0.01 (-0.48, 0.46)	0.34	NA
CBT	Passive control	2	0.45 (-0.42, 1.30)	1.01	**70.4**
Education	Passive control	1	0.90 (0.05, 1.75)	0.36	NA

Table S5.10. Pairwise meta-analyses for subjective total sleep time

At immediate post-intervention					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	1	0.18 (-0.51, 0.86)	0.61	NA
CBT	Inert treatment	2	0.07 (-0.92, 1.06)	0.89	**79.0**
CBT	Mindful psychotherapy	1	-0.10 (-0.65, 0.45)	0.73	NA
CBT	Passive control	4	0.03 (-0.25, 0.31)	0.82	0.0
Education	Passive control	1	-0.09 (-0.90, 0.72)	0.83	NA
Exercise	Passive control	1	0.13 (-0.51, 0.77)	0.69	NA
Relaxation	Inert treatment	1	-0.13 (-0.85,0.59)	0.72	NA
At short-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Inert treatment	1	0.15 (-0.31, 0.61)	0.53	NA
CBT	Passive control	1	0.29 (-0.22, 0.80)	0.26	NA
At mid-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	1	0.29 (-0.40, 0.98)	0.41	NA
CBT	Inert treatment	1	0.07 (-0.40, 0.54)	0.76	NA
CBT	Passive control	2	0.35 (-0.01, 0.70)	0.06	0.0
Education	Passive control	1	0.15 (-0.66, 0.95)	0.73	NA

Table S5.11. Pairwise meta-analyses for subjective wake time after sleep onset

At immediate post-intervention					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	1	0.55 (-0.15, 1.24)	0.12	NA
CBT	Inert treatment	2	0.54 (-0.12, 1.20)	0.11	**53.4**
CBT	Mindful psychotherapy	1	**0.59 (0.02, 1.15)**	**0.04**	NA
CBT	Passive control	3	**0.48 (0.18, 0.77)**	**0.00**	0.0
Education	Passive control	1	0.02 (-0.78, 0.83)	0.95	NA
Exercise	Passive control	1	0.30 (-0.34, 0.94)	0.36	NA
Relaxation	Inert treatment	1	0.23 (-0.49,0.95)	0.53	NA
At short-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Inert treatment	1	0.42 (-0.05, 0.88)	0.08	NA
CBT	Passive control	1	**0.55 (0.03, 1.07)**	**0.04**	NA
At mid-term follow-up					

Treatment 1	Treatment 2	N of studies	SMD (95% CI)	P value	I^2 (%)
CBT	Education	1	0.54 (-0.16, 1.24)	0.13	NA
CBT	Inert treatment	1	0.08 (-0.39, 0.55)	0.73	NA
CBT	Passive control	2	**0.59 (0.23, 0.95)**	**0.00**	0.0
Education	Passive control	1	-0.09 (-0.90, 0.72)	0.83	NA

Table S5.12. Pairwise meta-analyses for pain

At immediate post-intervention					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
Acupuncture	Inert treatment	3	**0.89 (0.43, 1.36)**	**0.00**	**52.9**
Acupuncture	Passive control	1	**0.54 (0.02, 1.05)**	**0.04**	NA
Assistive technique	Inert treatment	1	0.47 (-0.33, 1.27)	0.25	NA
Assistive technique	Passive control	1	**0.43 (0.04, 0.81)**	**0.03**	NA
CBT	Education	7	**0.15 (0.02, 0.29)**	**0.03**	0.0
CBT	Exercise	1	0.04 (-0.58, 0.66)	0.90	NA
CBT	Inert treatment	2	-0.15 (-0.77, 0.47)	0.42	0.0
CBT	Mindful psychotherapy	2	-0.15 (-0.77, 0.47)	0.63	**90.3**
CBT	Passive control	12	**0.41 (0.25, 0.57)**	**0.00**	27.2
Education	Passive control	2	**0.81 (0.27, 1.34)**	**0.00**	0.0
Exercise	Education	3	0.38 (-0.17, 0.93)	0.18	**56.4**
Exercise	Inert treatment	1	**0.42 (0.07, 0.76)**	**0.02**	NA
Exercise	Mindful psychotherapy	2	**0.38 (0.07, 0.69)**	**0.02**	4.6
Exercise	Physical agents	3	0.33 (-0.10, 0.75)	0.13	42.5
Exercise	Passive control	5	**0.61 (0.10, 1.12)**	**0.02**	**63.6**
Inert treatment	Passive control	2	0.28 (-0.11, 0.68)	0.16	53.2
Manual therapy	Inert treatment	1	**1.27 (0.37, 2.17)**	**0.01**	NA
Manual therapy	Relaxation	2	-0.04 (-0.58, 0.49)	0.88	0.0
Manual therapy	Passive control	4	**0.68 (0.10, 1.18)**	**0.05**	**84.1**
Mind-body exercise	Manual therapy	1	**1.31 (0.58, 2.05)**	**0.00**	NA
Mind-body exercise	Education	4	**0.65 (0.27, 1.04)**	**0.00**	48.0
Mind-body exercise	Exercise	7	**0.34 (0.14, 0.53)**	**0.00**	31.0
Mind-body exercise	Inert treatment	2	**1.44 (0.64, 2.24)**	**0.00**	0.0
Mind-body exercise	Passive control	7	**0.81 (0.49, 1.12)**	**0.00**	46.1
Mindful psychotherapy	Inert treatment	1	-0.04 (-0.39, 0.31)	0.82	NA
Mindful psychotherapy	Relaxation	1	0.30 (-0.54, 1.15)	0.48	NA
Mindful psychotherapy	Passive control	4	**0.33 (0.22, 0.57)**	**0.00**	0.0
Non-invasive brain stimulation	Inert treatment	11	**0.64 (0.35, 0.94)**	**0.00**	**56.1**
Nutritional therapy	Education	1	**1.2 (0.57, 1.83)**	**0.00**	NA
Nutritional therapy	Inert treatment	3	0.44 (-0.28, 1.15)	0.23	**79.6**
Physical agents	Inert treatment	6	**0.64 (0.12, 1.17)**	**0.02**	**73.9**
Physical agents	Passive control	1	**0.62 (0.21, 1.04)**	**0.00**	NA
Relaxation	Education	1	**0.65 (0.14, 1.18)**	**0.01**	NA
Relaxation	Inert treatment	3	0.02 (-0.41, 0.44)	0.95	38.8
Relaxation	Passive control	1	0.35 (-0.09, 0.70)	0.06	NA
At short-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
Acupuncture	Inert treatment	1	**1.12 (0.58, 1.67)**	**0.00**	NA
CBT	Education	2	0.25 (-0.55, 1.05)	0.54	**82.7**
CBT	Inert treatment	2	0.21 (-0.12, 0.54)	0.21	0.0
CBT	Passive control	3	**0.36 (0.07, 0.64)**	**0.02**	0.0

Exercise	Physical agents	2	0.37 (-0.57, 1.31)	0.44	**87.7**
Mind-body exercise	Education	1	**0.85 (0.20, 1.50)**	**0.01**	NA
Mind-body exercise	Exercise	3	0.08 (-0.57, 0.12)	0.66	**60.3**
Mind-body exercise	Passive control	1	**0.54 (0.14, 0.94)**	**0.01**	NA
Mindful psychotherapy	Passive control	2	0.12 (-0.18, 0.42)	0.45	14.0
Non-invasive brain stimulation	Inert treatment	2	0.43 (-0.17, 1.03)	0.16	0.0
Nutritional therapy	Inert treatment	1	0.05 (-0.40, 0.50)	0.82	NA
Physical agents	Inert treatment	1	0.32 (0.18, 0.47)	0.18	NA
At mid-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	5	0.03 (-0.15, 0.20)	0.74	0.0
CBT	Exercise	1	0.64 (-0.03, 1.27)	0.05	NA
CBT	Inert treatment	1	-0.01 (-0.49, 0.46)	0.96	NA
CBT	Mindful psychotherapy	2	-0.28 (-1.02, 0.46)	0.46	**93.0**
CBT	Passive control	6	0.35 (0.10, 0.60)	0.07	45.3
Education	Passive control	1	0.20 (-0.62, 1.02)	0.63	NA
Exercise	Inert treatment	1	-0.09 (-0.45, 0.27)	0.62	NA
Exercise	Mindful psychotherapy	1	0.21 (-0.15, 0.57)	0.26	NA
Exercise	Physical agents	1	**0.92 (0.54, 1.31)**	**0.00**	NA
Exercise	Passive control	1	0.23 (-0.39, 0.86)	0.46	NA
Mind-body exercise	Education	1	0.59 (-0.05, 1.22)	0.07	NA
Mind-body exercise	Exercise	2	0.09 (-0.42, 0.60)	0.72	**81.0**
Mind-body exercise	Passive control	1	**0.50 (0.10, 0.90)**	**0.01**	NA
Mindful psychotherapy	Inert treatment	1	-0.29 (-0.67, 0.09)	0.13	NA
Mindful psychotherapy	Passive control	1	**0.34 (0.10, 0.58)**	**0.01**	NA
Non-invasive brain stimulation	Inert treatment	1	0.18 (-0.29, 0.64)	0.46	NA
Physical agents	Inert treatment	1	-0.06 (-0.46, 0.34)	0.77	NA
At long-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	1	0.06 (-0.18, 0.29)	0.62	NA
CBT	Exercise	1	0.37 (-0.25, 0.99)	0.24	NA
Exercise	Inert treatment	1	-0.01 (-0.38, 0.36)	0.96	NA
Exercise	Mindful psychotherapy	2	0.18 (-0.14, 0.49)	0.28	0.0
Exercise	Passive control	2	0.35 (-0.11, 0.80)	0.14	0.0
Mind-body exercise	Exercise	1	-0.10 (-0.50, 0.30)	0.63	NA
Mindful psychotherapy	Inert treatment	1	-0.21 (-0.58, 0.17)	0.28	NA
Mindful psychotherapy	Passive control	1	0.30 (-0.37, 0.92)	0.35	NA

Table S5.13. Pairwise meta-analyses for disability at immediate post-intervention

At immediate post-intervention					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
Acupuncture	Passive control	1	0.34 (-0.17, 0.85)	0.19	NA
Assistive technique	Inert treatment	1	0.37 (-0.42, 1.17)	0.36	NA
Assistive technique	Passive control	1	0.04 (-0.34, 0.42)	0.85	NA
CBT	Education	4	0.29 (-0.12, 0.70)	0.17	**59.2**
CBT	Exercise	1	-0.26 (-0.89, 0.36)	0.41	NA
CBT	Inert treatment	1	0.73 (-0.09, 1.55)	0.08	NA
CBT	Mindful psychotherapy	3	-0.12 (-0.68, 0.43)	0.68	**87.5**
CBT	Passive control	10	**0.57 (0.20, 0.95)**	**0.00**	**84.7**
Education	Passive control	1	-0.12 (-0.78, 0.55)	0.73	NA

Exercise	Education	3	0.25 (-0.85, 1.36)	0.65	**88.4**
Exercise	Physical agents	3	**0.45 (0.16, 0.74)**	**0.00**	0.5
Exercise	Passive control	3	0.64 (-0.34, 1.65)	0.21	**85.7**
Inert treatment	Passive control	2	0.17 (-0.10, 0.43)	0.22	0.0
Manual therapy	Passive control	3	**0.57 (0.26, 0.87)**	**0.00**	0.0
Mind-body exercise	Manual therapy	1	0.70 (0.01, 1.38)	0.05	NA
Mind-body exercise	Education	4	**0.87 (0.34, 1.40)**	**0.00**	**70.6**
Mind-body exercise	Exercise	6	**0.25 (0.09, 0.42)**	**0.00**	0.0
Mind-body exercise	Inert treatment	2	1.09 (-0.06, 2.25)	0.06	48.4
Mind-body exercise	Passive control	5	**0.87 (0.61, 1.12)**	**0.00**	0.0
Mindful psychotherapy	Relaxation	1	0.43 (-0.42, 1.27)	0.33	NA
Mindful psychotherapy	Passive control	3	**0.29 (0.11, 0.47)**	**0.00**	0.0
Non-invasive brain stimulation	Inert treatment	8	**0.62 (0.36, 0.88)**	**0.00**	24.2
Nutritional therapy	Education	1	**1.03 (0.41, 1.65)**	**0.00**	NA
Nutritional therapy	Inert treatment	3	-0.02 (-0.48, 0.44)	0.94	**54.0**
Physical agents	Inert treatment	3	0.34 (-0.21, 0.88)	0.23	**61.2**
Physical agents	Passive control	1	0.17 (-0.24, 0.58)	0.41	NA
Relaxation	Education	1	**0.65 (0.13, 1.17)**	**0.01**	NA
Relaxation	Inert treatment	1	-0.09 (-0.44, 0.25)	0.59	NA
Relaxation	Passive control	1	-0.06 (-0.36, 0.35)	0.98	NA
At short-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	2	**0.56 (0.25, 0.87)**	**0.00**	0.0
CBT	Inert treatment	1	0.33 (-0.15, 0.81)	0.18	NA
CBT	Passive control	2	1.76 (-0.93, 4.44)	0.20	**97.3**
Exercise	Physical agents	2	**0.36 (0.05, 0.67)**	**0.02**	0.0
Mind-body exercise	Education	1	**1.12 (0.45, 1.79)**	**0.00**	NA
Mind-body exercise	Exercise	3	0.13 (-0.21, 0.47)	0.46	**54.8**
Mind-body exercise	Passive control	1	**0.65 (0.24, 1.05)**	**0.00**	NA
Mindful psychotherapy	Passive control	2	0.14 (-0.14, 0.41)	0.33	0.0
Non-invasive brain stimulation	Inert treatment	2	0.05 (-1.32, 1.42)	0.94	**85.8**
Nutritional therapy	Inert treatment	1	-0.18 (-0.63, 0.27)	0.44	NA
Physical agents	Inert treatment	1	-0.01 (0.66, 0.64)	0.97	NA
At mid-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Education	3	0.04 (-0.43, 0.52)	0.86	**57.4**
CBT	Exercise	1	0.04 (-0.58, 0.66)	0.90	NA
CBT	Mindful psychotherapy	2	-0.33 (-1.23, 0.55)	0.46	**95.1**
CBT	Passive control	5	0.93 (0.02, 1.84)	0.05	**95.2**
Exercise	Physical agents	1	**0.63 (0.25, 1.01)**	**0.00**	NA
Mind-body exercise	Education	1	**0.80 (0.15, 1.44)**	**0.02**	NA
Mind-body exercise	Exercise	2	-0.01 (-0.37, 0.35)	0.95	**61.5**
Mind-body exercise	Passive control	1	**0.58 (0.18, 0.99)**	**0.00**	NA
Mindful psychotherapy	Passive control	1	0.21 (-0.03, 0.45)	0.08	NA
Non-invasive brain stimulation	Inert treatment	1	0.22 (-0.48, 0.91)	0.54	NA
Physical agents	Inert treatment	1	-0.13 (-0.54, 0.27)	0.52	NA
At long-term follow-up					
Treatment 1	**Treatment 2**	**N of studies**	**SMD (95% CI)**	**P value**	**I^2 (%)**
CBT	Exercise	1	-0.01 (-0.63, 0.61)	0.98	NA
Mind-body exercise	Exercise	1	-0.13 (-0.53, 0.27)	0.52	NA

Table S5.14. Pairwise meta-analyses for acceptability

Treatment 1	Treatment 2	N of studies	OR (95% CI)	P value	I^2 (%)
Acupuncture	Inert treatment	2	1.05 (0.42, 2.67)	0.91	0.0
Acupuncture	Passive control	1	5.75 (0.70, 47.35)	0.10	NA
Assistive technique	Inert treatment	1	1.31 (0.19, 9.02)	0.78	NA
Assistive technique	Passive control	1	0.98 (0.33, 2.97)	0.98	NA
CBT	Education	7	1.40 (0.86, 2.27)	0.18	0.0
CBT	Exercise	1	1.99 (0.21, 3.78)	0.87	NA
CBT	Inert treatment	2	1.52 (0.28, 8.11)	0.63	**51.2**
CBT	Mindful psychotherapy	3	0.83 (0.59, 1.16)	0.27	0.0
CBT	Passive control	13	1.27 (0.96 1.68)	0.09	0.0
Education	Passive control	2	0.50 (0.11, 2.28)	0.37	0.0
Exercise	Education	1	9.97(0.53, 186.19)	0.12	NA
Exercise	Inert treatment	1	0.64 (0.36, 1.14)	0.13	NA
Exercise	Mindful psychotherapy	2	0.72 (0.42, 1.24)	0.23	0.0
Exercise	Physical agents	2	1.39 (0.31, 6.30)	0.67	26.6
Exercise	Relaxation	1	0.74 (0.31, 1.75)	0.49	NA
Exercise	Passive control	3	1.09 (0.43, 2.76)	0.86	0.0
Inert treatment	Passive control	2	0.55 (0.09, 3.25)	0.51	74.5
Manual therapy	Inert treatment	1	0.20 (0.02, 1.92)	0.16	NA
Manual therapy	Passive control	3	0.74 (0.16, 3.38)	0.70	44.5
Mind-body exercise	Education	3	0.46 (0.14, 1.51)	0.20	0.0
Mind-body exercise	Exercise	7	0.94 (0.62, 1.46)	0.78	0.0
Mind-body exercise	Inert treatment	2	1.06 (0.24, 4.67)	0.94	0.0
Mind-body exercise	Passive control	7	0.84 (0.38, 2.53)	0.76	29.9
Mind-body exercise	Manual therapy	1	6.29 (0.70, 56.72)	0.10	NA
Mindful psychotherapy	Inert treatment	1	0.91 (0.53, 1.55)	0.72	NA
Mindful psychotherapy	Passive control	5	1.41 (0.96, 2.07)	0.08	2.5
Non-invasive brain stimulation	Inert treatment	9	0.91 (0.54, 1.51)	0.71	0.0
Nutritional therapy	Inert treatment	3	1.11 (0.26, 4.76)	0.89	0.0
Physical agents	Inert treatment	2	1.07 (0.41, 2.82)	0.89	0.0
Physical agents	Passive control	1	1.37 (0.41, 4.63)	0.61	NA
Relaxation	Education	1	3.67 (0.45, 30.21)	0.23	NA
Relaxation	Inert treatment	3	0.98 (0.34, 2.83)	0.97	0.0
Relaxation	Passive control	2	0.76 (0.04, 15.38)	0.86	**70.6**

Table S5.15. Pairwise meta-analyses for safety

Treatment 1	Treatment 2	N of studies	OR (95% CI)	P value	I^2 (%)
Acupuncture	Inert treatment	1	1.16 (0.32, 4.22)	0.42	NA
Acupuncture	Passive control	1	6.31 (0.32, 122.93)	0.20	NA
CBT	Education	1	1.44 (0.84, 2.48)	0.18	NA
CBT	Passive control	2	4.39 (0.62, 31.06)	0.15	48.3
Exercise	Education	1	9.80 (0.44, 219.25)	0.17	NA
Exercise	Physical agents	1	0.47 (0.08, 2.69)	0.21	NA
Inert treatment	Passive control	1	2.94 (0.17, 73.95)	0.49	NA
Manual therapy	Passive control	1	1.10 (0.07, 18.37)	0.47	NA
Mind-body exercise	Exercise	4	1.08 (0.55, 2.12)	0.84	0.0
Mind-body exercise	Passive control	3	3.53 (0.32, 38.45)	0.30	43.6
Non-invasive brain stimulation	Inert treatment	7	1.15 (0.65, 2.05)	0.63	0.0
Physical agents	Inert treatment	1	8.23 (0.97, 69.72)	0.06	NA
Physical agents	Passive control	1	17.22 (0.95, 310.98)	0.08	NA

Abbreviations: CBT: Cognitive Behavioral Therapy, CI: Confidence Interval, N: Number, OR: Odd Ratio, SMD: Standardized Mean Difference.
Footnote: Results in bold indicate significance at $p<0.05$ or significant heterogeneity of I^2.

Appendix 20. Assessment of transitivity in Chapter 7

Table S5.16. General characteristics of interventions nodes

Nodes	N of arms (%)	N of participants (%)	Mean age (SD)	Mean percentage of female (SD)	Mean baseline pain severity* (SD)	Mean baseline sleep severity* (SD)	Mean treatment length (SD)
Acupuncture	4 (1.8)	139 (1.7)	58.7 (14.6)	69.9 (15.0)	50.3 (6.3)	47.4 (10.1)	5.3 (2.2)
Assistive technique	2 (0.9)	77 (0.9)	48.0 (4.6)	98.2 (2.6)	37.4 (17.8)	39.1 (28.2)	14.0 (2.8)
CBT	27 (12.2)	1,625 (20.0)	52.4 (8.4)	82.7 (17.7)	54.5 (12.8)	58.0 (12.9)	7.9 (2.5)
Education	18 (8.1)	761 (9.4)	54.9 (8.5)	88.9 (17.0)	55.4 (15.7)	53.6 (13.4)	9.5 (4.9)
Exercise	22 (9.9)	839 (10.3)	50.5 (6.6)	85.2 (19.2)	58.7 (15.0)	54.0 (13.7)	12.0 (5.9)
Manual therapy	8 (3.6)	194 (2.4)	46.8 (6.0)	79.5 (23.3)	64.3 (9.7)	46.3 (20.8)	5.4 (2.0)
Mind-body exercise	21 (9.5)	713 (8.8)	51.8 (7.8)	94.8 (8.7)	61.0 (13.6)	52.3 (14.0)	11.4 (5.9)
Mindful psychotherapy	10 (4.5)	527 (6.5)	53.2 (6.5)	88.1 (13.7)	53.1 (16.2)	54.2 (10.7)	8.2 (1.4)
Non-invasive brain stimulation	12 (5.4)	336 (4.1)	51.4 (7.4)	95.5 (9.9)	63.6 (13.5)	61.2 (12.5)	5.9 (4.5)
Nutritional therapy	4 (1.8)	139 (1.7)	49.9 (9.8)	82.3 (30.6)	58.9 (12.3)	53.1(17.1)	7.8 (5.9)
Physical agents	9 (4.1)	224 (2.8)	49.5 (8.8)	78.0 (30.1)	63.2 (15.4)	58.6 (21.8)	5.1 (4.1)
Relaxation	10 (4.5)	337 (4.1)	47.9 (9.6)	78.6 (20.6)	49.5 (14.6)	48.5 (19.3)	6.0 (3.7)
Inert treatment	35 (15.8)	887 (10.9)	53.1 (8.6)	89.6 (16.4)	58.7 (14.0)	54.3 (13.2)	5.8 (4.2)
Passive control	40 (18.0)	1,323 (16.3)	51.6 (5.5)	88.6 (16.9)	55.6 (15.8)	54.2 (15.4)	8.6 (4.0)
Range	2 to 40	77 to 1,625	48.0 to 58.7	69.9 to 98.2	37.4 to 64.3	39.1 to 61.2	5.3 to 14.0
Total/Mean	222	8,121	51.8 (7.8)	87.1 (17.7)	57.4 (14.5)	54.1 (14.8)	8.2 (4.8)
Q1			47.5	78.2	47.2	42.4	5.0
Q2			51.0	96.3	57.7	54.7	8.0
Q3			54.6	100.0	69.6	64.9	10.0

Abbreviations: CBT: Cognitive Behavioral Therapy, N: Number, Q1: First Quartile, Q2: Second Quartile, Q3: Third Quartile.
Footnote: *Baseline pain intensity and sleep were converted to standardized scales (0 to 100). Number of studies are unavailable for analysis: age (n=4), gender (n=6), baseline pain (n=9), baseline sleep (n=5), treatment length (n=2).

Table S5.17. General characteristics of pairwise comparisons

Nodes	N of arms (%)	N of participants (%)	Mean age	Mean percentage of female	Mean baseline pain severity*	Mean baseline sleep severity*	Mean treatment length
AM	3 (2.4)	189 (2.3)	63.3	67.2	53.0	49.3	5.0
AN	1 (0.8)	67 (0.8)	49.43	62.28	44.0	40.34	6.0
BM	1 (0.8)	30 (0.4)	49.7	100.0	53.5	60.5	16.0
BN	1 (0.8)	121 (1.5)	44.7	97.2	29.2	20.4	12.0
CD	9 (7.3)	1,123 (13.8)	53.0	87.8	56.7	56.1	7.0
CE	1 (0.8)	40 (0.5)	NI	100.0	70.5	80.0	8.0
CH	4 (3.3)	410 (5.0)	54.4	78.0	46.9	52.1	8.0
CM	3 (2.4)	211 (2.6)	52.4	87.4	51.5	57.7	5.5
CN	14 (11.4)	1,095 (13.5)	50.7	80.6	54.3	54.2	8.9
DE	3 (2.4)	146 (1.8)	57.1	87.9	46.2	47.6	10.3
DG	4 (3.3)	231 (2.8)	58.8	97.6	55.2	47.5	16.0
DJ	1 (0.8)	61 (0.7)	58.0	100.0	76.5	71.6	3.0
DL	1 (0.8)	80 (1.0)	45.4	82.5	47.8	63.3	8.0
DN	2 (1.6)	35 (0.4)	46.2	98.5	41.0	41.9	8.0
EG	7 (5.7)	691 (8.5)	49.6	86.1	65.6	54.2	13.6
EH	2 (1.6)	120 (1.5)	48.9	90.0	65.3	55.5	10.0
EK	3 (2.4)	211 (2.6)	41.2	46.1	55.4	49.3	9.3
EL	1 (0.8)	130 (1.6)	51.5	100.0	NI	51.7	15.0
EM	1 (0.8)	100 (1.2)	54.2	NI	58.7	47.5	8.0
EN	6 (4.9)	236 (2.9)	51.7	95.6	54.6	55.6	13.3
FG	1 (0.8)	43 (0.5)	37.0	100.0	76.9	32.8	4.0
FL	2 (1.6)	54 (0.7)	40.6	50.4	49.0	34.8	5.0
FM	1 (0.8)	30 (0.4)	53.0	100.0	49.8	52.3	4.0
FN	4 (3.3)	267 (3.3)	49.7	82.1	73.9	56.3	6.3
GM	2 (1.6)	42 (0.5)	53.0	100.0	58.3	56.7	8.0
GN	7 (5.7)	353 (4.3)	62.5	97.8	55.4	54.6	8.4
HL	1 (0.8)	22 (0.3)	58.5	68.2	54.1	42.5	8.0
HM	1 (0.8)	100 (1.2)	54.2	NI	58.5	48.0	8.0
HN	6 (4.9)	426 (5.2)	50.7	89.3	55.6	52.1	8.5
IM	12 (9.8)	576 (7.1)	51.4	95.3	62.8	59.5	5.9
JM	3 (2.4)	188 (2.3)	46.6	77.1	53.9	47.9	9.3
KM	6 (4.9)	225 (2.8)	54.3	88.5	67.2	59.4	2.9
KN	1 (0.8)	46 (0.6)	55.6	98.9	55.0	50.2	2.5
LM	3 (2.4)	141 (1.7)	50.9	90.6	47.9	40.8	3.7
LN	3 (2.4)	186 (2.3)	48.5	85.2	70.7	64.4	4.0
MN	2 (1.6)	109 (1.3)	53.1	96.2	63.3	52.0	3.3
Range	1 to 14	22 to 1,123	37 to 63.3	46.1 to 100.0	29.2 to 76.9	20.4 to 80	2.5 to 16
Total/Mean	123	8,121	52.1	87.3	53.4	53.5	8.1
Q1			47.6	79.2	47.6	42.3	5.0
Q2			50.7	96.0	57.4	52.9	8.0
Q3			54.2	100.0	69.3	64.0	10.0

Abbreviations: A: Acupuncture, B: Assistive Technique, C: Cognitive Behavioral Therapy, D: Education, E: Exercise, F: Manual Therapy, G: Mind-body Exercise, H: Mindful Psychotherapy, I: Non-invasive Brain Stimulation, J: Nutritional Therapy, K: Physical Agents, L: Relaxation, M: Inert Treatment, N: Passive control, N: Number, NI: No Information, Q1: First Quartile, Q2: Second Quartile, Q3: Third Quartile.

Footnote: *Baseline pain intensity and sleep were converted to standardized scales (0 to 100). Number of studies are unavailable for analysis: age (n=4), gender (n=6), baseline pain (n=9), baseline sleep (n=5), treatment length (n=2).

Appendix 21. Assessment of heterogeneity in Chapter 7

The heterogeneity of entire NMA models was estimated by a common heterogeneity variance (τ^2), which was compared with empirical distributions by Rhodes et al. (2015) [442] for continuous and Turner et al (2015) [443]. for dichotomous data. Heterogeneity was quantified as low (from 0.01 to 0.025), moderate (>0.025 to 1.0), and high (>1.0) [613].

Table S5.18. Continuous outcomes from Rhodes et al (2015)

Outcome	**Time points**	**Heterogeneity variance (tau^2)**	**Outcome types used as comparator**	**Predictive distribution of tau^2 Median (95% range)**	**Judgement on heterogeneity**
Sleep quality	Immediate post-intervention	0.2274	Mental health outcome	0.058 (0.001, 2.58)	Moderate
	Short-term	0.446	Mental health outcome	0.058 (0.001, 2.58)	Moderate
	Mid-term	0.344	Mental health outcome	0.058 (0.001, 2.58)	Moderate
	Long-term	0.00	Mental health outcome	0.058 (0.001, 2.58)	Low
Objective sleep efficiency	Immediate post-intervention	0.00	Mental health outcome	0.058 (0.001, 2.58)	Low
Objective sleep onset latency	Immediate post-intervention	0.00	Mental health outcome	0.058 (0.001, 2.58)	Low
Objective total sleep time	Immediate post-intervention	0.00	Mental health outcome	0.058 (0.001, 2.58)	Low
Objective wake time after sleep onset	Immediate post-intervention	0.00	Mental health outcome	0.058 (0.001, 2.58)	Low
Subjective sleep efficiency	Immediate post-intervention	0.0553	Mental health outcome	0.058 (0.001, 2.58)	Moderate
Subjective sleep onset latency	Immediate post-intervention	0.2418	Mental health outcome	0.058 (0.001, 2.58)	Moderate
Subjective total sleep time	Immediate post-intervention	0.0328	Mental health outcome	0.058 (0.001, 2.58)	Moderate
Subjective wake time after sleep onset	Immediate post-intervention	0.0021	Mental health outcome	0.058 (0.001, 2.58)	Low
Pain	Immediate post-intervention	0.0844	Pain and quality of life	0.050 (0.0006, 4.00)	Moderate
	Short-term	0.0595	Pain and quality of life	0.050 (0.0006, 4.00)	Moderate
	Mid-term	0.08	Pain and quality of life	0.050 (0.0006, 4.00)	Moderate
	Long-term	0.00	Pain and quality of life	0.050 (0.0006, 4.00)	Low
Disability	Immediate post-intervention	0.1392	Pain and quality of life	0.050 (0.0006, 4.00)	Moderate
	Short-term	0.3142	Pain and quality of life	0.050 (0.0006, 4.00)	Moderate
	Mid-term	0.4828	Pain and quality of life	0.050 (0.0006, 4.00)	Moderate

Table S5.19. Dichotomous outcomes from Turner et al (2015)

Outcome	Time points	Between study variance (tau)	Outcome types used as comparator	Predictive distribution of tau Median (95% CI)	Judgement on heterogeneity
Acceptability	NA	0.0917	Withdrawals	0.12 (0.08 to 0.16)	Moderate
Safety	NA	0.0	Adverse events	0.15 (0.13, 0.18)	Low

Abbreviations: CI: Confidence Interval, N: Number, NA: Not Available.

Appendix 22. Assessment of inconsistency in Chapter 7

Table S5.20. Estimated global inconsistency in networks

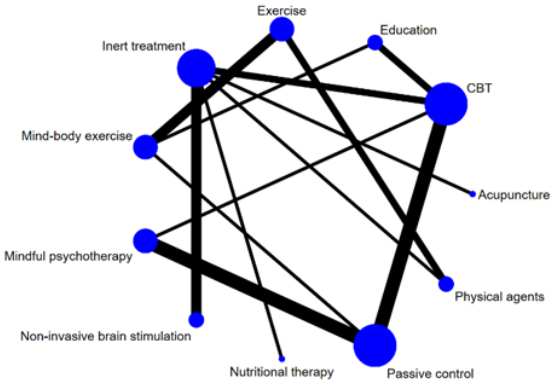
Primary outcomes	**Time-point**	**Chi square**	**Prob > chi2**
Sleep	Immediate post-intervention	Chi2 (29) = 34.19	Prob > chi2 = 0.2363
	Short-term	Chi2 (4) = 1.51	Prob > chi2 = 0.8247
	Mid-term	Chi2 (10) = 2.41	Prob > chi2 = 0.9921
	Long-term	Chi2(2) = 0.03	Prob > chi2 = 0.9865
Acceptability	NA	Chi2 (28) = 28.13	Prob > chi2 = 0.4574
Secondary outcomes			
Objective sleep efficiency	Immediate post-intervention	Chi2 (2) = 0.45	Prob > chi2 = 0.7971
Objective sleep onset latency	Immediate post-intervention	Chi2 (2) = 1.09	Prob > chi2 = 0.5788
Objective total sleep time	Immediate post-intervention	Chi2 (2) = 0.85	Prob > chi2 = 0.6553
Objective wake time after sleep onset	Immediate post-intervention	Chi2 (2) = 0.05	Prob > chi2 = 0.9752
Subjective sleep efficiency	Immediate post-intervention	Chi2 (2) = 0.00	Prob > chi2 = 0.9879
Subjective sleep onset latency	Immediate post-intervention	Chi2 (1) = 0.00	Prob > chi2 = 0.9564
Subjective total sleep time	Immediate post-intervention	Chi2 (1) = 0.01	Prob > chi2 = 0.9380
Subjective wake time after sleep onset	Immediate post-intervention	Chi2 (1) = 0.05	Prob > chi2 = 0.8223
Pain	Immediate post-intervention	Chi2 (27) = 29.79	Prob > chi2 = 0.3235
	Short-term	Chi2 (2) = 0.73	Prob > chi2 = 0.6949
	Mid-term	Chi2 (10) = 13.55	Prob > chi2 = 0.1945
	Long-term	Chi2 (2) = 0.13	Prob > chi2 = 0.9392
Disability	Immediate post-intervention	Chi2 (19) = 12.79	Prob > chi2 = 0.8491
	Short-term	Chi2 (2) = 1.44	Prob > chi2 = 0.4859
	Mid-term	Chi2 (4) = 0.88	Prob > chi2 = 0.9278
Safety	NA	Chi2 (9) = 5.45	Prob > chi2 = 0.7931

Abbreviations: NA: Not Available.

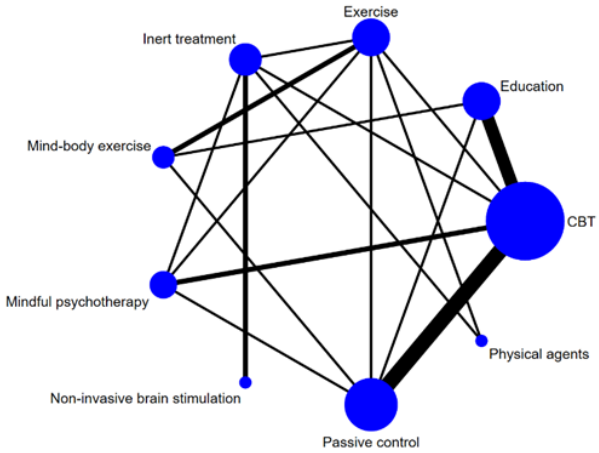
Appendix 23. Network plots in Chapter 7

Figure S5.8. The network plots for sleep quality

a) At short-term follow-up



b) At mid-term follow-up



c) At long-term follow-up

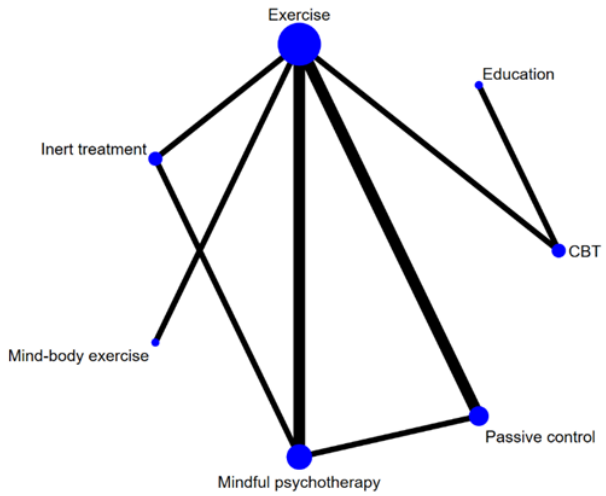


Figure S5.9. The network plot for objective sleep efficiency at immediate post-intervention

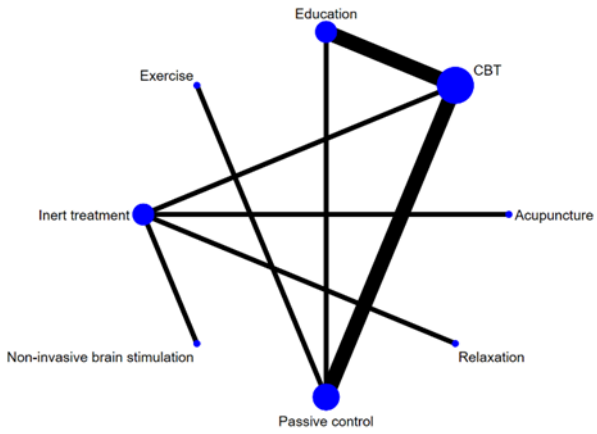


Figure S5.10. The network plot for objective sleep onset latency at immediate post-intervention

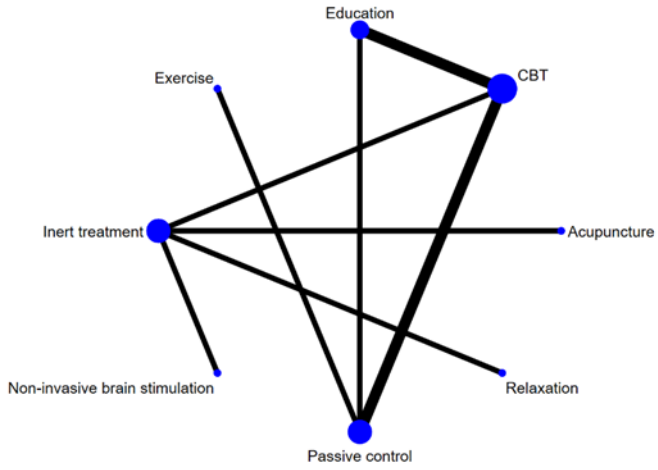


Figure S5.11. The network plot for objective total sleep time at immediate post-intervention

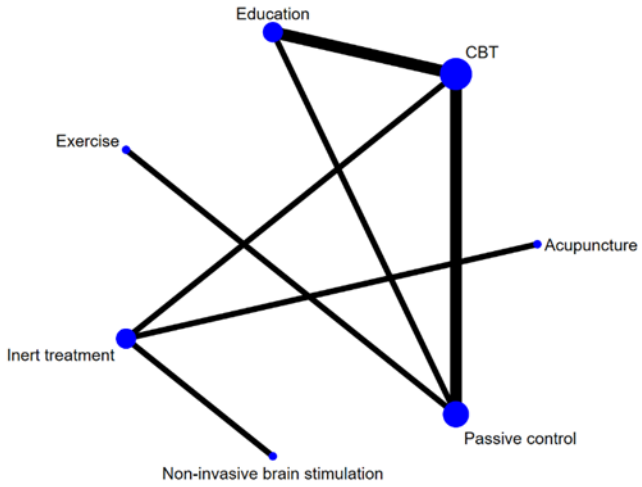


Figure S5.12. The network plot for objective wake time after sleep onset at immediate post-intervention

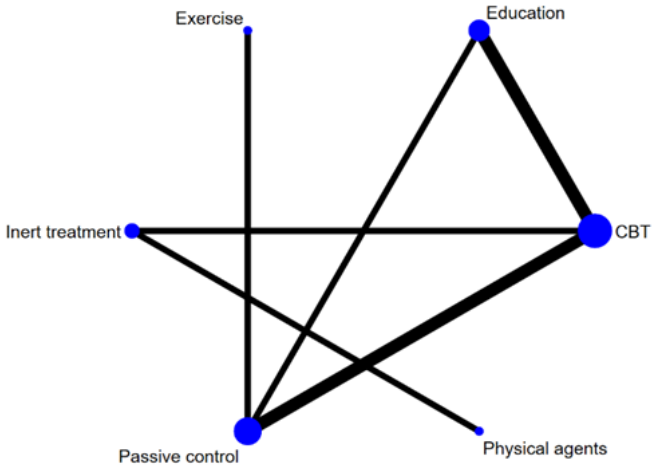


Figure S5.13. The network plot for subjective sleep efficiency at immediate post-intervention

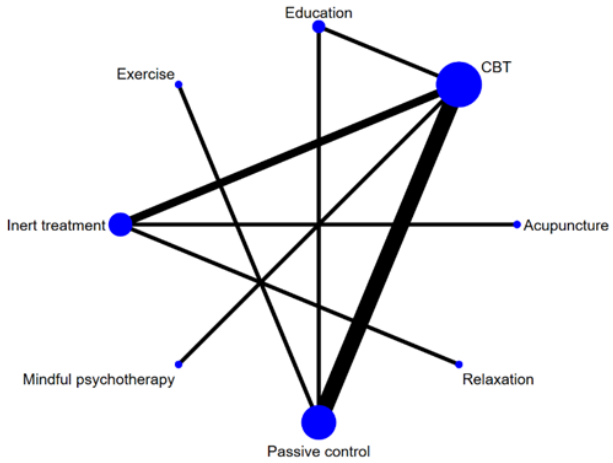


Figure S5.14. The network plot for subjective sleep onset latency at immediate post-intervention

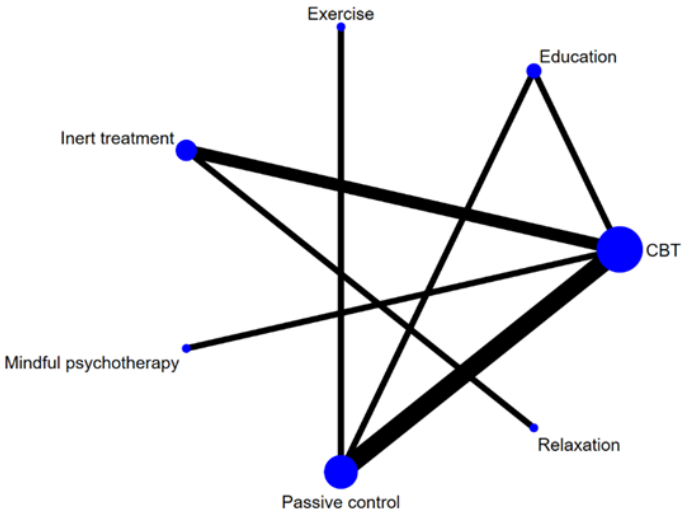


Figure S5.15. The network plot for subjective total sleep time at immediate post-intervention

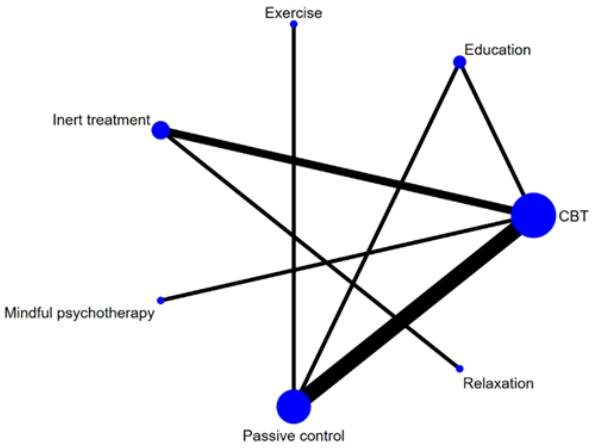


Figure S5.16. The network plot for subjective wake time after sleep onset at immediate post-intervention

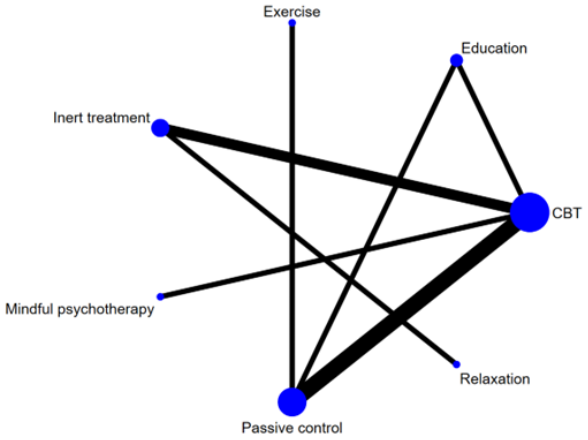
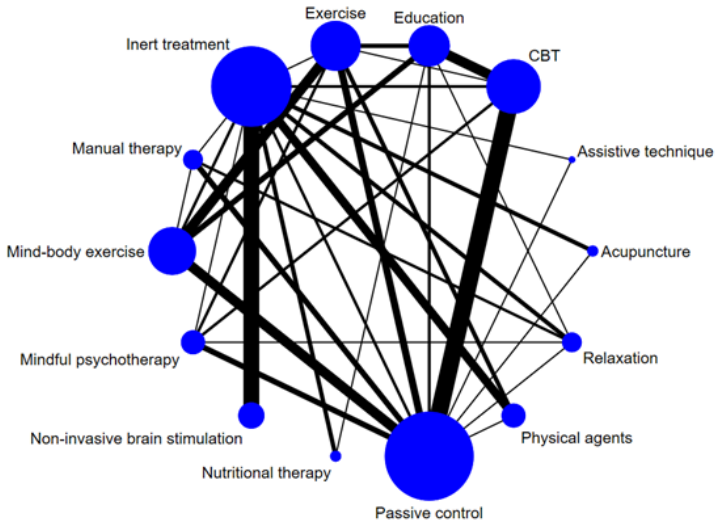
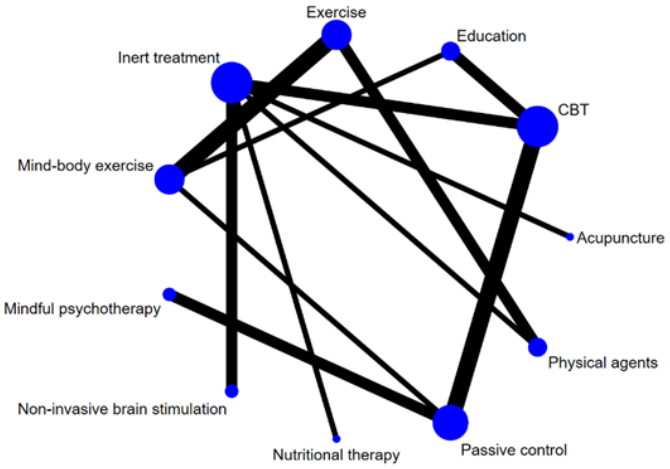


Figure S5.17. The network plots for pain

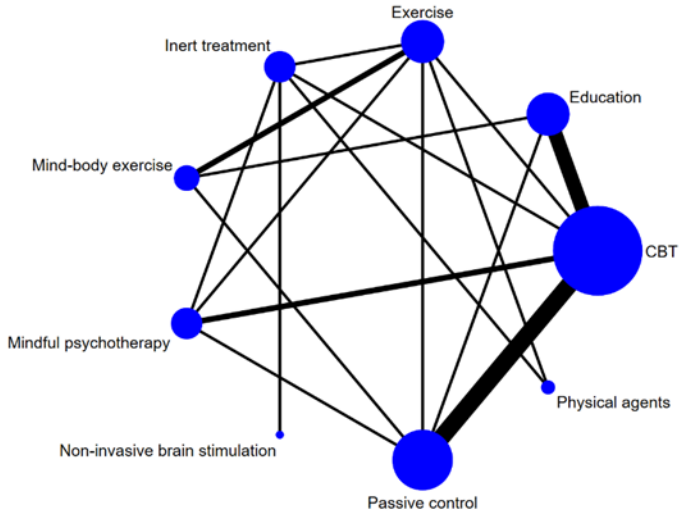
a) At immediate post-intervention



b) At short-term follow-up



c) At mid-term follow-up



d) At long-term follow-up

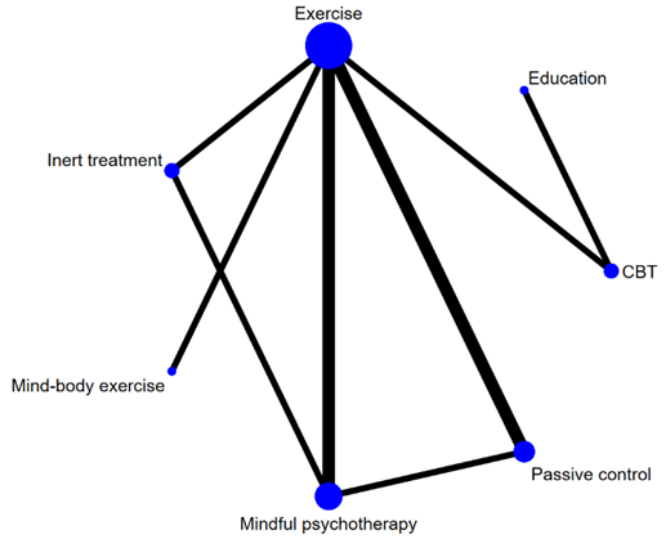
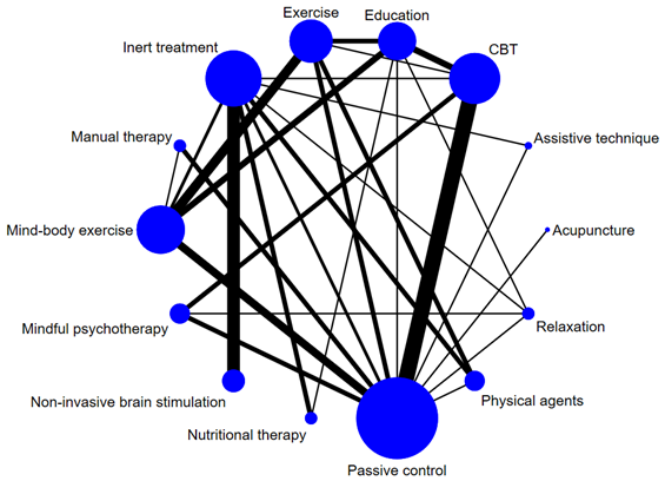
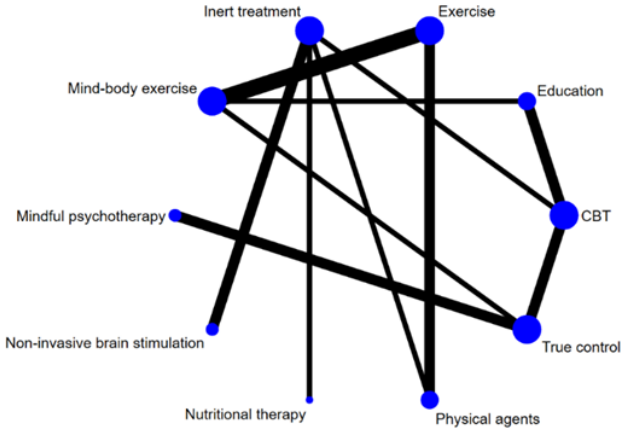


Figure S5.18. The network plots for disability

a) At immediate post-intervention



b) At short-term follow-up



c) At mid-term follow-up

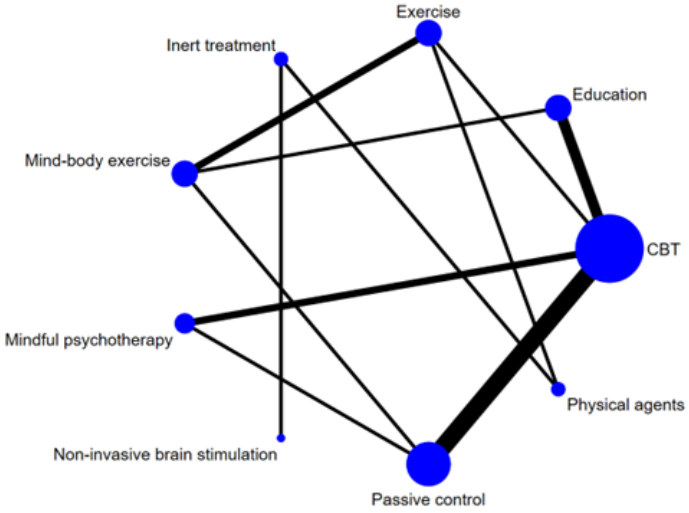


Figure S5.19. The network plot for acceptability

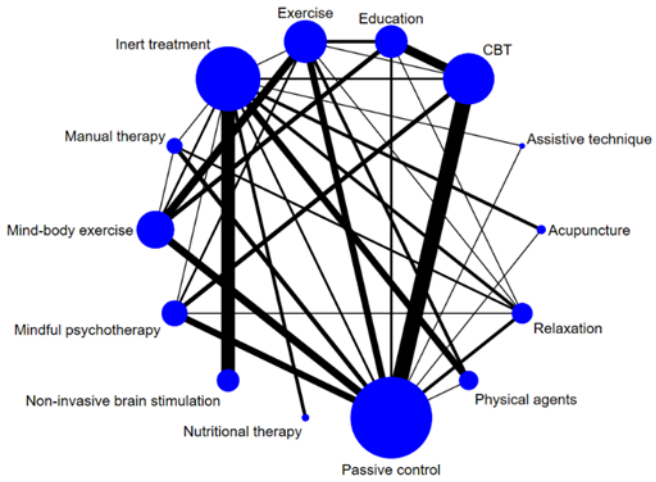
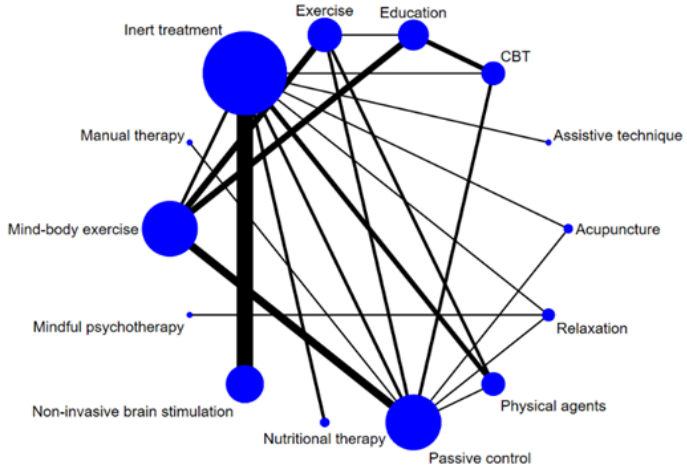


Figure S5.20. The network plot for safety



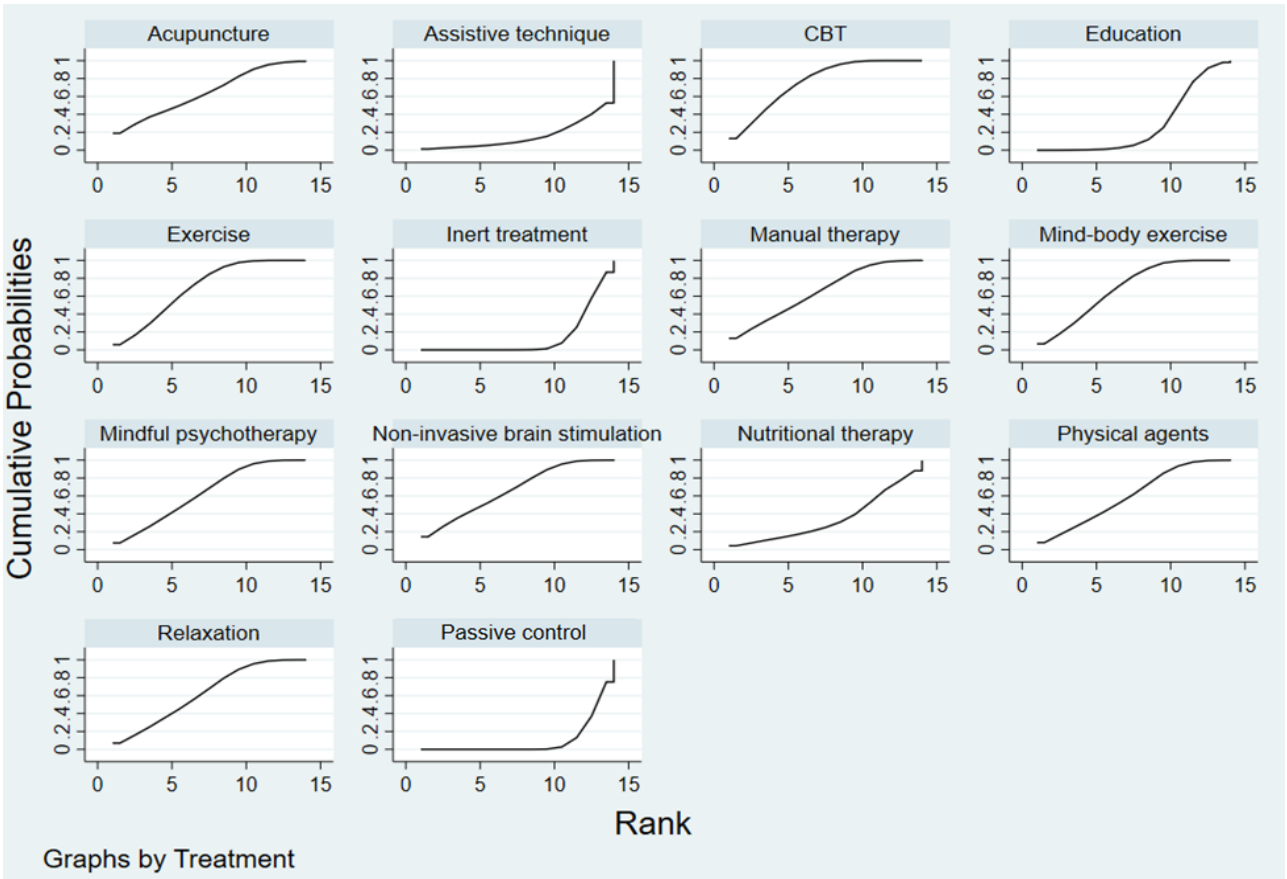
Abbreviations: CBT: Cognitive Behavioral Therapy.
Footnote: The size of the nodes is weighted by the number of participants for that intervention, and the width of the edges is weighted by the number of studies for that comparison.

Appendix 24. Rank results and SUCRA in Chapter 7

Table S5.21. The treatment ranking and SUCRA for sleep quality

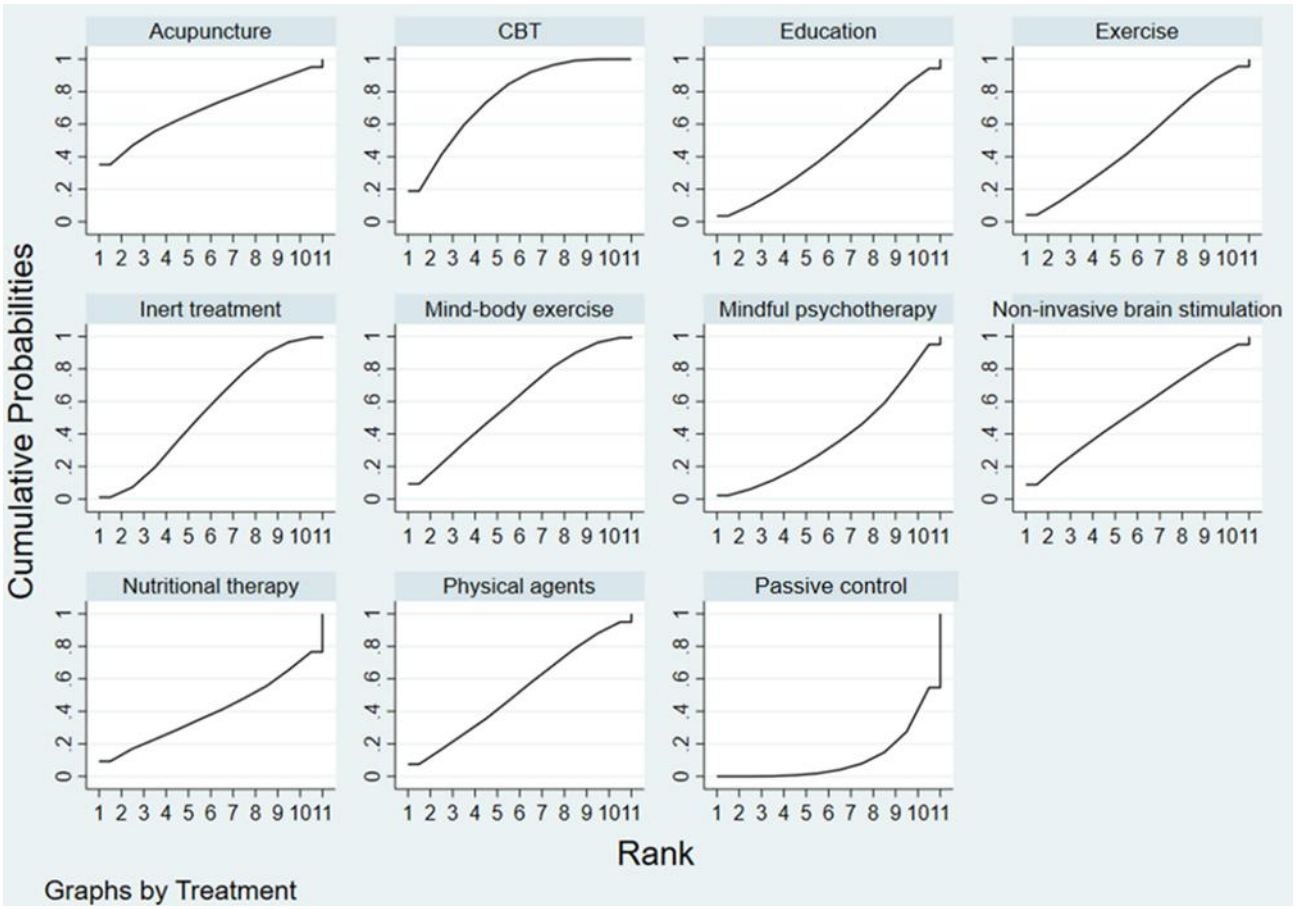
a) At immediate post-intervention

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	CBT	76.5	13.3	4.1
2nd	Exercise	69.2	5.3	5.0
3rd	Mind-body exercise	69.0	6.7	5.0
4th	Non-invasive brain stimulation	66.9	13.9	5.3
5th	Manual therapy	66.2	13.3	5.4
6th	Acupuncture	65.2	20.1	5.5
7th	Mindful psychotherapy	64.0	7.6	5.7
8th	Relaxation	62.9	7.5	5.8
9th	Physical agents	61.2	8.8	6.0
10th	Nutritional therapy	32.3	2.0	9.8
11th	Education	27.6	0.0	10.4
12th	Assistive technique	15.9	1.5	11.9
13th	Inert treatment	13.7	0.0	12.2
14th	Passive control	9.6	0.0	12.8



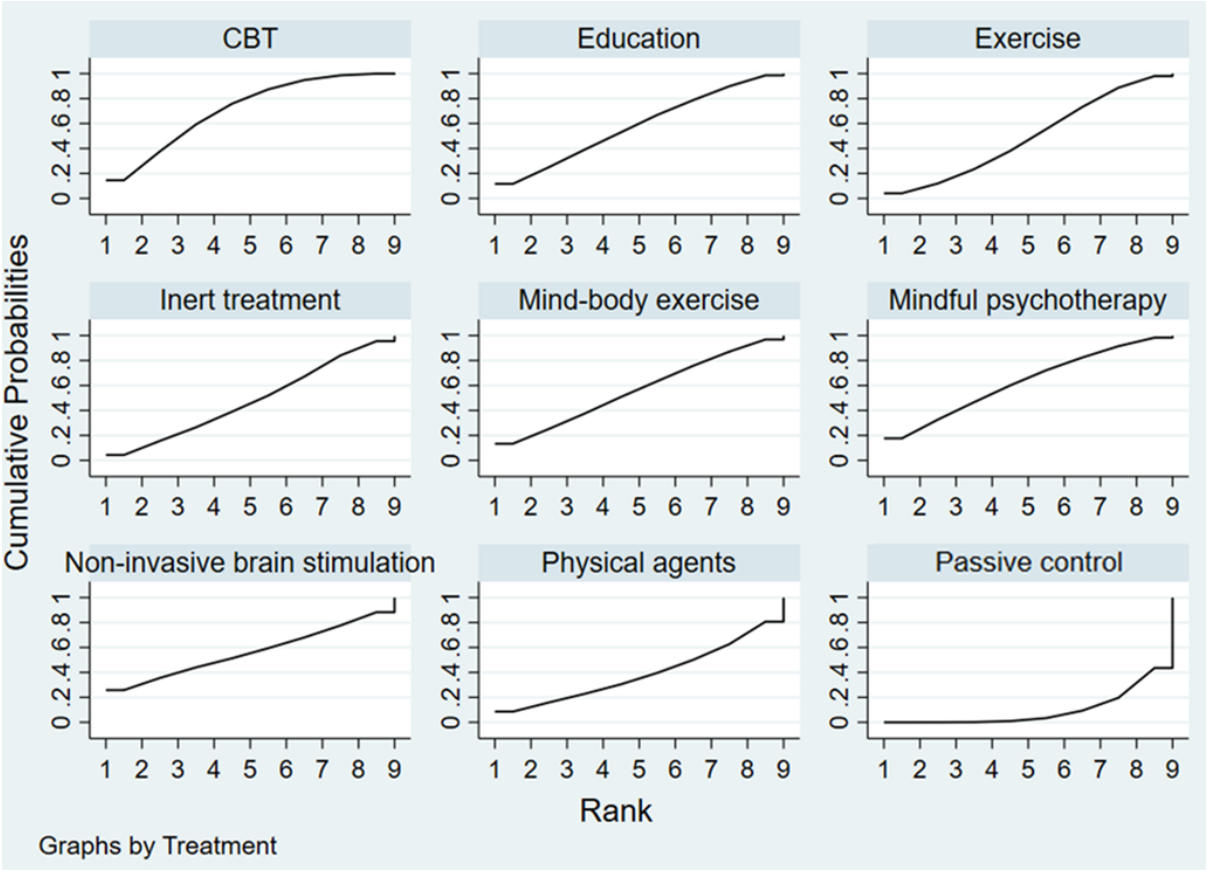
b) At short-term follow-up

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	CBT	76.5	18.9	3.3
2nd	Acupuncture	69.3	35.1	4.1
3rd	Mind-body exercise	60.6	9.3	4.9
4th	Inert treatment	54.3	1.1	5.6
5th	Non-invasive brain stimulation	54.3	8.9	5.6
6th	Physical agents	52.0	7.5	5.8
7th	Exercise	49.1	4.2	6.1
8th	Education	45.0	3.6	6.5
9th	Nutritional therapy	40.0	9.3	7.0
10th	Mindful psychotherapy	37.7	2.2	7.2
11th	Passive control	11.2	0.0	9.9



c) At mid-term follow-up

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	CBT	71.1	14.5	3.3
2nd	Mindful psychotherapy	62.7	17.6	4.0
3rd	Education	57.9	11.7	4.4
4th	Mind-body exercise	56.3	13.4	4.5
5th	Non-invasive brain stimulation	56.3	25.8	4.5
6th	Exercise	49.2	4.1	5.1
7th	Inert treatment	48.0	4.3	5.2
8th	Physical agents	38.9	8.6	5.9
9th	Passive control	9.6	0.0	8.2



d) At long-term follow-up

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Mind-body exercise	71.1	83.6	1.8
2nd	CBT	62.7	0.2	2.8
3rd	Exercise	57.9	0.0	3.0
4th	Passive control	56.3	0.0	4.0
5th	Mindful psychotherapy	56.3	4.1	4.7
6th	Inert treatment	49.2	2.4	5.2
7th	Education	48.0	9.6	5.5

Table S5.22. The treatment ranking and SUCRA for objective sleep efficiency at immediate post-intervention

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Acupuncture	94.2	72.7	1.4
2nd	Exercise	61.5	13.2	3.7
3rd	CBT	59.6	1.0	3.8
4th	Relaxation	59.4	11.1	3.8
5th	Inert treatment	47.7	0.1	4.7
6th	Non-invasive brain stimulation	30.1	1.9	5.9
7th	Education	28.5	0.1	6.0
8th	Passive control	19.1	0.0	6.7

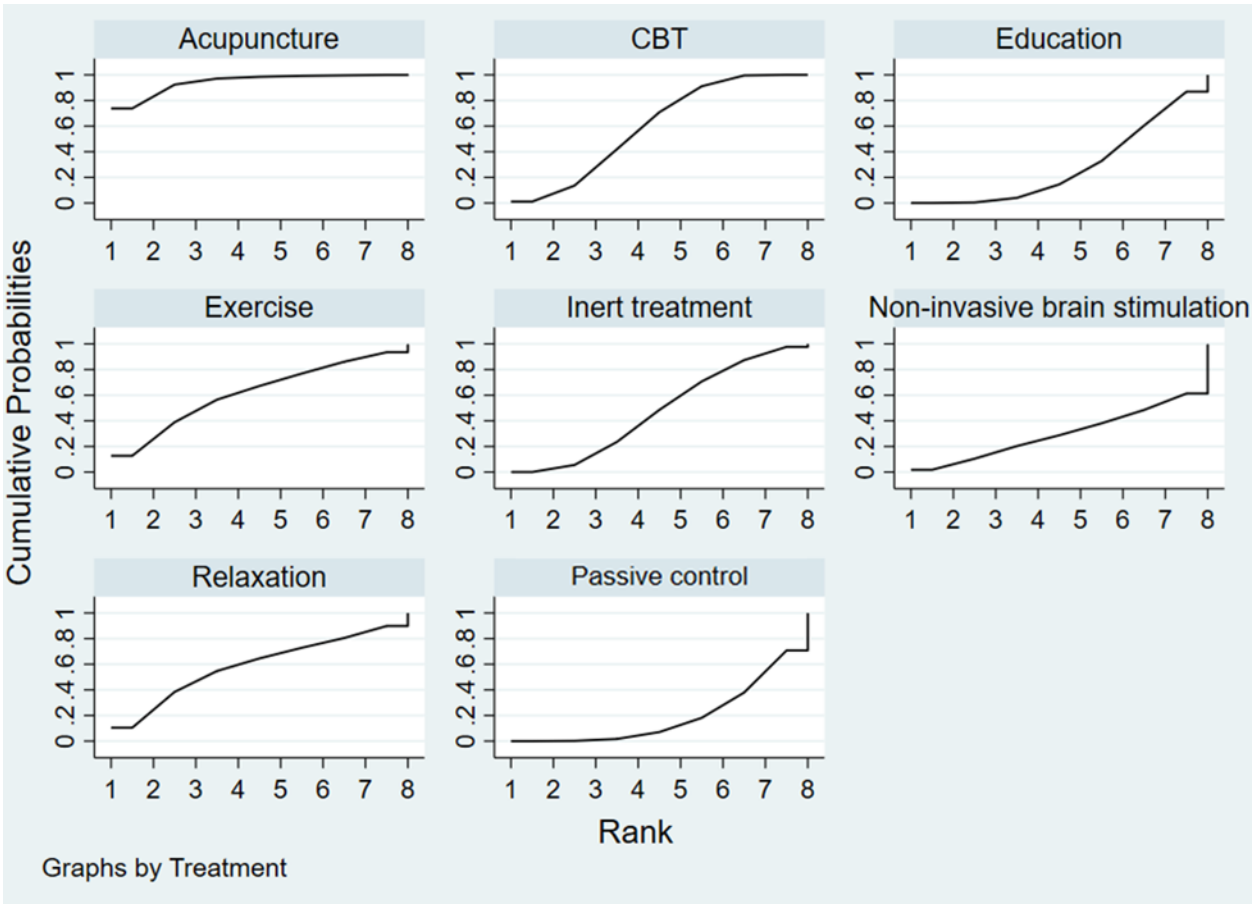


Table S5.23. The treatment ranking and SUCRA for objective sleep onset latency at immediate post-intervention

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Relaxation	99.5	97.3	1.0
2nd	Acupuncture	76.2	2.1	2.7
3rd	Inert treatment	67.4	0.1	3.3
4th	Education	51.4	0.2	4.4
5th	Non-invasive brain stimulation	43.6	0.3	4.9
6th	CBT	38.7	0.0	5.3
7th	Passive control	21.5	0.0	6.5
8th	Exercise	1.7	0.0	7.9

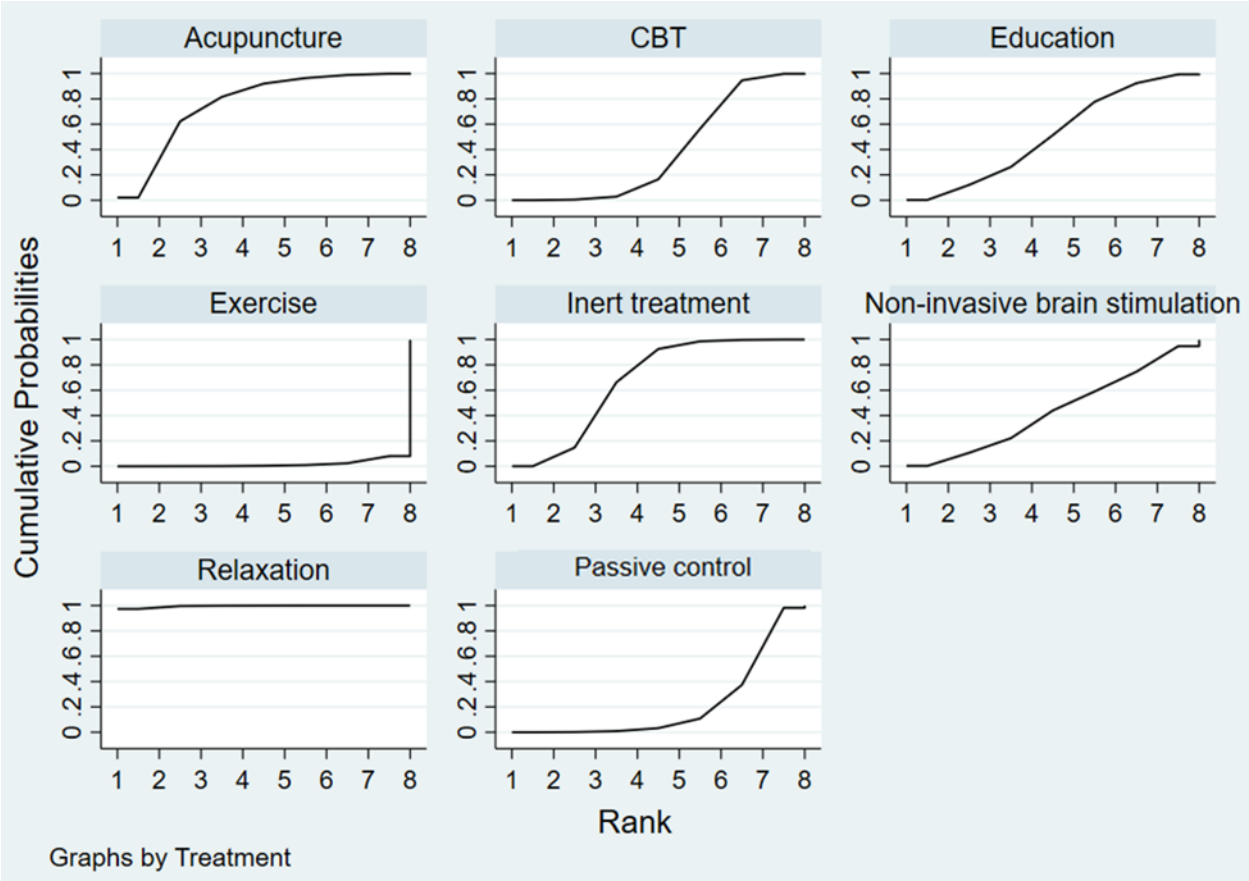


Table S5.24. The treatment ranking and SUCRA for objective total sleep time at immediate post-intervention

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Acupuncture	94.0	74.3	1.4
2nd	Inert treatment	66.1	1.1	3.0
3rd	Non-invasive brain stimulation	65.6	16.8	3.1
4th	Exercise	45.5	6.5	4.3
5th	Education	33.0	1.1	5.0
6th	CBT	32.5	0.1	5.0
7th	Passive control	13.2	0.0	6.2

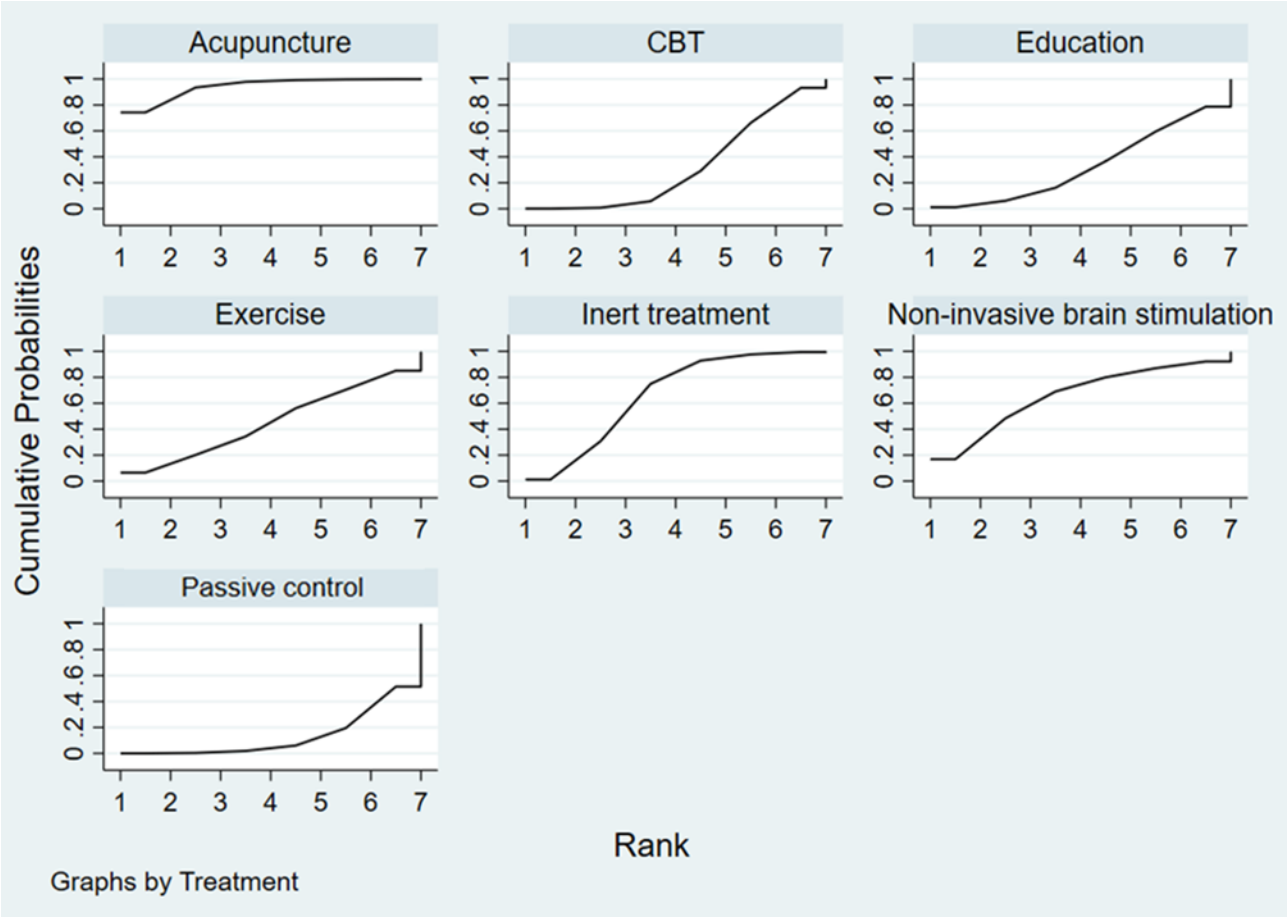


Table S5.25. The treatment ranking and SUCRA for objective wake time after sleep onset at immediate post-intervention

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Physical agents	85.6	66.7	1.7
2nd	Exercise	71.1	27.0	2.4
3rd	CBT	59.0	4.0	3.0
4th	Passive control	35.3	0.8	4.2
5th	Education	30.8	1.4	4.5
6th	Inert treatment	18.2	0.1	5.1

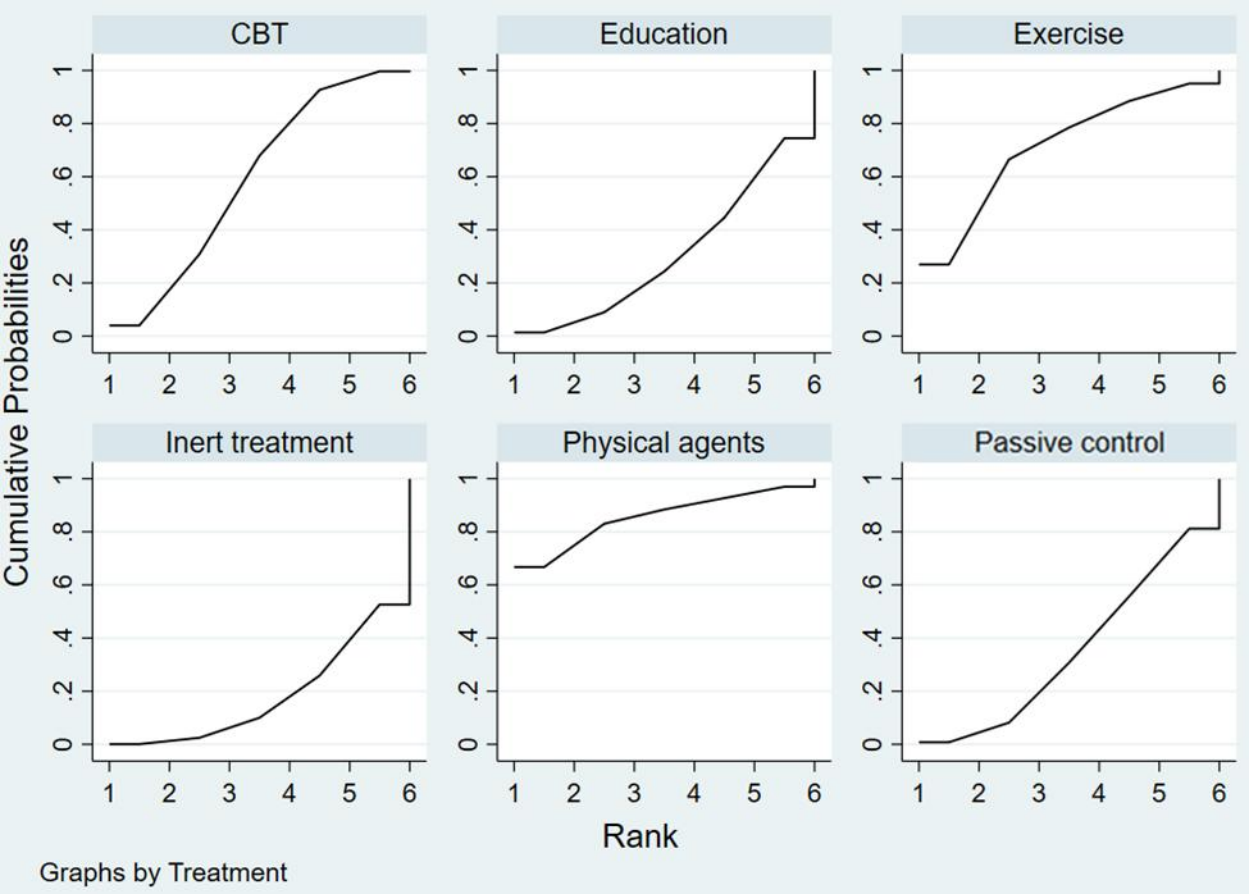


Table S5.26. The treatment ranking and SUCRA for subjective sleep efficiency at immediate post-intervention

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	CBT	86.6	36.5	1.9
2nd	Relaxation	78.6	44.3	2.5
3rd	Acupuncture	54.2	9.3	4.2
4th	Education	41.6	4.1	5.1
5th	Inert treatment	41.4	0.2	5.1
6th	Mindful psychotherapy	35.2	2.7	5.5
7th	Passive control	31.6	0.0	5.8
8th	Exercise	30.7	2.8	5.8

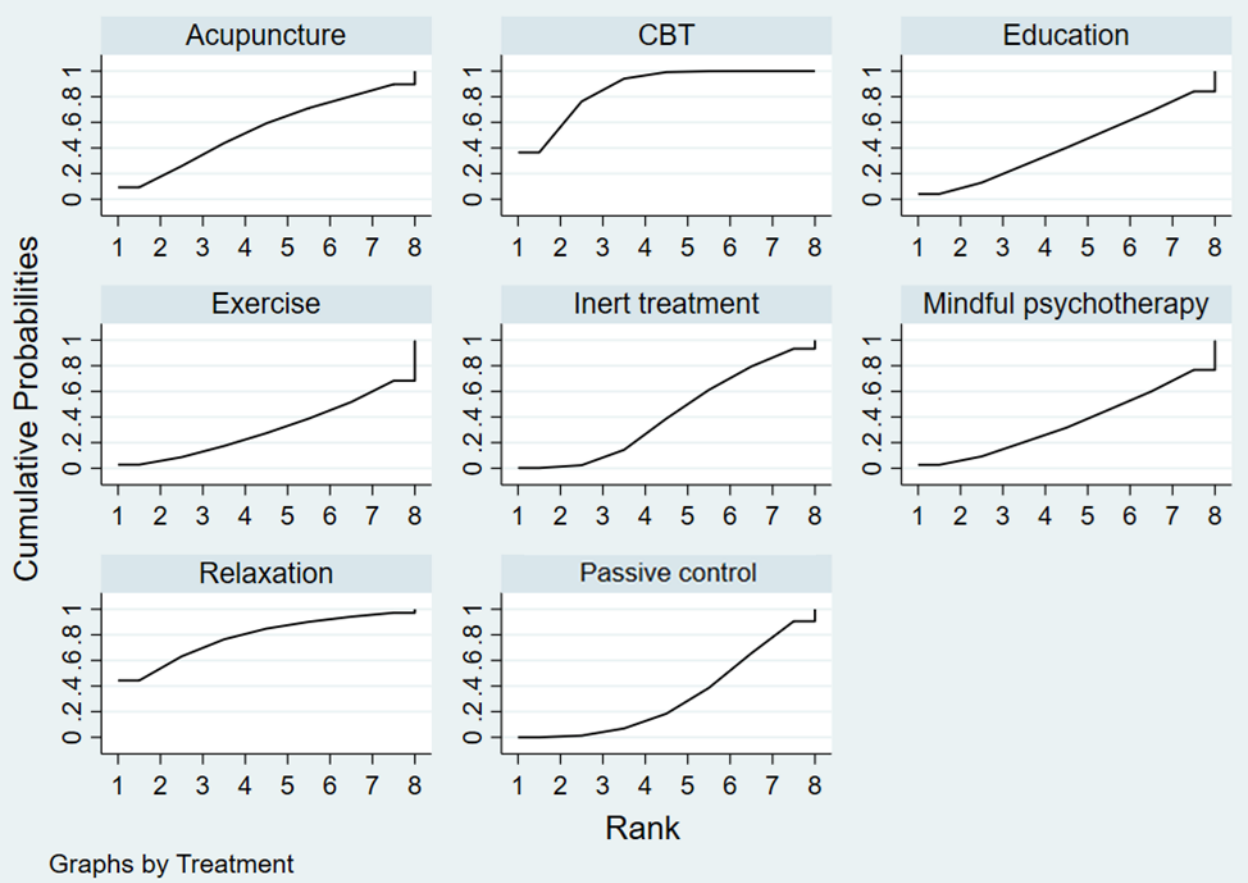


Table S5.27. The treatment ranking and SUCRA for subjective sleep onset latency at immediate post-intervention

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	CBT	74.5	16.4	2.5
2nd	Relaxation	70.8	41.2	2.8
3rd	Education	63.8	23.0	3.2
4th	Exercise	40.4	10.2	4.6
5th	Mindful psychotherapy	40.0	8.0	4.6
6th	Inert treatment	36.7	1.2	4.8
7th	Passive control	23.8	0.1	5.6

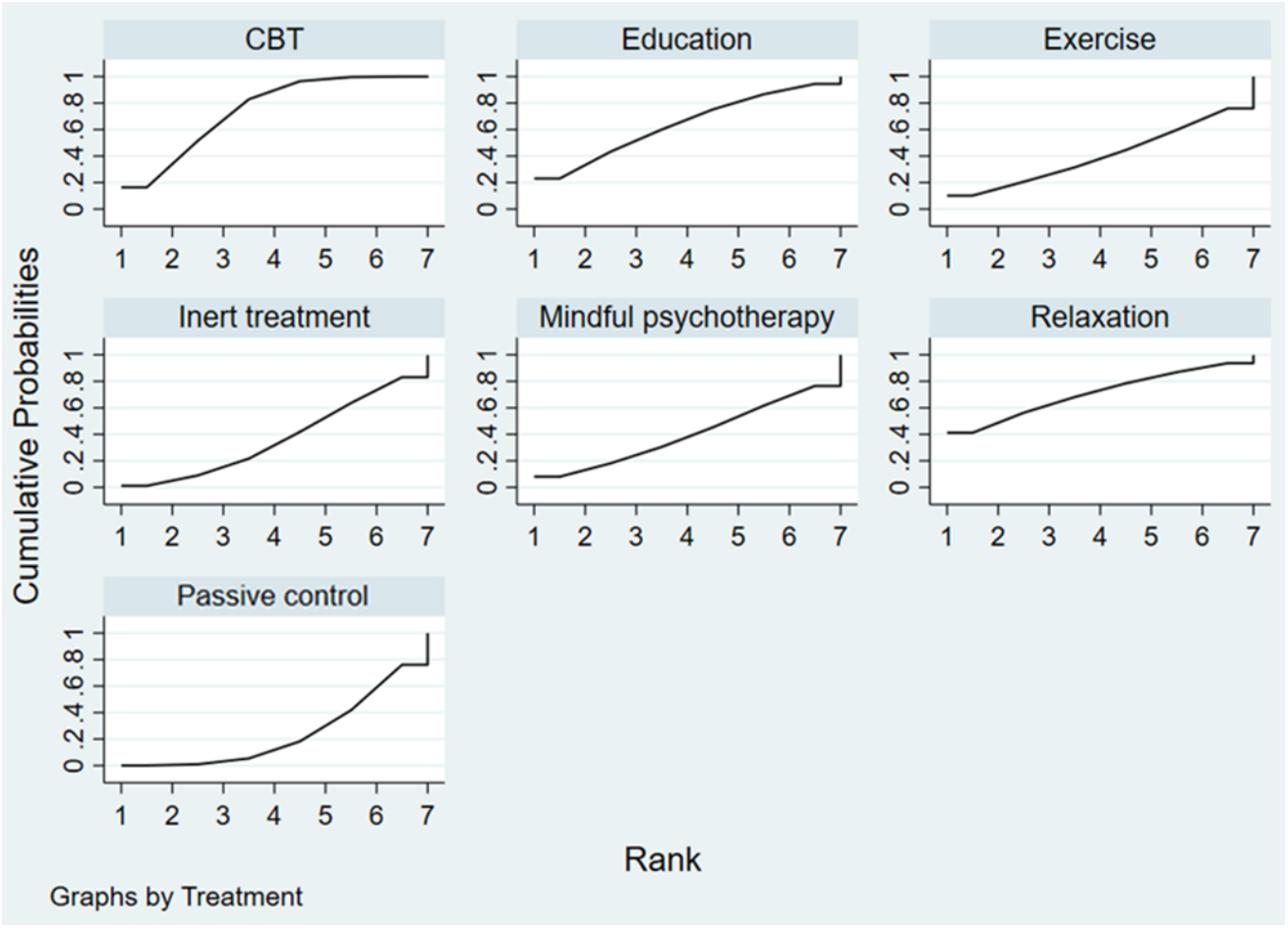


Table S5.28. The treatment ranking and SUCRA for subjective total sleep time at immediate post-intervention

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Inert treatment	60.2	15.7	3.4
2nd	Mindful psychotherapy	59.0	24.0	3.5
3rd	Exercise	57.8	27.1	3.5
4th	CBT	48.9	2.6	4.1
5th	Relaxation	47.0	19.7	4.2
6th	Passive control	43.0	2.4	4.4
7th	Education	34.1	8.4	5.0

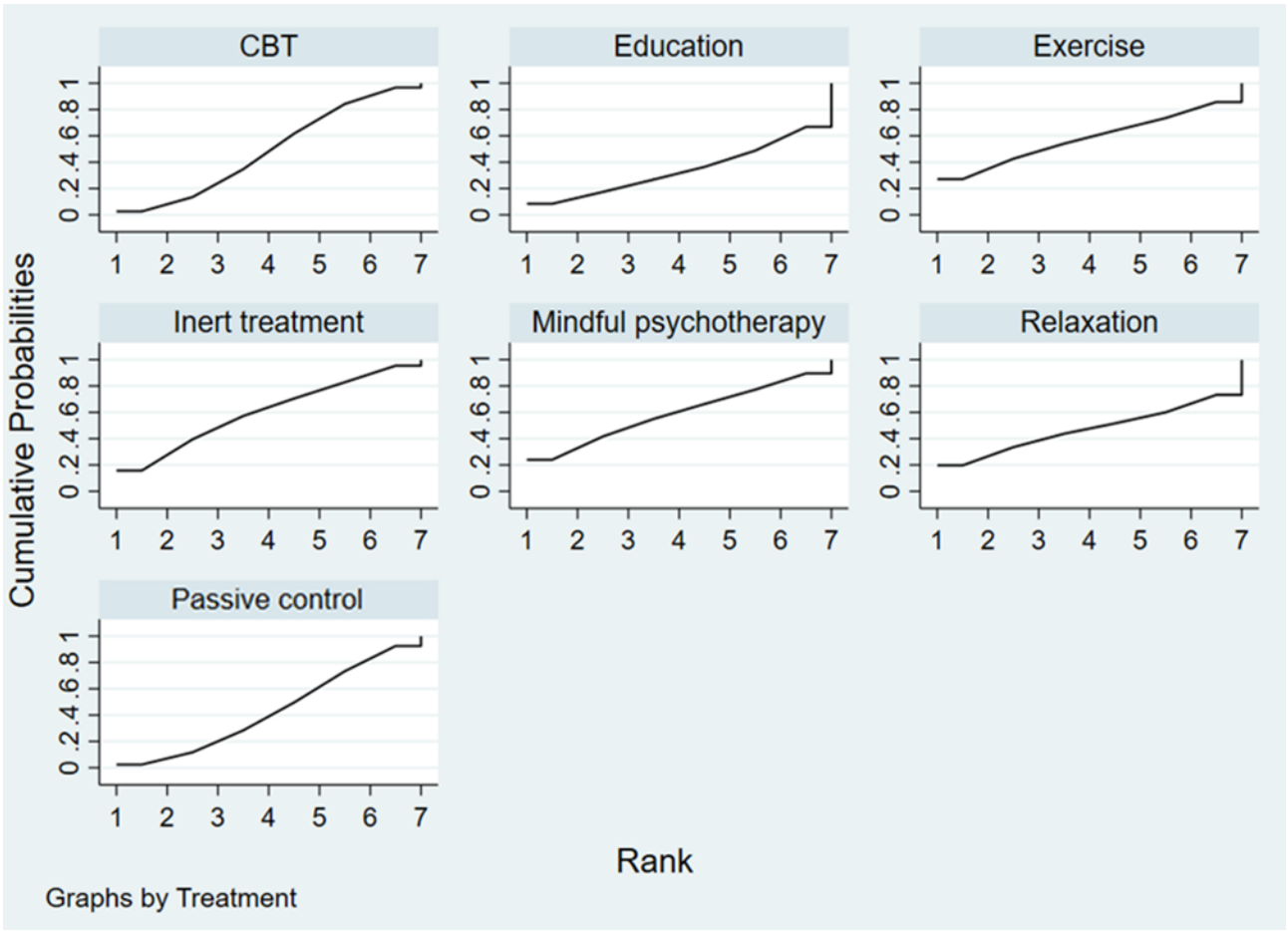


Table S5.29. The treatment ranking and SUCRA for subjective wake time after sleep onset at immediate post-intervention

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	CBT	87.6	41.9	1.7
2nd	Exercise	66.3	26.0	3.0
3rd	Relaxation	62.7	27.1	3.2
4th	Inert treatment	39.5	0.3	4.6
5th	Passive control	34.6	0.0	4.9
6th	Education	33.3	3.5	5.0
7th	Mindful psychotherapy	26.0	1.2	5.4

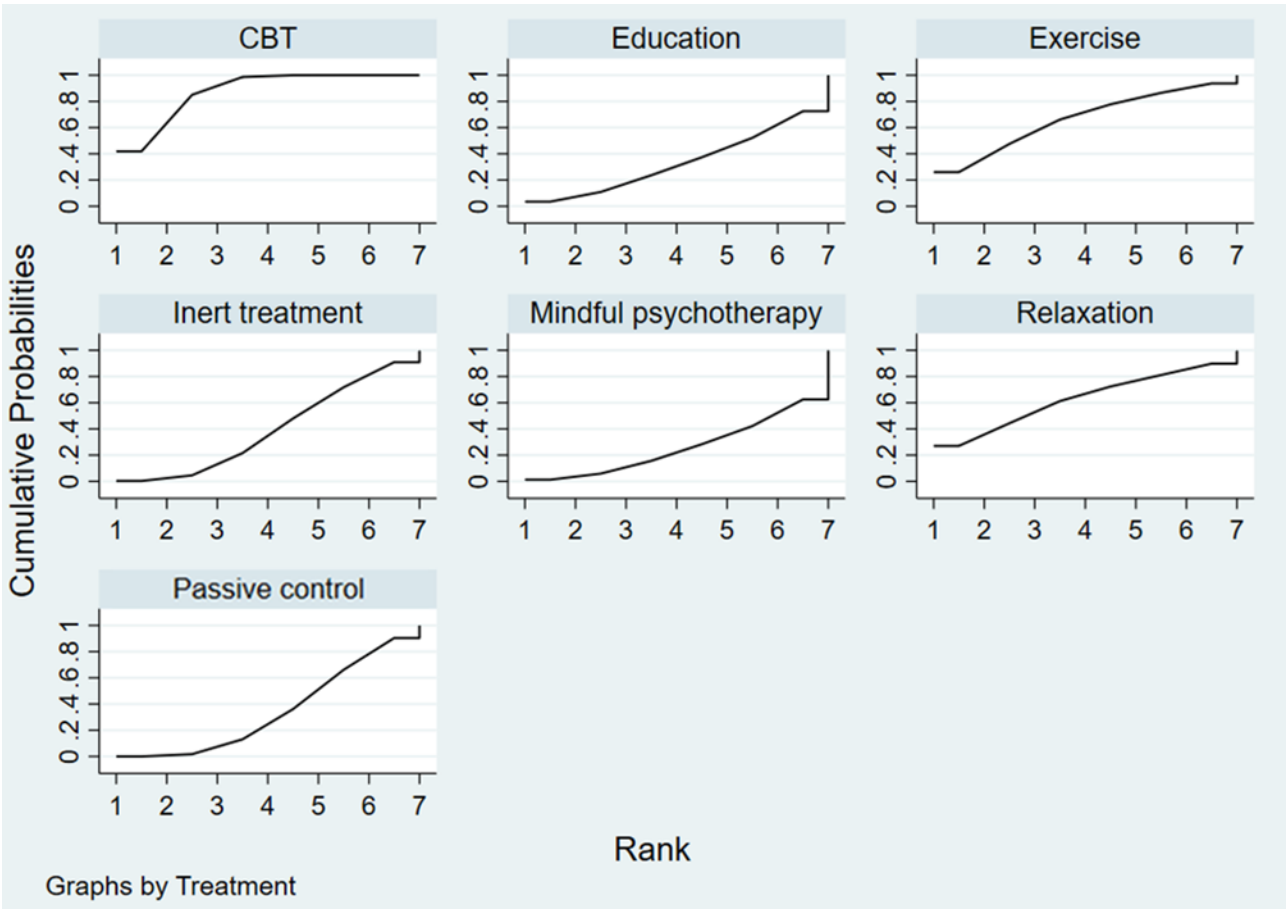
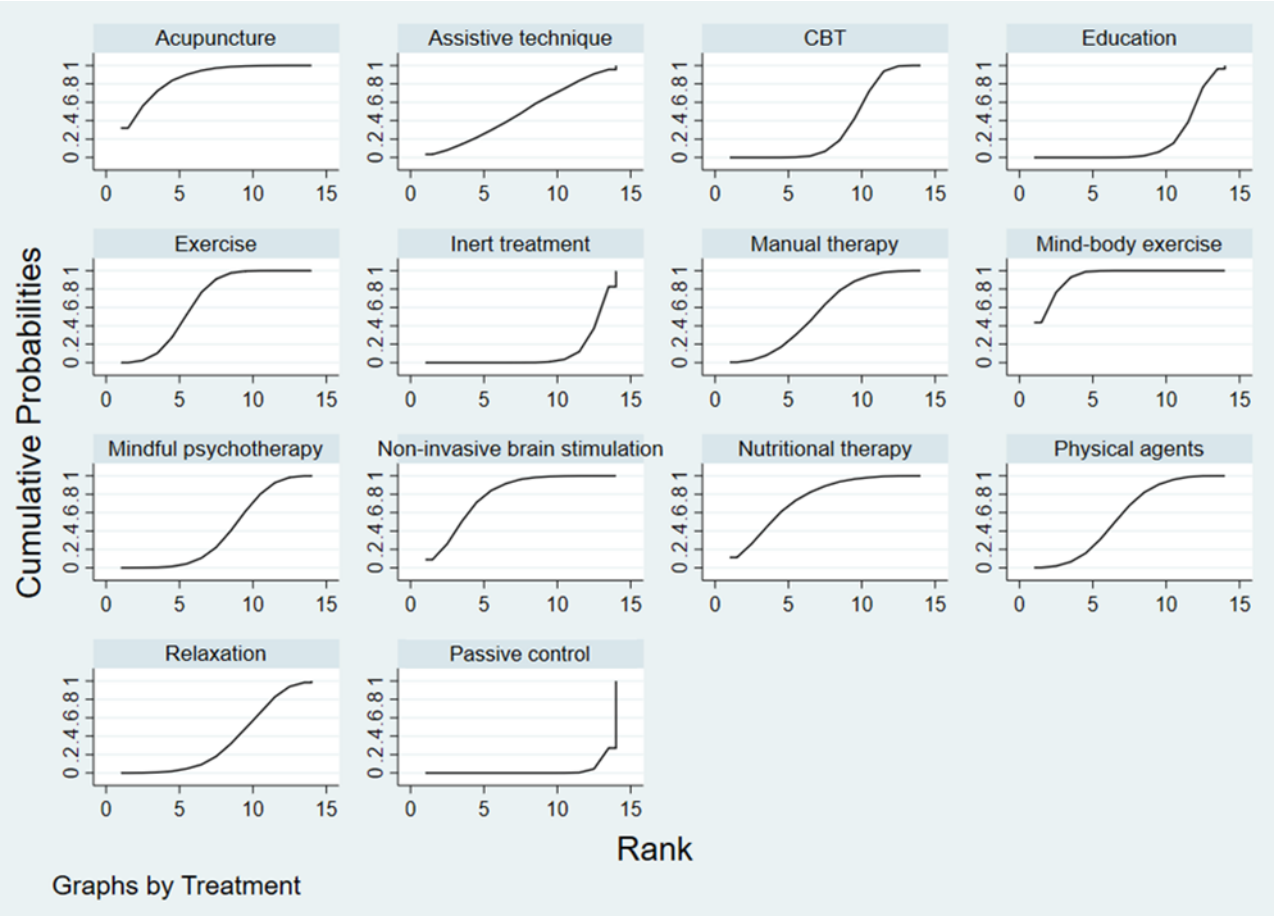


Table S5.30. The treatment ranking and SUCRA for pain

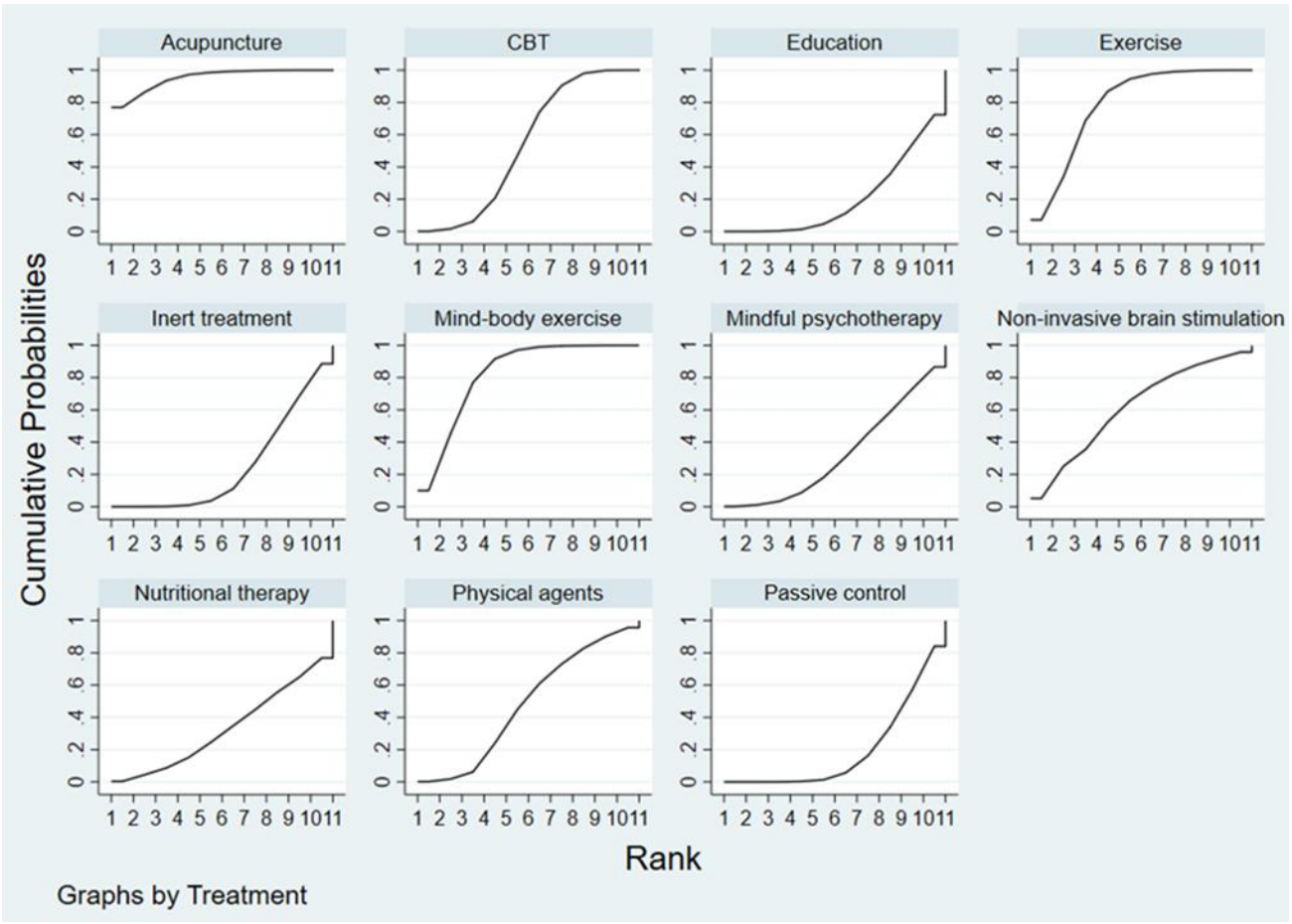
a) At immediate post-intervention

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Mind-body exercise	93.2	43.6	1.9
2nd	Acupuncture	86.5	32.0	2.8
3rd	Non-invasive brain stimulation	78.9	8.9	3.7
4th	Nutritional therapy	75.0	11.3	4.3
5th	Exercise	65.9	0.0	5.4
6th	Physical agents	56.9	0.2	6.6
7th	Manual therapy	55.9	0.5	6.7
8th	Assistive technique	48.8	3.4	7.7
9th	Mindful psychotherapy	39.4	0.0	8.9
10th	Relaxation	35.0	0.0	9.4
11th	CBT	33.5	0.0	9.6
12th	Education	18.1	0.0	11.6
13th	Inert treatment	10.5	0.0	12.6
14th	Passive control	2.5	0.0	13.7



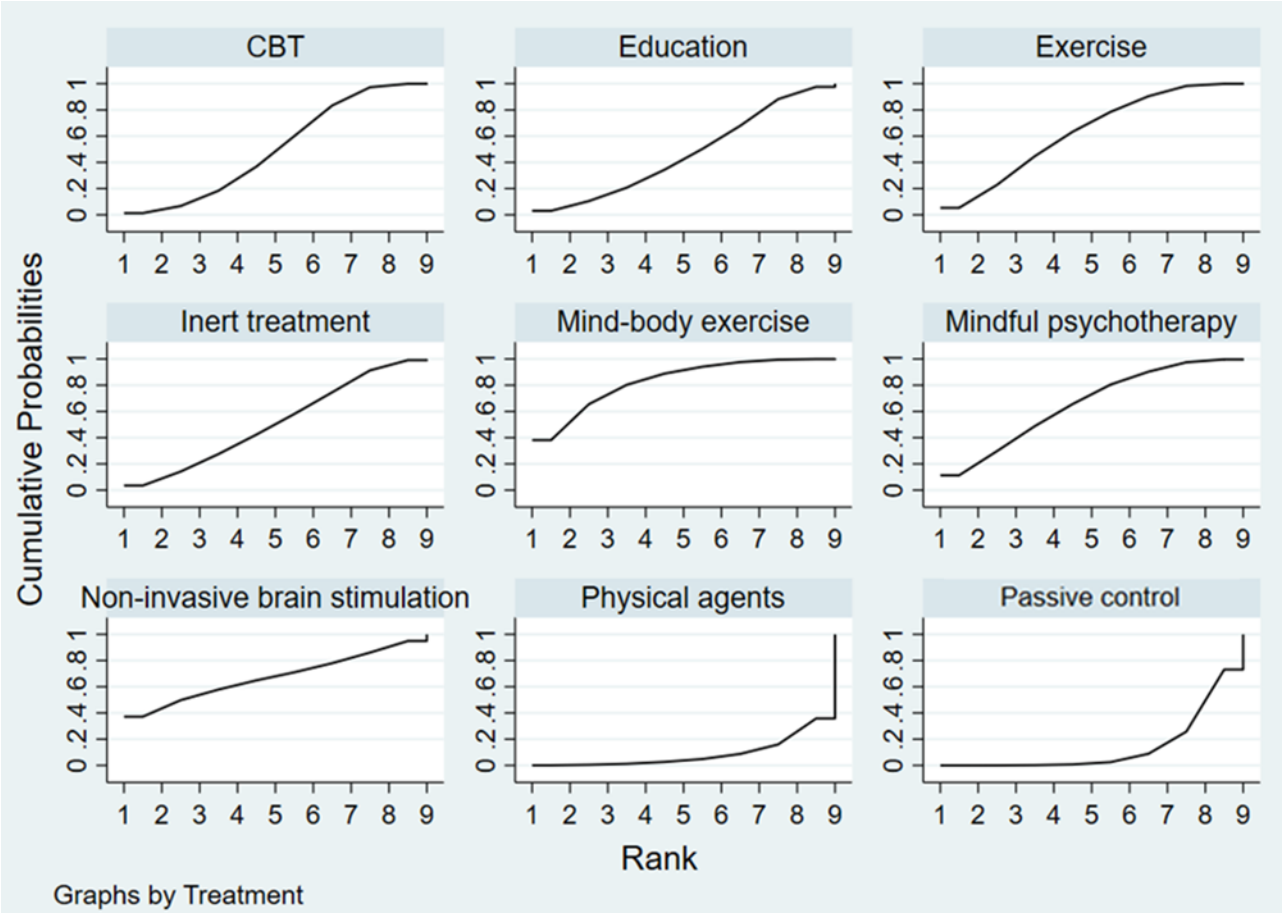
b) At short-term follow-up

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Acupuncture	94.6	75.1	1.5
2nd	Mind-body exercise	82.1	10.9	2.8
3rd	Exercise	78.7	7.7	3.1
4th	Non-invasive brain stimulation	60.8	5.2	4.9
5th	CBT	52.3	0.1	5.8
6th	Physical agents	48.3	0.2	6.2
7th	Mindful psychotherapy	34.5	0.3	7.5
8th	Nutritional therapy	32.5	0.4	7.8
9th	Inert treatment	24.1	0.0	8.6
10th	Passive control	22.0	0.0	8.8
11th	Education	20.0	0.0	9.0



c) At mid-term follow-up

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Mind-body exercise	83.0	38.1	2.4
2nd	Non-invasive brain stimulation	67.5	37.2	3.6
3rd	Mindful psychotherapy	65.5	11.3	3.8
4th	Exercise	63.0	5.4	4.0
5th	Inert treatment	51.3	3.5	4.9
6th	CBT	50.5	1.3	5.0
7th	Education	46.6	3.1	5.3
8th	Passive control	13.9	0.0	7.9
9th	Physical agents	8.8	0.1	8.3



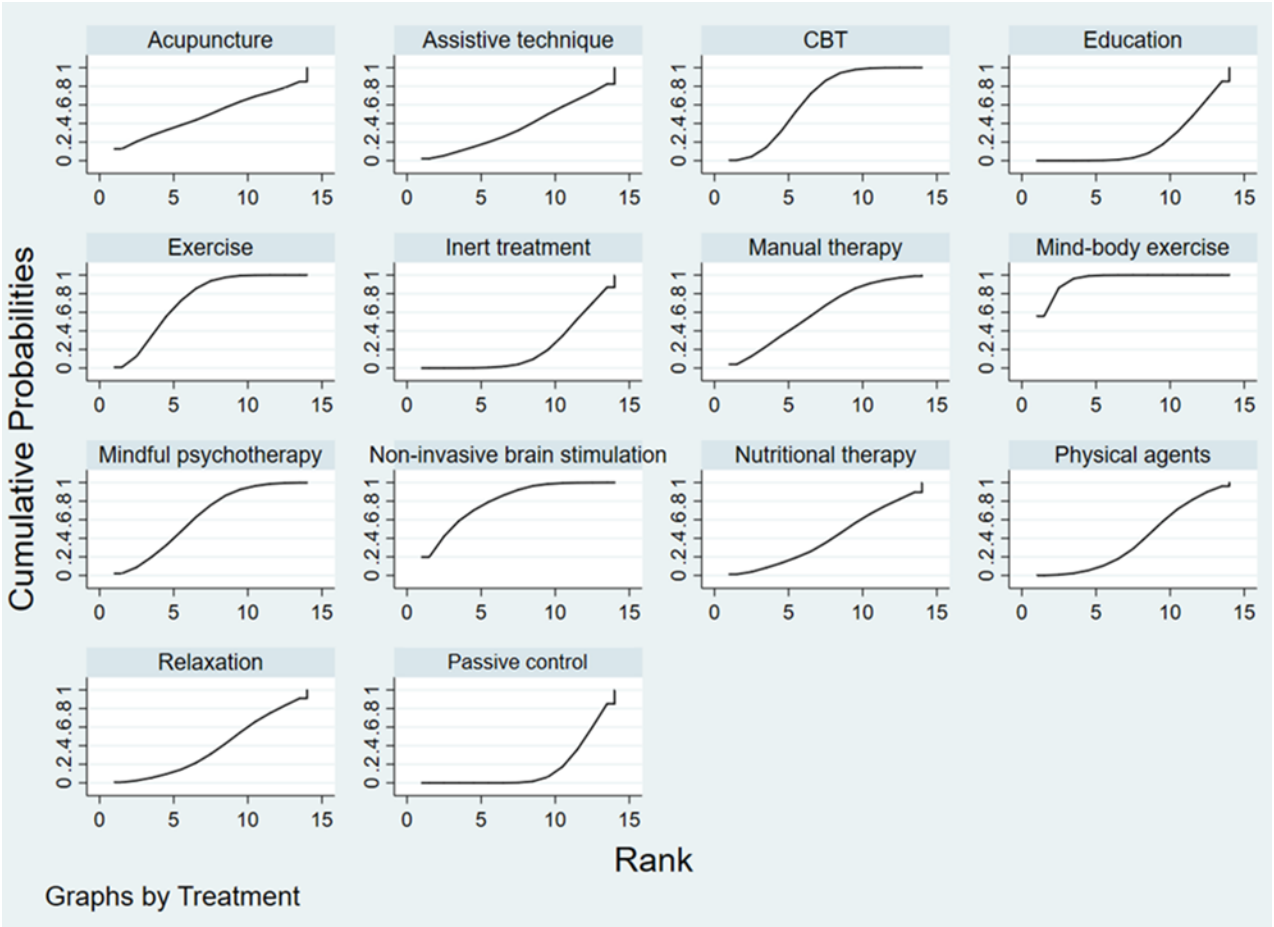
d) At long-term follow-up

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	CBT	85.4	0.5	1.9
2nd	Education	79.1	75.3	2.3
3rd	Mind-body exercise	57.7	2.7	3.3
4th	Inert treatment	50.0	3.0	4.1
5th	Exercise	46.2	2.6	4.7
6th	Mindful psychotherapy	25.3	0.4	5.1
7th	Passive control	6.5	15.4	5.5

Table S5.31. The treatment ranking and SUCRA for disability

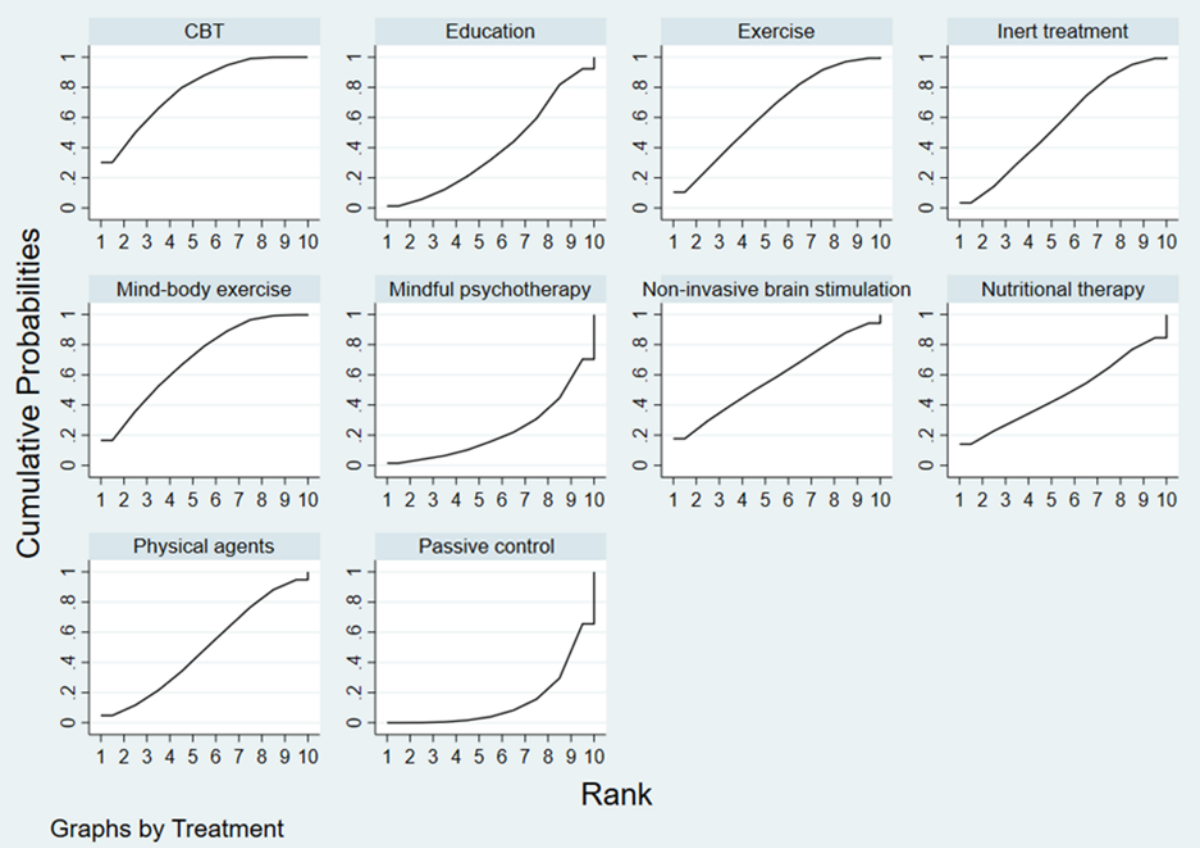
a) At immediate post-intervention

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Mind-body exercise	95.4	58.0	1.6
2nd	Non-invasive brain stimulation	80.1	19.2	3.6
3rd	Exercise	73.4	0.7	4.5
4th	CBT	65.6	0.4	5.5
5th	Mindful psychotherapy	63.2	2.1	5.8
6th	Manual therapy	60.1	3.3	6.2
7th	Acupuncture	49.7	12.4	7.5
8th	Nutritional therapy	43.8	0.9	8.3
9th	Physical agents	38.5	0.1	9.0
10th	Relaxation	37.9	0.7	9.1
11th	Assistive technique	36.7	2.1	9.2
12th	Inert treatment	20.6	0.0	11.3
13th	Education	19.8	0.0	11.4
14th	Passive control	15.2	0.0	12.0



b) At short-term follow-up

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	CBT	78.6	30.2	2.9
2nd	Mind-body exercise	70.6	16.5	3.6
3rd	Exercise	63.7	10.5	4.3
4th	Non-invasive brain stimulation	58.3	17.7	4.8
5th	Inert treatment	56	3.4	5
6th	Physical agents	49.2	4.8	5.6
7th	Nutritional therapy	48	14.1	5.7
8th	Education	38.9	1.3	6.5
9th	Mindful psychotherapy	22.8	1.5	7.9
10th	Passive control	13.9	0	8.7



c) At mid-term follow-up

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Mind-body exercise	62.2	13.7	4
2nd	Mindful psychotherapy	61.4	21.5	4.1
3rd	Exercise	60.5	10.6	4.2
4th	CBT	57.8	6.5	4.4
5th	Non-invasive brain stimulation	50.4	25.6	5
6th	Education	49.8	7.3	5
7th	Inert treatment	44.3	9.5	5.5
8th	Physical agents	39.5	5.1	5.8
9th	Passive control	24.2	0.2	7.1

Table S5.32. The treatment ranking and SUCRA for acceptability

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Manual therapy	92.9	65.7	1.9
2nd	Mind-body exercise	66.8	2.7	5.3
3rd	Education	65.8	4.2	5.5
4th	Exercise	63.5	0.8	5.7
5th	Passive control	56.8	0.1	6.6
6th	Non-invasive brain stimulation	52.4	2.6	7.2
7th	Relaxation	52.2	2.5	7.2
8th	Physical agents	51.4	3.5	7.3
9th	Assistive technique	45.9	6.7	8.0
10th	Nutritional therapy	40.7	10.4	8.7
11th	Inert treatment	40.3	0.0	8.8
12th	CBT	27.3	0.0	10.5
13th	Mindful psychotherapy	22.5	0.0	11.1
14th	Acupuncture	21.5	0.8	11.2

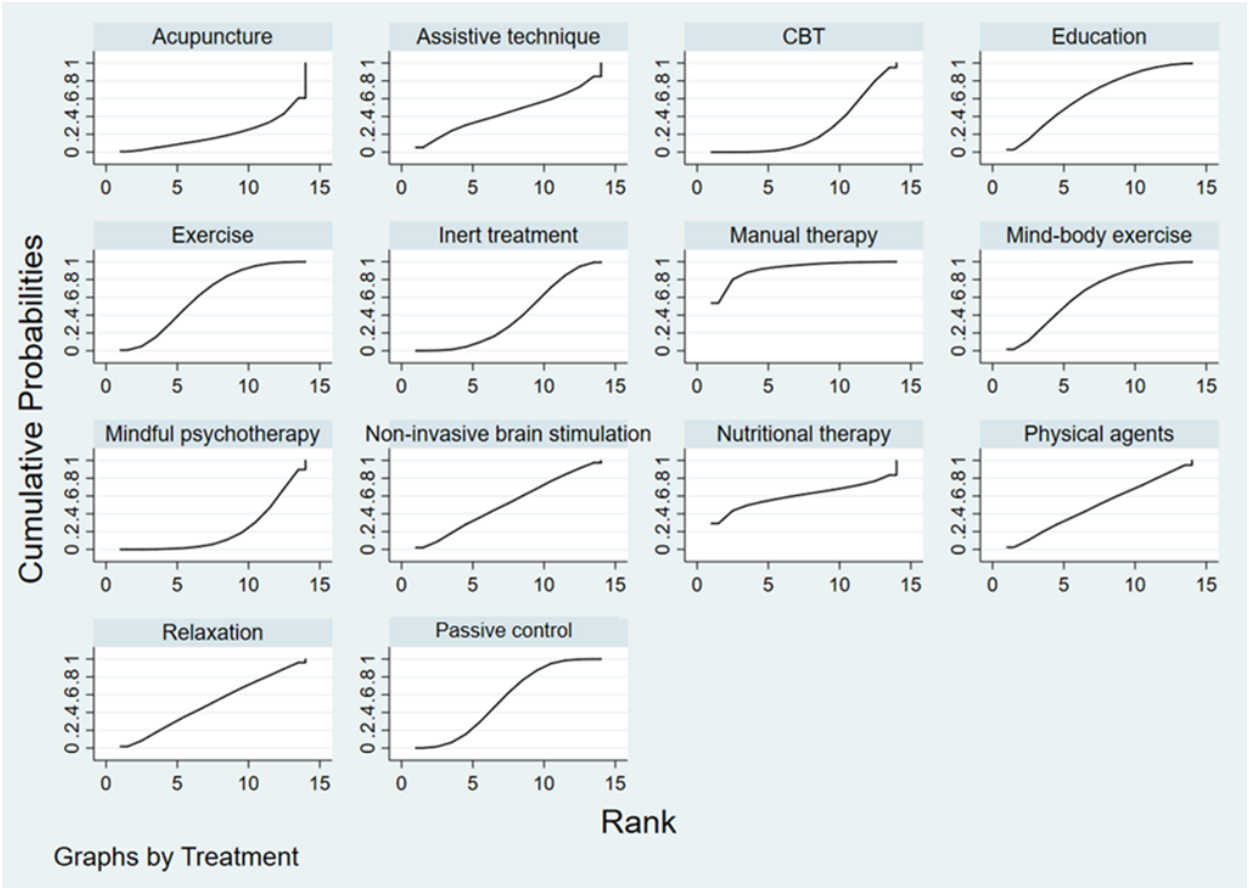
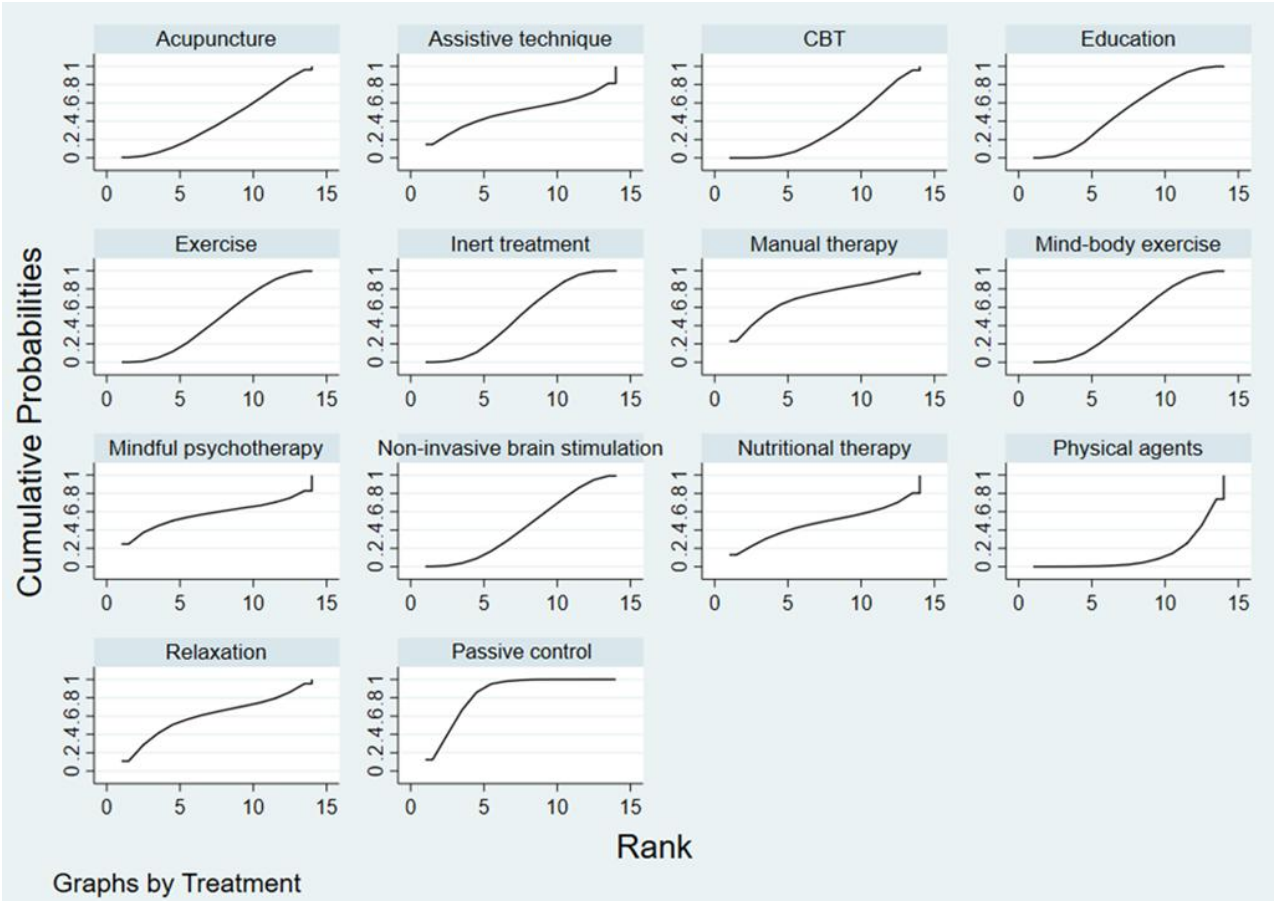


Table S5.33. The treatment ranking and SUCRA for safety

Rank	Treatment node	SUCRA	PrBest	Mean rank
1st	Passive control	84.1	12.4	3.1
2nd	Manual therapy	70.6	22.7	4.8
3rd	Relaxation	60.9	11.4	6.1
4th	Mindful psychotherapy	57.4	25.7	6.5
5th	Nutritional therapy	54.6	10.5	6.9
6th	Education	51.0	0.2	7.4
7th	Assistive technique	50.8	16.1	7.4
8th	Inert treatment	49.8	0.1	7.5
9th	Exercise	46.4	0.1	8.0
10th	Mind-body exercise	46.4	0.1	8.0
11th	Non-invasive brain stimulation	42.7	0.2	8.5
12th	Acupuncture	40.0	0.5	8.8
13th	CBT	32.2	0.0	9.8
14th	Physical agents	12.9	0.0	12.3



Appendix 25. League tables of the network meta-analysis in Chapter 7

Table S5.34. The league tables for sleep quality

a) At short-term follow-up

CBT										
-0.04 (-2.38,2.30)	**Acupuncture**									
0.34 (-1.09,1.77)	0.38 (-2.20,2.96)	**Mind-body exercise**								
0.46 (-0.81,1.73)	0.50 (-1.47,2.47)	0.12 (-1.55,1.79)	**Inert treatment**							
0.45 (-1.29,2.20)	0.49 (-1.81,2.80)	0.11 (-1.94,2.17)	-0.01 (-1.21,1.19)	**Non-invasive brain stimulation**						
0.53 (-1.19,2.24)	0.57 (-1.99,3.12)	0.19 (-1.34,1.71)	0.07 (-1.56,1.69)	0.07 (-1.95,2.10)	**Physical agents**					
0.57 (-1.05,2.19)	0.61 (-2.00,3.22)	0.23 (-0.83,1.29)	0.11 (-1.61,1.83)	0.12 (-1.97,2.21)	0.04 (-1.22,1.31)	**Exercise**				
0.67 (-0.56,1.90)	0.71 (-1.88,3.31)	0.33 (-1.16,1.83)	0.21 (-1.47,1.90)	0.22 (-1.85,2.29)	0.15 (-1.75,2.04)	0.10 (-1.62,1.83)	**Education**			
0.90 (-1.44,3.23)	0.94 (-1.84,3.71)	0.56 (-2.02,3.13)	0.44 (-1.52,2.39)	0.44 (-1.85,2.74)	0.37 (-2.18,2.92)	0.33 (-2.28,2.93)	0.22 (-2.36,2.81)	**Nutritional therapy**		
0.89 (-0.35,2.12)	0.93 (-1.69,3.55)	0.55 (-1.15,2.24)	0.43 (-1.30,2.15)	0.43 (-1.67,2.54)	0.36 (-1.64,2.36)	0.32 (-1.56,2.19)	0.21 (-1.46,1.89)	-0.01 (-2.62,2.60)	**Mindful psychotherapy**	
1.56 (0.62,2.49)	1.60 (-0.89,4.09)	1.22 (-0.22,2.66)	1.10 (-0.42,2.62)	1.11 (-0.83,3.04)	1.03 (-0.77,2.84)	0.99 (-0.67,2.65)	0.89 (-0.57,2.34)	0.66 (-1.81,3.14)	0.67 (-0.29,1.63)	**Passive control**

b) At mid-term follow-up

CBT								
0.12 (-1.04,1.28)	**Mindful psychotherapy**							
0.20 (-0.67,1.08)	0.08 (-1.34,1.49)	**Education**						
0.24 (-1.03,1.50)	0.12 (-1.45,1.68)	0.04 (-1.31,1.38)	**Mind-body exercise**					
0.20 (-1.83,2.24)	0.08 (-2.05,2.21)	0.00 (-2.18,2.18)	-0.04 (-2.28,2.20)	**Non-invasive brain stimulation**				
0.36 (-0.74,1.46)	0.24 (-1.10,1.59)	0.16 (-1.14,1.47)	0.12 (-1.05,1.30)	0.16 (-1.88,2.20)	**Exercise**			
0.39 (-0.98,1.76)	0.27 (-1.25,1.78)	0.19 (-1.39,1.77)	0.15 (-1.51,1.81)	0.19 (-1.31,1.69)	0.03 (-1.36,1.41)	**Inert treatment**		
0.62 (-1.17,2.42)	0.50 (-1.43,2.43)	0.42 (-1.52,2.37)	0.38 (-1.55,2.32)	0.42 (-1.79,2.63)	0.26 (-1.36,1.88)	0.23 (-1.39,1.86)	**Physical agents**	
1.23 (0.44,2.03)	1.11 (-0.15,2.37)	1.03 (-0.05,2.12)	0.99 (-0.26,2.25)	1.03 (-1.08,3.14)	0.87 (-0.27,2.01)	0.84 (-0.64,2.33)	0.61 (-1.24,2.46)	**Passive control**

c) At long-term follow-up

Mind-body exercise						
0.16 (-0.57,0.90)	**CBT**					
0.20 (-0.20,0.60)	0.04 (-0.58,0.66)	**Exercise**				
0.31 (-0.27,0.90)	0.15 (-0.61,0.90)	0.11 (-0.32,0.54)	**Passive control**			
0.35 (-0.16,0.85)	0.18 (-0.51,0.88)	0.14 (-0.17,0.45)	0.04 (-0.43,0.51)	**Mindful psychotherapy**		
0.45 (-0.09,0.98)	0.28 (-0.43,1.00)	0.24 (-0.11,0.60)	0.13 (-0.40,0.67)	0.10 (-0.26,0.46)	**Inert treatment**	
0.89 (0.11,1.66)	**0.72 (0.48,0.96)**	**0.68 (0.02,1.35)**	0.57 (-0.22,1.36)	0.54 (-0.20,1.27)	0.44 (-0.32,1.19)	**Education**

Table S5.35. The league table for objective sleep efficiency at immediate post-intervention

Acupuncture							
0.52 (-0.48,1.52)	**Exercise**						
0.61 (-0.09,1.32)	0.09 (-0.62,0.80)	**CBT**					
0.53 (-0.42,1.48)	0.01 (-1.12,1.13)	-0.08 (-0.96,0.79)	**Relaxation**				
0.68 (0.12,1.24)	0.16 (-0.67,0.98)	0.07 (-0.36,0.50)	0.15 (-0.61,0.91)	**Inert treatment**			
0.88 (-0.05,1.82)	0.36 (-0.76,1.47)	0.27 (-0.59,1.13)	0.35 (-0.72,1.42)	0.20 (-0.55,0.95)	**Non-invasive brain stimulation**		
0.83 (0.09,1.57)	0.31 (-0.43,1.05)	0.22 (-0.00,0.44)	0.30 (-0.60,1.20)	0.15 (-0.33,0.64)	-0.05 (-0.94,0.84)	**Education**	
0.91 (0.15,1.68)	0.39 (-0.26,1.04)	**0.30 (0.01,0.59)**	0.38 (-0.54,1.31)	0.23 (-0.28,0.75)	0.03 (-0.88,0.94)	0.08 (-0.28,0.44)	**Passive control**

Table S5.36. The league table for objective sleep onset latency at immediate post-intervention

Relaxation							
1.00 (0.02,1.98)	**Acupuncture**						
1.18 (0.36,2.00)	0.18 (-0.36,0.73)	**Inert treatment**					
1.40 (0.35,2.45)	0.40 (-0.45,1.26)	0.22 (-0.44,0.88)	**Education**				
1.48 (0.37,2.60)	0.48 (-0.44,1.41)	0.30 (-0.45,1.05)	0.08 (-0.92,1.08)	**Non-invasive brain stimulation**			
1.54 (0.62,2.47)	0.54 (-0.15,1.24)	0.36 (-0.07,0.80)	0.14 (-0.36,0.64)	0.06 (-0.81,0.93)	**CBT**		
1.77 (0.78,2.76)	0.77 (-0.01,1.55)	**0.59 (0.03,1.15)**	0.37 (-0.21,0.95)	0.29 (-0.65,1.23)	0.23 (-0.13,0.59)	**Passive control**	
2.40 (1.21,3.59)	**1.40 (0.38,2.42)**	**1.22 (0.35,2.08)**	**1.00 (0.12,1.87)**	0.92 (-0.23,2.06)	**0.86 (0.11,1.60)**	0.63 (-0.03,1.29)	**Exercise**

Table S5.37. The league table for objective total sleep time at immediate post-intervention

Acupuncture						
0.47 (-0.08,1.03)	**Inert treatment**					
0.42 (-0.50,1.35)	-0.05 (-0.80,0.70)	**Non-invasive brain stimulation**				
0.71 (-0.31,1.73)	0.24 (-0.62,1.10)	0.29 (-0.85,1.43)	**Exercise**			
0.83 (-0.03,1.70)	0.36 (-0.30,1.03)	0.41 (-0.59,1.41)	0.12 (-0.74,0.98)	**Education**		
0.84 (0.13,1.54)	0.36 (-0.08,0.80)	0.41 (-0.45,1.28)	0.12 (-0.61,0.86)	0.00 (-0.50,0.50)	**CBT**	
1.01 (0.22,1.80)	0.53 (-0.03,1.10)	0.58 (-0.35,1.52)	0.29 (-0.35,0.94)	0.17 (-0.40,0.75)	0.17 (-0.19,0.53)	**Passive control**

Table S5.38. The league table for objective wake time after sleep onset at immediate post-intervention

Physical agents					
0.38 (-1.05,1.81)	**Exercise**				
0.59 (-0.55,1.74)	0.21 (-0.64,1.07)	**CBT**			
0.76 (-0.51,2.04)	0.38 (-0.26,1.03)	0.17 (-0.39,0.73)	**Passive control**		
0.82 (-0.43,2.07)	0.44 (-0.49,1.37)	0.23 (-0.28,0.73)	0.06 (-0.61,0.73)	**Education**	
0.94 (-0.12,2.00)	0.56 (-0.40,1.51)	0.34 (-0.09,0.78)	0.17 (-0.53,0.88)	0.12 (-0.55,0.78)	**Inert treatment**

Table S5.39. The league table for subjective sleep efficiency at immediate post-intervention

CBT							
-0.01 (-1.05,1.04)	**Relaxation**						
0.38 (-0.52,1.27)	0.38 (-0.71,1.48)	**Acupuncture**					
0.54 (-0.21,1.29)	0.55 (-0.73,1.83)	0.17 (-1.00,1.33)	**Education**				
0.51 (-0.08,1.10)	0.52 (-0.34,1.38)	0.14 (-0.54,0.81)	-0.03 (-0.98,0.92)	**Inert treatment**			
0.62 (-0.11,1.34)	0.63 (-0.64,1.90)	0.24 (-0.91,1.40)	0.08 (-0.97,1.12)	0.11 (-0.83,1.04)	**Mindful psychotherapy**		
0.64 (0.25,1.03)	0.64 (-0.46,1.75)	0.26 (-0.70,1.23)	0.10 (-0.68,0.87)	0.13 (-0.56,0.82)	0.02 (-0.81,0.84)	**Passive control**	
0.70 (-0.18,1.58)	0.71 (-0.64,2.06)	0.33 (-0.92,1.57)	0.16 (-0.94,1.26)	0.19 (-0.86,1.23)	0.08 (-1.06,1.22)	0.06 (-0.72,0.85)	**Exercise**

Table S5.40. The league table for subjective sleep onset latency at immediate post-intervention

CBT						
-0.09 (-1.57,1.38)	**Relaxation**					
0.09 (-0.99,1.17)	0.19 (-1.64,2.02)	**Education**				
0.50 (-0.83,1.83)	0.59 (-1.39,2.58)	0.41 (-1.19,2.01)	**Exercise**			
0.50 (-0.61,1.62)	0.60 (-1.25,2.45)	0.41 (-1.14,1.96)	0.00 (-1.73,1.74)	**Mindful psychotherapy**		
0.50 (-0.34,1.35)	0.60 (-0.61,1.81)	0.41 (-0.96,1.78)	0.00 (-1.57,1.57)	-0.00 (-1.40,1.40)	**Inert treatment**	
0.70 (0.05,1.35)	0.80 (-0.81,2.41)	0.61 (-0.50,1.71)	0.20 (-0.96,1.36)	0.20 (-1.09,1.49)	0.20 (-0.86,1.26)	**Passive control**

Table S5.41. The league table for subjective total sleep time at immediate post-intervention

Inert treatment						
-0.00 (-0.87,0.86)	**Mindful psychotherapy**					
0.01 (-0.97,0.98)	0.01 (-1.03,1.04)	**Exercise**				
0.10 (-0.47,0.67)	0.10 (-0.55,0.75)	0.09 (-0.72,0.90)	**CBT**			
0.13 (-0.67,0.92)	0.13 (-1.04,1.31)	0.12 (-1.14,1.38)	0.03 (-0.95,1.01)	**Relaxation**		
0.14 (-0.51,0.79)	0.14 (-0.60,0.88)	0.13 (-0.60,0.86)	0.04 (-0.31,0.39)	0.01 (-1.02,1.04)	**Passive control**	
0.26 (-0.64,1.16)	0.26 (-0.70,1.21)	0.25 (-0.77,1.28)	0.16 (-0.54,0.86)	0.13 (-1.07,1.33)	0.12 (-0.60,0.84)	**Education**

Table S5.42. The league table for subjective wake time after sleep onset at immediate post-intervention

CBT						
0.17 (-0.54,0.88)	**Exercise**					
0.20 (-0.61,1.01)	0.02 (-1.05,1.10)	**Relaxation**				
0.43 (0.05,0.80)	0.25 (-0.55,1.05)	0.23 (-0.49,0.95)	**Inert treatment**			
0.47 (0.18,0.76)	0.30 (-0.34,0.94)	0.27 (-0.59,1.14)	0.04 (-0.43,0.52)	**Passive control**		
0.51 (-0.12,1.14)	0.33 (-0.58,1.25)	0.31 (-0.72,1.34)	0.08 (-0.65,0.81)	0.04 (-0.61,0.68)	**Education**	
0.58 (0.02,1.15)	0.41 (-0.49,1.32)	0.39 (-0.60,1.38)	0.16 (-0.52,0.83)	0.11 (-0.52,0.75)	0.08 (-0.77,0.92)	**Mindful psychotherapy**

Table S5.43. The league tables for pain

a) At immediate post-intervention

Mind-body exercise												
0.06 (-0.40,0.52)	**Acupuncture**											
0.17 (-0.22,0.56)	0.11 (-0.37,0.59)	**Non-invasive brain stimulation**										
0.20 (-0.27,0.68)	0.14 (-0.42,0.70)	0.03 (-0.46,0.52)	**Nutritional therapy**									
0.31 (0.10,0.53)	0.25 (-0.21,0.71)	0.14 (-0.24,0.52)	0.11 (-0.36,0.58)	**Exercise**								
0.39 (0.04,0.73)	0.32 (-0.16,0.81)	0.22 (-0.19,0.62)	0.18 (-0.31,0.68)	0.07 (-0.24,0.39)	**Physical agents**							
0.41 (0.05,0.77)	0.34 (-0.17,0.86)	0.23 (-0.22,0.69)	0.20 (-0.33,0.73)	0.09 (-0.28,0.46)	0.02 (-0.42,0.45)	**Manual therapy**						
0.47 (-0.13,1.06)	0.40 (-0.29,1.09)	0.29 (-0.35,0.93)	0.26 (-0.44,0.96)	0.15 (-0.44,0.75)	0.08 (-0.55,0.71)	0.06 (-0.58,0.70)	**Assistive technique**					
0.55 (0.23,0.86)	0.48 (-0.00,0.97)	0.38 (-0.04,0.79)	0.34 (-0.16,0.84)	0.23 (-0.07,0.54)	0.16 (-0.23,0.55)	0.14 (-0.26,0.54)	0.08 (-0.53,0.70)	**Mindful psychotherapy**				
0.59 (0.21,0.97)	**0.53 (0.02,1.04)**	0.42 (-0.02,0.86)	0.39 (-0.13,0.91)	0.28 (-0.10,0.65)	0.20 (-0.23,0.63)	0.19 (-0.22,0.59)	0.13 (-0.52,0.77)	0.04 (-0.35,0.44)	**Relaxation**			
0.60 (0.35,0.85)	**0.53 (0.08,0.98)**	**0.43 (0.05,0.80)**	0.39 (-0.07,0.85)	**0.28 (0.04,0.53)**	0.21 (-0.14,0.56)	0.19 (-0.17,0.55)	0.13 (-0.45,0.72)	0.05 (-0.23,0.33)	0.01 (-0.36,0.37)	**CBT**		
0.75 (0.50,0.99)	**0.68 (0.22,1.15)**	**0.57 (0.18,0.97)**	**0.54 (0.08,1.00)**	**0.43 (0.18,0.68)**	0.36 (-0.00,0.72)	0.34 (-0.04,0.72)	0.28 (-0.32,0.88)	0.20 (-0.12,0.52)	0.15 (-0.22,0.53)	0.15 (-0.07,0.37)	**Education**	
0.83 (0.55,1.12)	**0.77 (0.37,1.17)**	**0.66 (0.39,0.93)**	**0.63 (0.22,1.04)**	**0.52 (0.24,0.79)**	**0.44 (0.14,0.75)**	**0.43 (0.06,0.80)**	0.37 (-0.21,0.95)	0.29 (-0.04,0.61)	0.24 (-0.11,0.59)	0.24 (-0.03,0.50)	0.09 (-0.20,0.38)	**Inert treatment**
0.94 (0.73,1.16)	**0.88 (0.45,1.31)**	**0.77 (0.41,1.13)**	**0.74 (0.29,1.19)**	**0.63 (0.41,0.85)**	**0.55 (0.23,0.88)**	**0.54 (0.22,0.85)**	0.48 (-0.09,1.04)	**0.40 (0.13,0.66)**	**0.35 (0.01,0.70)**	**0.35 (0.16,0.53)**	0.20 (-0.04,0.43)	0.11 (-0.13,0.35)

b) At short-term follow-up

Acupuncture										
0.44 (-0.50,1.38)	**Mind-body exercise**									
0.48 (-0.47,1.44)	0.05 (-0.30,0.39)	**Exercise**								
0.69 (-0.32,1.69)	0.25 (-0.67,1.17)	0.20 (-0.73,1.14)	**Non-invasive brain stimulation**							
0.86 (0.01,1.70)	0.42 (-0.10,0.93)	0.37 (-0.20,0.94)	0.17 (-0.66,0.99)	**CBT**						
0.85 (-0.10,1.80)	0.41 (-0.11,0.93)	0.37 (-0.07,0.80)	0.16 (-0.77,1.10)	-0.01 (-0.63,0.62)	**Physical agents**					
1.03 (0.03,2.04)	0.60 (-0.07,1.26)	0.55 (-0.17,1.27)	0.35 (-0.64,1.34)	0.18 (-0.39,0.75)	0.18 (-0.59,0.96)	**Mindful psychotherapy**				
1.07 (0.10,2.05)	0.63 (-0.25,1.52)	0.59 (-0.31,1.49)	0.39 (-0.58,1.35)	0.22 (-0.57,1.01)	0.22 (-0.68,1.13)	0.04 (-0.92,1.00)	**Nutritional therapy**			
1.12 (0.40,1.85)	**0.69 (0.09,1.29)**	**0.64 (0.02,1.26)**	0.44 (-0.26,1.14)	0.27 (-0.17,0.70)	0.27 (-0.35,0.89)	0.09 (-0.61,0.79)	0.05 (-0.61,0.71)	**Inert treatment**		
1.14 (0.24,2.05)	**0.70 (0.21,1.20)**	**0.66 (0.09,1.23)**	0.46 (-0.43,1.34)	0.29 (-0.08,0.65)	0.29 (-0.35,0.94)	0.11 (-0.33,0.55)	0.07 (-0.78,0.92)	0.02 (-0.53,0.56)	**Passive control**	
1.19 (0.26,2.12)	**0.75 (0.19,1.31)**	**0.71 (0.08,1.33)**	0.50 (-0.41,1.42)	0.33 (-0.09,0.76)	0.34 (-0.35,1.03)	0.16 (-0.53,0.84)	0.12 (-0.77,1.00)	0.07 (-0.52,0.65)	0.05 (-0.48,0.57)	**Education**

c) At mid-term follow-up

Mind-body exercise								
0.07 (-0.84,0.98)	**Non-invasive brain stimulation**							
0.15 (-0.35,0.66)	0.08 (-0.80,0.96)	**Mindful psychotherapy**						
0.16 (-0.22,0.54)	0.09 (-0.77,0.95)	0.01 (-0.43,0.45)	**Exercise**					
0.24 (-0.31,0.79)	0.17 (-0.55,0.90)	0.09 (-0.40,0.59)	0.08 (-0.38,0.54)	**Inert treatment**				
0.25 (-0.18,0.69)	0.18 (-0.68,1.05)	0.10 (-0.26,0.46)	0.09 (-0.30,0.48)	0.01 (-0.45,0.47)	**CBT**			
0.28 (-0.20,0.76)	0.21 (-0.70,1.12)	0.13 (-0.34,0.59)	0.12 (-0.35,0.59)	0.03 (-0.51,0.58)	0.03 (-0.29,0.34)	**Education**		
0.55 (0.11,0.98)	0.48 (-0.41,1.36)	0.40 (-0.00,0.79)	0.38 (-0.02,0.79)	0.30 (-0.20,0.80)	0.29 (0.02,0.57)	0.27 (-0.12,0.66)	**Passive control**	
0.70 (0.06,1.33)	0.63 (-0.27,1.53)	0.55 (-0.08,1.18)	0.54 (0.00,1.07)	0.45 (-0.08,0.99)	0.45 (-0.16,1.05)	0.42 (-0.24,1.08)	0.15 (-0.47,0.77)	**Physical agents**

d) At long-term follow-up

CBT						
0.06 (-0.17,0.29)	**Education**					
0.27 (-0.47,1.02)	0.22 (-0.56,0.99)	**Mind-body exercise**				
0.35 (-0.37,1.07)	0.29 (-0.47,1.05)	0.07 (-0.46,0.61)	**Inert treatment**			
0.37 (-0.25,1.00)	0.31 (-0.36,0.98)	0.10 (-0.30,0.50)	0.02 (-0.33,0.38)	**Exercise**		
0.54 (-0.16,1.24)	0.48 (-0.26,1.22)	0.26 (-0.24,0.77)	0.19 (-0.17,0.55)	0.1 7 (-0.14,0.48)	**Mindful psychotherapy**	
0.76 (-0.00,1.52)	0.70 (-0.10,1.49)	0.48 (-0.11,1.07)	0.41 (-0.12,0.94)	0.38 (-0.05,0.81)	0.22 (-0.26,0.69)	**Passive control**

Table S5.44. The league tables for disability

a) At immediate post-intervention

Mind-body exercise													
0.20 (-0.36,0.76)	**Non-invasive brain stimulation**												
0.30 (0.02,0.59)	0.10 (-0.46,0.67)	**Exercise**											
0.39 (0.04,0.73)	0.19 (-0.37,0.75)	0.08 (-0.27,0.44)	**CBT**										
0.40 (-0.06,0.86)	0.20 (-0.43,0.84)	0.10 (-0.37,0.57)	0.02 (-0.36,0.40)	**Mindful psychotherapy**									
0.43 (-0.11,0.96)	0.23 (-0.49,0.94)	0.12 (-0.44,0.68)	0.04 (-0.50,0.58)	0.02 (-0.59,0.64)	**Manual therapy**								
0.53 (-0.44,1.51)	0.33 (-0.73,1.40)	0.23 (-0.75,1.21)	0.15 (-0.81,1.11)	0.13 (-0.87,1.13)	0.11 (-0.94,1.16)	**Acupuncture**							
0.60 (0.00,1.20)	0.40 (-0.21,1.01)	0.30 (-0.31,0.90)	0.22 (-0.39,0.82)	0.20 (-0.48,0.87)	0.18 (-0.58,0.93)	0.07 (-1.03,1.16)	**Nutritional therapy**						
0.65 (0.18,1.12)	0.45 (-0.13,1.03)	0.35 (-0.09,0.78)	0.26 (-0.23,0.76)	0.25 (-0.33,0.82)	0.22 (-0.43,0.88)	0.12 (-0.92,1.15)	0.05 (-0.59,0.69)	**Physical agents**					
0.67 (0.08,1.25)	0.47 (-0.22,1.16)	0.36 (-0.23,0.96)	0.28 (-0.29,0.85)	0.26 (-0.34,0.87)	0.24 (-0.49,0.97)	0.13 (-0.94,1.21)	0.07 (-0.67,0.80)	0.02 (-0.65,0.68)	**Relaxation**				
0.69 (-0.05,1.43)	0.49 (-0.32,1.30)	0.39 (-0.36,1.14)	0.31 (-0.43,1.04)	0.29 (-0.50,1.07)	0.27 (-0.58,1.11)	0.16 (-1.00,1.32)	0.09 (-0.76,0.95)	0.04 (-0.76,0.84)	0.02 (-0.84,0.89)	**Assistive technique**			
0.83 (0.40,1.25)	**0.63 (0.27,0.98)**	**0.52 (0.09,0.96)**	**0.44 (0.01,0.87)**	0.42 (-0.10,0.94)	0.40 (-0.22,1.02)	0.29 (-0.72,1.30)	0.22 (-0.27,0.72)	0.18 (-0.28,0.63)	0.16 (-0.44,0.75)	0.13 (-0.59,0.86)	**Inert treatment**		
0.83 (0.51,1.16)	**0.63 (0.07,1.20)**	**0.53 (0.19,0.88)**	**0.45 (0.11,0.79)**	0.43 (-0.04,0.90)	0.41 (-0.16,0.98)	0.30 (-0.68,1.28)	0.23 (-0.36,0.82)	0.18 (-0.31,0.68)	0.17 (-0.40,0.73)	0.14 (-0.61,0.90)	0.01 (-0.43,0.45)	**Education**	
0.87 (0.58,1.17)	**0.67 (0.14,1.21)**	**0.57 (0.25,0.89)**	**0.49 (0.23,0.74)**	**0.47 (0.09,0.85)**	0.45 (-0.04,0.94)	0.34 (-0.59,1.27)	0.27 (-0.31,0.86)	0.22 (-0.23,0.68)	0.21 (-0.34,0.75)	0.18 (-0.52,0.88)	0.05 (-0.35,0.44)	0.04 (-0.29,0.37)	**Passive control**

b) At short-term follow-up

CBT									
0.17 (-0.98,1.32)	**Mind-body exercise**								
0.28 (-1.01,1.57)	0.11 (-0.69,0.91)	**Exercise**							
0.37 (-1.30,2.05)	0.20 (-1.59,2.00)	0.09 (-1.69,1.88)	**Non-invasive brain stimulation**						
0.42 (-0.83,1.68)	0.25 (-1.16,1.67)	0.15 (-1.25,1.54)	0.05 (-1.06,1.16)	**Inert treatment**					
0.54 (-0.86,1.94)	0.37 (-0.80,1.55)	0.26 (-0.70,1.23)	0.17 (-1.53,1.87)	0.12 (-1.17,1.41)	**Physical agents**				
0.60 (-1.33,2.53)	0.43 (-1.60,2.47)	0.32 (-1.70,2.35)	0.23 (-1.61,2.07)	0.18 (-1.29,1.64)	0.06 (-1.89,2.01)	**Nutritional therapy**			
0.76 (-0.18,1.69)	0.59 (-0.58,1.76)	0.48 (-0.87,1.82)	0.39 (-1.46,2.23)	0.33 (-1.14,1.81)	0.22 (-1.28,1.71)	0.16 (-1.92,2.23)	**Education**		
1.23 (-0.17,2.64)	1.06 (-0.47,2.60)	0.95 (-0.72,2.63)	0.86 (-1.25,2.97)	0.81 (-0.99,2.61)	0.69 (-1.11,2.50)	0.63 (-1.69,2.95)	0.48 (-1.12,2.07)	**Mindful psychotherapy**	
1.37 (0.41,2.33)	**1.20 (0.06,2.34)**	1.09 (-0.23,2.42)	1.00 (-0.85,2.84)	0.95 (-0.53,2.42)	0.83 (-0.65,2.31)	0.77 (-1.31,2.85)	0.61 (-0.61,1.84)	0.14 (-0.89,1.16)	**Passive control**

c) At mid-term follow-up

Mind-body exercise									
-0.01 (-2.15,2.14)	**Mindful psychotherapy**								
0.04 (-1.40,1.48)	0.05 (-2.23,2.32)	**Exercise**							
0.13 (-1.44,1.70)	0.14 (-1.40,1.68)	0.09 (-1.62,1.81)	**CBT**						
0.32 (-4.00,4.64)	0.33 (-4.34,4.99)	0.28 (-3.79,4.36)	0.19 (-4.23,4.61)	**Non-invasive brain stimulation**					
0.29 (-1.39,1.96)	0.29 (-1.67,2.26)	0.25 (-1.67,2.17)	0.15 (-1.09,1.40)	-0.03 (-4.54,4.47)	**Education**				
0.54 (-3.06,4.13)	0.55 (-3.45,4.55)	0.50 (-2.79,3.79)	0.41 (-3.31,4.12)	0.22 (-2.18,2.62)	0.25 (-3.56,4.06)	**Inert treatment**			
0.67 (-2.07,3.41)	0.68 (-2.57,3.93)	0.63 (-1.69,2.96)	0.54 (-2.35,3.43)	0.35 (-2.99,3.69)	0.38 (-2.63,3.40)	0.13 (-2.20,2.46)	**Physical agents**		
0.94 (-0.68,2.56)	0.95 (-0.72,2.62)	0.91 (-0.93,2.74)	0.81 (-0.18,1.80)	0.62 (-3.85,5.09)	0.66 (-0.87,2.18)	0.40 (-3.37,4.18)	0.27 (-2.69,3.24)	**Passive control**	

Table S5.45. The league table for acceptability

Manual therapy												
1.89 (0.72,4.93)	**Mind-body exercise**											
1.90 (0.69,5.26)	1.01 (0.53,1.92)	**Education**										
1.97 (0.76,5.08)	1.05 (0.67,1.62)	1.04 (0.56,1.93)	**Exercise**									
2.12 (0.88,5.11)	1.12 (0.68,1.87)	1.12 (0.64,1.95)	1.08 (0.69,1.69)	**Passive control**								
2.18 (0.73,6.58)	1.16 (0.51,2.62)	1.15 (0.48,2.75)	1.11 (0.52,2.38)	1.03 (0.49,2.16)	**Non-invasive brain stimulation**							
2.18 (0.76,6.28)	1.16 (0.54,2.49)	1.15 (0.51,2.60)	1.11 (0.56,2.20)	1.03 (0.51,2.06)	1.00 (0.40,2.49)	**Relaxation**						
2.21 (0.70,7.00)	1.17 (0.50,2.76)	1.17 (0.46,2.93)	1.12 (0.51,2.46)	1.04 (0.47,2.31)	1.01 (0.40,2.59)	1.01 (0.38,2.68)	**Physical agents**					
2.38 (0.60,9.43)	1.26 (0.39,4.07)	1.26 (0.38,4.15)	1.21 (0.39,3.78)	1.12 (0.39,3.28)	1.09 (0.31,3.81)	1.09 (0.31,3.83)	1.08 (0.29,3.96)	**Assistive technique**				
2.69 (0.46,15.86)	1.43 (0.28,7.15)	1.42 (0.27,7.31)	1.36 (0.28,6.66)	1.27 (0.26,6.13)	1.23 (0.25,6.06)	1.23 (0.23,6.50)	1.21 (0.23,6.49)	1.13 (0.17,7.32)	**Nutritional therapy**			
2.47 (0.95,6.43)	1.31 (0.72,2.40)	1.30 (0.66,2.56)	1.25 (0.74,2.13)	1.16 (0.71,1.92)	1.13 (0.65,1.96)	1.13 (0.55,2.35)	1.12 (0.52,2.38)	1.04 (0.34,3.19)	0.92 (0.21,4.10)	**Inert treatment**		
2.81 (1.11,7.10)	1.49 (0.86,2.59)	1.48 (0.89,2.45)	1.43 (0.87,2.33)	1.32 (0.95,1.85)	1.29 (0.60,2.75)	1.29 (0.62,2.66)	1.27 (0.56,2.88)	1.18 (0.39,3.58)	1.04 (0.21,5.09)	1.14 (0.67,1.92)	**CBT**	
2.99 (1.16,7.70)	1.59 (0.89,2.83)	1.58 (0.86,2.90)	1.52 (0.92,2.51)	1.41 (0.95,2.10)	1.37 (0.64,2.93)	1.37 (0.65,2.88)	1.35 (0.59,3.09)	1.26 (0.41,3.88)	1.11 (0.23,5.43)	1.21 (0.72,2.05)	1.07 (0.71,1.60)	**Mindful psychotherapy**
3.58 (0.98,13.08)	1.90 (0.65,5.50)	1.88 (0.62,5.70)	1.81 (0.65,5.07)	1.69 (0.62,4.57)	1.64 (0.56,4.77)	1.64 (0.52,5.15)	1.62 (0.50,5.23)	1.50 (0.36,6.24)	1.33 (0.23,7.68)	1.45 (0.58,3.62)	1.27 (0.46,3.53)	1.19 (0.43,3.33)

Table S5.46. The league table for safety

Passive control												
1.10 (0.07,18.37)	**Manual therapy**											
1.68 (0.05,54.46)	1.52 (0.02,134.07)	**Relaxation**										
1.68 (0.01,337.79)	1.52 (0.00,618.89)	1.00 (0.02,54.83)	**Mindful psychotherapy**									
2.40 (0.10,55.47)	2.18 (0.03,148.15)	1.43 (0.02,124.95)	1.43 (0.00,578.02)	**Nutritional therapy**								
3.16 (1.15,8.63)	2.87 (0.14,57.06)	1.88 (0.05,67.98)	1.88 (0.01,406.75)	1.31 (0.05,32.76)	**Education**							
2.89 (0.04,198.11)	2.63 (0.02,422.19)	1.73 (0.01,341.85)	1.73 (0.00,1311.81)	1.20 (0.01,156.92)	0.92 (0.01,66.47)	**Assistive technique**						
3.29 (0.80,13.54)	2.99 (0.13,69.89)	1.96 (0.06,63.73)	1.96 (0.01,395.31)	1.37 (0.08,22.59)	1.04 (0.22,5.05)	1.14 (0.02,61.08)	**Inert treatment**					
3.46 (1.15,10.43)	3.15 (0.15,64.72)	2.06 (0.06,73.22)	2.06 (0.01,440.70)	1.44 (0.06,33.44)	1.10 (0.32,3.78)	1.20 (0.02,82.26)	1.05 (0.25,4.38)	**Exercise**				
3.46 (1.24,9.72)	3.15 (0.16,63.17)	2.07 (0.06,72.36)	2.07 (0.01,437.41)	1.44 (0.06,33.30)	1.10 (0.34,3.55)	1.20 (0.02,82.04)	1.05 (0.26,4.33)	1.00 (0.52,1.94)	**Mind-body exercise**			
3.76 (0.82,17.20)	3.42 (0.14,83.90)	2.24 (0.07,76.15)	2.24 (0.01,465.27)	1.57 (0.09,27.28)	1.19 (0.22,6.35)	1.30 (0.02,72.58)	1.14 (0.66,2.00)	1.09 (0.24,5.03)	1.09 (0.24,4.97)	**Non-invasive brain stimulation**		
4.14 (0.77,22.16)	3.76 (0.14,99.74)	2.47 (0.06,93.93)	2.47 (0.01,552.31)	1.72 (0.08,36.39)	1.31 (0.21,8.26)	1.43 (0.02,91.75)	1.26 (0.38,4.20)	1.20 (0.21,6.84)	1.19 (0.21,6.73)	1.10 (0.29,4.15)	**Acupuncture**	
4.75 (1.89,11.91)	4.32 (0.22,83.46)	2.83 (0.08,100.29)	2.83 (0.01,603.93)	1.98 (0.08,48.45)	1.50 (0.89,2.53)	1.64 (0.02,117.56)	1.44 (0.31,6.75)	1.37 (0.40,4.68)	1.37 (0.43,4.38)	1.26 (0.24,6.51)	1.15 (0.19,7.01)	**CBT**
9.76 (2.39,39.93)	8.87 (0.38,206.73)	5.82 (0.16,211.92)	5.82 (0.03,1264.54)	4.06 (0.19,88.47)	3.09 (0.64,14.83)	3.37 (0.05,221.30)	2.96 (0.82,10.66)	2.82 (0.79,10.02)	2.82 (0.75,10.64)	2.59 (0.64,10.47)	2.36 (0.44,12.68)	2.06 (0.44,9.61)

Abbreviation: CBT: Cognitive Behavioral Therapy.
Footnote: Results are presented as odd ratio and 95% confidence intervals. For each comparison (column vs. row) a difference > 1 indicates the intervention in the column is superior to the comparator in the row. Numbers in bold represent statistically significant results.

Appendix 26. Adverse events in Chapter 7

Table S5.47. Adverse events

Author	Year	Intervention	Number of patients received the intervention	Number of adverse events	Type of adverse events
Akodu et al [509] *	2021	Exercise	17	4	Discontinued intervention due to worsening of symptoms (n =4).
Alves et al [511]	2013	Nutritional therapy	16	0	
		Inert treatment	16	0	
Amirova et al [512]	2017	Relaxation	67	0	
		Inert treatment	66	0	
		Passive control	58	0	
Bakir et al [514]	2018	Manual therapy	31	1	Discontinued intervention due to worsening of symptoms (n =1).
		Passive control	34	1	Discontinued intervention due to worsening of symptoms (n =1).
Bestas et al [516]	2022	Physical agents	20	0	
		Exercise	60	0	
Blodt et al [517]	2015	Mind-body exercise	64	10	Muscle soreness (n = 10), muscle tenseness (n = 7), dizziness (n = 12), mood fluctuation (n = 2), neck blockage (n = 1), other pain (n = 3), back pain (n = 3), and increased pain (n = 2).
		Exercise	63	10	Muscle soreness (n = 19), muscle tenseness (n = 14), dizziness (n = 3), mood fluctuation (n = 1), strain on the back (n = 2), other pain (n = 4), and low back pain (n = 1).
Bongi et al [518]	2010	Mind-body exercise	22	0	
		Passive control	19	0	
Calandre et al [522]	2009	Mind-body exercise	42	3	Chlorine hypersensitivity (n =1) and increased pain (n= 2).
		Exercise	39	0	
Caumo et al [528]	2022	Non-invasive brain stimulation	32	3.2	Headache, neck pain, mood swings, and concentration difficulties.
		Inert treatment	16	0.64	
Cheung et al [529]	2014	Mind-body exercise	17	0	
		Passive control	18	0	
Colbert et al [530]	1999	Assistive support	16	0	
		Inert treatment	14	0	
Dall'Agnol et al [532]	2014	Non-invasive brain stimulation	12	0	
		Inert treatment	12	0	
	2021	CBT	88	0	

Darnall et al [533]		Education	88	0	
De Medeiros et al [534] *	2020	Mind-body exercise	21	1	Discontinued intervention due to worsening of symptoms (n =1).
Deluze [535]	1992	Acupuncture	36	6	Worsening of symptoms (n =2), unpleasantness of needle insertion (n =3), and ankle oedema (n =1).
		Inert treatment	34	5	Increase in symptoms (n =4) and unpleasantness of needle insertion (n =1).
Ericsson et al [539] *	2016	Exercise	50	5	Discontinued intervention due to increase in symptoms (n =5).
Franco et al [544]	2022	Exercise	49	1	Foot blisters (n =1).
		Mind-body exercise	48	1	Vaginismus (n =1).
Gur et al [547]	2002	Physical agents	20	0	
		Inert treatment	20	0	
Hagiwara et al [549] *	2017	Assistive technique	59	2	Discontinued intervention due to itching (n = 2).
Hargrove et al [550]	2012	Non-invasive brain stimulation	40	5	Short-lived headache (n =2), eye movement/flutter during treatment (n =1), increased perception of restlessness (n =1), and nausea (n =1).
		Inert treatment	45	3	Short-lived headache (n =1), eye movement/flutter during treatment (n =1), and temporary worsening of symptoms (n =1).
Hedman-Lagerlöf et al [552]	2018	CBT	70	24	Worsening of symptoms (n =9).
		Passive control	70	4	NI
Innes et al [555]	2018	Mindful psychotherapy	11	0	
		Relaxation	11	0	
Jones et al [556]	2012	Mind-body exercise	51	0	
		Education	48	0	
Kilic et al [558] *	2021	Relaxation	37	1	Discontinued intervention due to psychological problems (n =1).
Lai et al [559]	2014	Physical agents	24	0	
		Inert treatment	24	0	
Latocha et al [561]	2022	CBT	31	1	Discontinued intervention due to increase stress and anxiety (n =1).
		Passive control	31	1	Discontinued intervention due to knee pain (n =1).
Lauche et al [562]	2016	Physical agents	47	7	Increased pain (n =2) and acute torticollis (n =5).
		Inert treatment	48	1	Increased pain (n =1).
		Passive control	46	0	
Lee et al [563] *	2022	Inert treatment	29	1	Discontinued intervention due to discomfort (n =1).
Lin et al [564]	2022	Non-invasive brain stimulation	18	13	Stinging (n =3), scalp pain (n =2), itch (n =2), drowsiness (n =2), headache (n =1), burning sensation (n =1), difficulty concentrating (n =1), and other (n =1).
		Inert treatment	17	10	Scalp pain (n =2), itch (n =2), other (n =2), neck pain (n =1), stinging (n =1), drowsiness (n =1), and burning sensation (n =1).

Liu et al [565]	2012	Mind-body exercise	8	0	
		Inert treatment	6	0	
Loeppenthin et al [566]	2022	Exercise	17	0	
		Passive control	21	0	
Lu et al [567]	2017	Mind-body exercise	23	0	
		Education	23	0	
Lumley et al [568]	2017	CBT	67	0	
		Education	68	0	
Lynch et al [569]	2012	Mind-body exercise	53	2	Increased shoulder pain (n =1) and episode of plantar fasciitis (n =1).
		Passive control	47	0	
Maddali et al [571]	2016	Mind-body exercise	22	0	
		Education	22	0	
Maestu et al [572]	2013	Non-invasive brain stimulation	28	0	
		Inert treatment	28	0	
McCurry et al [479]	2022	CBT	139	37	NI
		Education	154	31	NI
McKenna et al [574]	2021	Exercise	10	3	Musculoskeletal pain (n =3).
		Education	10	0	
Mhalla et al [474]	2011	Non-invasive brain stimulation	20	7	Discontinued intervention due to headache (n =1), transient headache (n =5), and transient dizziness (n =1).
		Inert treatment	20	6	Discontinued intervention due to headache (n =2), and transient headache (n =4).
Murphy et al [577]	2019	Acupuncture	37	4	Bruising (n =1), skin break (n =1), muscle spasm (n =1), and headache (n =1).
		Passive control	23	0	
Nelson et al [579]	2010	Non-invasive brain stimulation	21	0	
		Inert treatment	21	0	
Passard et al [582]	2007	Non-invasive brain stimulation	15	5	Headache (n =4) and nausea (n =1).
		Inert treatment	15	8	Headache (n =5), transient tinnitus (n =2) and dizziness (n =1).
Peng et al [583]	2022	Exercise	51	2	Low back pain and other pain.
		Physical agents	50	4	
Redondo et al [586] *	2004	Exercise	19	1	Discontinued intervention due to concomitant illnesses (n =1).
Roizenblatt et al [588]	2007	Non-invasive brain stimulation	22	8	Sleeping (n =4) and headache (n =4).
		Inert treatment	10	3	Sleeping (n =1) and headache (n =2).

Samartin-Veiga et al [589]	2022	Non-invasive brain stimulation	91	6	Discontinued intervention due to adverse effects (n =6).
		Inert treatment	28	3	Discontinued intervention due to adverse effects (n =3).
Schmidt et al [593]	2011	Mindful psychotherapy	12	0	
		Passive control	12	0	
Smith et al [595] *	2015	CBT	50	3	A rash from wearing the actigraphy and tenderness (n =3).
		Inert treatment	50		
Song et al [597]	2022	Mind-body exercise	20	0	
		Education	20	0	
Stegner et al [598]	2021	Exercise	28	0	
		Passive control	26	0	
Wang et al [604]	2018	Mind-body exercise	151	8	Most were minor musculoskeletal events.
		Exercise	75	4	
Ward et al [605]	2018	Mind-body exercise	13	6	Musculoskeletal pain (n =5) and nausea (n =1).
		Passive control	13	0	
Wong et al [608]	2018	Mind-body exercise	18	0	
		Passive control	19	1	Shingles (n =1).

Abbreviations: CBT: Cognitive Behavioral Therapy, NI: No Information.
Footnote: *Studies were not included in quantitative analysis due to no sufficient information for effect size.

Appendix 27. Sensitivity analyses for sleep quality in Chapter 7

Table S5.48. Sensitivity analyses with removing studies with high risk of bias

a) At immediate post-intervention

CBT												
0.06 (-0.70,0.81)	**Non-invasive brain stimulation**											
0.13 (-0.40,0.66)	0.08 (-0.68,0.83)	**Exercise**										
0.18 (-0.54,0.90)	0.12 (-0.66,0.91)	0.05 (-0.61,0.70)	**Physical agents**									
0.20 (-0.35,0.74)	0.14 (-0.65,0.93)	0.07 (-0.40,0.53)	0.02 (-0.71,0.75)	**Mind-body exercise**								
0.20 (-0.37,0.77)	0.14 (-0.66,0.95)	0.07 (-0.51,0.64)	0.02 (-0.75,0.79)	0.00 (-0.61,0.62)	**Mindful psychotherapy**							
0.31 (-0.47,1.10)	0.25 (-0.69,1.20)	0.18 (-0.59,0.95)	0.13 (-0.79,1.05)	0.11 (-0.64,0.86)	0.11 (-0.70,0.93)	**Manual therapy**						
0.39 (-0.27,1.05)	0.34 (-0.46,1.13)	0.26 (-0.40,0.92)	0.21 (-0.58,1.00)	0.19 (-0.48,0.87)	0.19 (-0.50,0.88)	0.08 (-0.66,0.82)	**Relaxation**					
0.55 (-0.39,1.49)	0.49 (-0.49,1.47)	0.41 (-0.53,1.36)	0.36 (-0.64,1.37)	0.35 (-0.62,1.31)	0.34 (-0.65,1.34)	0.23 (-0.88,1.34)	0.15 (-0.84,1.15)	**Nutritional therapy**				
0.80 (-0.66,2.25)	0.74 (-0.82,2.30)	0.66 (-0.79,2.12)	0.62 (-0.92,2.15)	0.60 (-0.86,2.05)	0.60 (-0.87,2.07)	0.49 (-1.06,2.03)	0.41 (-1.10,1.91)	0.25 (-1.42,1.92)	**Acupuncture**			
0.65 (0.20,1.11)	0.59 (-0.18,1.37)	0.52 (0.02,1.02)	0.47 (-0.26,1.20)	0.45 (-0.03,0.94)	0.45 (-0.16,1.06)	0.34 (-0.44,1.12)	0.26 (-0.39,0.91)	0.11 (-0.81,1.02)	-0.15 (-1.61,1.32)	**Education**		
0.74 (0.17,1.31)	0.68 (0.18,1.18)	0.61 (0.03,1.18)	0.56 (-0.05,1.16)	0.54 (-0.08,1.16)	0.54 (-0.10,1.17)	0.43 (-0.38,1.23)	0.35 (-0.27,0.96)	0.19 (-0.65,1.04)	-0.06 (-1.54,1.42)	0.09 (-0.51,0.68)	**Inert treatment**	
0.89 (0.45,1.33)	**0.83 (0.11,1.55)**	**0.75 (0.32,1.19)**	**0.71 (0.04,1.37)**	**0.69 (0.24,1.13)**	**0.69 (0.19,1.18)**	0.58 (-0.12,1.27)	0.50 (-0.09,1.08)	0.34 (-0.58,1.27)	0.09 (-1.30,1.48)	0.24 (-0.23,0.70)	0.15 (-0.37,0.67)	**Passive control**

b) At short-term follow-up

CBT									
-0.03 (-2.33,2.26)	**Mind-body exercise**								
0.25 (-1.66,2.17)	0.29 (-2.71,3.28)	**Non-invasive brain stimulation**							
0.26 (-2.37,2.89)	0.29 (-1.00,1.58)	0.00 (-3.25,3.26)	**Exercise**						
0.30 (-2.64,3.24)	0.33 (-1.50,2.16)	0.05 (-3.46,3.55)	0.04 (-1.26,1.34)	**Physical agents**					
0.37 (-0.93,1.68)	0.40 (-2.24,3.05)	0.12 (-1.29,1.53)	0.11 (-2.82,3.05)	0.07 (-3.14,3.28)	**Inert treatment**				
0.55 (-0.75,1.86)	0.58 (-1.31,2.48)	0.30 (-2.02,2.62)	0.29 (-1.99,2.58)	0.25 (-2.38,2.88)	0.18 (-1.66,2.02)	**Education**			
0.81 (-1.45,3.06)	0.84 (-2.38,4.06)	0.55 (-1.76,2.87)	0.55 (-2.92,4.02)	0.51 (-3.19,4.21)	0.44 (-1.40,2.27)	0.26 (-2.35,2.86)	**Nutritional therapy**		
2.81 (1.04,4.57)	2.84 (-0.06,5.73)	2.55 (-0.06,5.16)	2.55 (-0.62,5.72)	2.50 (-0.92,5.93)	**2.43 (0.24,4.63)**	**2.25 (0.06,4.45)**	2.00 (-0.87,4.86)	**Mindful psychotherapy**	
3.20 (1.79,4.61)	**3.23 (0.54,5.93)**	**2.95 (0.57,5.33)**	2.94 (-0.04,5.93)	2.90 (-0.35,6.16)	**2.83 (0.91,4.75)**	**2.65 (0.73,4.57)**	2.39 (-0.26,5.05)	0.40 (-0.67,1.46)	**Passive control**

c) At mid-term follow-up

CBT								
-0.01 (-2.16,2.14)	**Mind-body exercise**							
0.11 (-1.93,2.14)	0.12 (-1.55,1.79)	**Exercise**						
0.09 (-3.14,3.32)	0.11 (-3.38,3.60)	-0.01 (-3.27,3.24)	**Non-invasive brain stimulation**					
0.15 (-1.37,1.68)	0.17 (-2.13,2.47)	0.05 (-2.00,2.09)	0.06 (-3.21,3.33)	**Mindful psychotherapy**				
0.29 (-1.58,2.16)	0.30 (-1.99,2.60)	0.18 (-1.73,2.10)	0.20 (-2.44,2.83)	0.14 (-1.81,2.08)	**Inert treatment**			
0.31 (-0.95,1.56)	0.32 (-1.77,2.41)	0.20 (-1.93,2.33)	0.21 (-3.17,3.60)	0.15 (-1.74,2.04)	0.02 (-2.11,2.14)	**Education**		
0.45 (-2.07,2.96)	0.46 (-2.10,3.01)	0.34 (-1.75,2.42)	0.35 (-3.01,3.71)	0.29 (-2.26,2.84)	0.15 (-1.93,2.24)	0.14 (-2.52,2.79)	**Physical agents**	
1.75 (0.44,3.07)	1.77 (-0.70,4.23)	1.65 (-0.70,3.99)	1.66 (-1.78,5.10)	1.60 (-0.21,3.41)	1.46 (-0.75,3.67)	1.45 (-0.36,3.25)	1.31 (-1.47,4.09)	**Passive control**

Table S5.49. Sensitivity analyses with removing studies with sample size less than 20

a) At immediate post-intervention

Relaxation													
0.22 (-0.78,1.23)	**Non-invasive brain stimulation**												
0.31 (-0.39,1.01)	0.09 (-0.82,1.00)	**CBT**											
0.36 (-0.60,1.31)	0.13 (-0.84,1.11)	0.04 (-0.81,0.90)	**Acupuncture**										
0.34 (-0.66,1.35)	0.12 (-1.05,1.29)	0.03 (-0.86,0.92)	-0.01 (-1.13,1.10)	**Manual therapy**									
0.44 (-0.28,1.15)	0.21 (-0.72,1.15)	0.12 (-0.43,0.68)	0.08 (-0.80,0.96)	0.09 (-0.83,1.02)	**Mind-body exercise**								
0.48 (-0.19,1.16)	0.26 (-0.64,1.17)	0.17 (-0.37,0.72)	0.13 (-0.72,0.98)	0.14 (-0.77,1.05)	0.05 (-0.39,0.49)	**Exercise**							
0.60 (-0.18,1.38)	0.38 (-0.58,1.34)	0.29 (-0.29,0.87)	0.25 (-0.66,1.15)	0.26 (-0.69,1.21)	0.17 (-0.49,0.82)	0.12 (-0.49,0.73)	**Mindful psychotherapy**						
0.77 (-0.09,1.63)	0.54 (-0.40,1.49)	0.45 (-0.30,1.20)	0.41 (-0.51,1.33)	0.42 (-0.62,1.47)	0.33 (-0.41,1.08)	0.28 (-0.39,0.95)	0.16 (-0.64,0.97)	**Physical agents**					
0.82 (-0.20,1.85)	0.60 (-0.46,1.66)	0.51 (-0.41,1.43)	0.47 (-0.58,1.52)	0.48 (-0.71,1.68)	0.39 (-0.55,1.33)	0.34 (-0.59,1.26)	0.22 (-0.77,1.21)	0.06 (-0.94,1.06)	**Nutritional therapy**				
0.86 (0.16,1.56)	0.64 (-0.30,1.57)	**0.55 (0.07,1.02)**	0.50 (-0.38,1.39)	0.52 (-0.42,1.46)	0.42 (-0.08,0.93)	0.37 (-0.16,0.91)	0.26 (-0.41,0.92)	0.09 (-0.68,0.86)	0.04 (-0.86,0.93)	**Education**			
0.92 (0.18,1.66)	**0.70 (0.02,1.38)**	**0.61 (0.01,1.21)**	0.57 (-0.13,1.26)	0.58 (-0.38,1.53)	0.49 (-0.16,1.13)	0.44 (-0.16,1.03)	0.32 (-0.36,1.00)	0.16 (-0.49,0.81)	0.10 (-0.71,0.91)	0.06 (-0.58,0.70)	**Inert treatment**		
1.08 (0.46,1.71)	0.86 (-0.01,1.74)	**0.77 (0.35,1.20)**	0.73 (-0.07,1.52)	0.74 (-0.04,1.53)	**0.65 (0.16,1.14)**	**0.60 (0.14,1.06)**	0.48 (-0.05,1.01)	0.32 (-0.37,1.01)	0.26 (-0.64,1.16)	0.23 (-0.29,0.74)	0.16 (-0.38,0.71)	**Passive control**	
1.44 (-0.02,2.89)	1.21 (-0.36,2.79)	1.12 (-0.26,2.50)	1.08 (-0.45,2.61)	1.09 (-0.44,2.62)	1.00 (-0.40,2.40)	0.95 (-0.44,2.34)	0.83 (-0.58,2.25)	0.67 (-0.81,2.15)	0.61 (-0.98,2.20)	0.58 (-0.83,1.99)	0.51 (-0.91,1.94)	0.35 (-0.96,1.66)	**Assistive technique**

b) At short-term follow-up

CBT									
-0.13 (-3.22,2.96)	**Acupuncture**								
0.37 (-1.41,2.16)	0.50 (-2.02,3.03)	**Inert treatment**							
0.67 (-1.46,2.80)	0.80 (-2.96,4.55)	0.29 (-2.48,3.07)	**Mind-body exercise**						
0.78 (-0.84,2.40)	0.91 (-2.58,4.40)	0.41 (-2.00,2.82)	0.11 (-1.93,2.16)	**Education**					
0.81 (-2.27,3.89)	0.94 (-2.63,4.50)	0.44 (-2.08,2.95)	0.14 (-3.61,3.89)	0.03 (-3.46,3.51)	**Nutritional therapy**				
0.96 (-1.62,3.53)	1.09 (-2.94,5.11)	0.58 (-2.55,3.71)	0.29 (-1.16,1.73)	0.17 (-2.33,2.68)	0.15 (-3.87,4.16)	**Exercise**			
1.00 (-2.13,4.13)	1.13 (-3.27,5.53)	0.63 (-2.97,4.23)	0.33 (-1.96,2.62)	0.22 (-2.86,3.29)	0.19 (-4.20,4.58)	0.04 (-1.74,1.82)	**Physical agents**		
1.75 (-0.51,4.00)	1.87 (-1.95,5.70)	1.37 (-1.51,4.25)	1.08 (-1.62,3.77)	0.96 (-1.67,3.60)	0.94 (-2.89,4.76)	0.79 (-2.27,3.85)	0.75 (-2.79,4.28)	**Mindful psychotherapy**	
1.93 (0.53,3.34)	2.06 (-1.33,5.45)	1.56 (-0.71,3.83)	1.26 (-0.76,3.29)	1.15 (-0.80,3.10)	1.12 (-2.26,4.51)	0.98 (-1.52,3.47)	0.93 (-2.13,3.99)	0.19 (-1.58,1.96)	**Passive control**

c) At mid-term follow-up

CBT								
0.26 (-1.23,1.74)	**Mindful psychotherapy**							
0.37 (-0.99,1.73)	0.11 (-1.83,2.05)	**Education**						
0.35 (-2.78,3.49)	0.10 (-3.11,3.30)	-0.01 (-3.37,3.34)	**Non-invasive brain stimulation**					
0.50 (-1.19,2.20)	0.25 (-1.73,2.22)	0.13 (-1.69,1.96)	0.15 (-3.18,3.47)	**Mind-body exercise**				
0.55 (-1.21,2.31)	0.29 (-1.59,2.18)	0.18 (-1.95,2.31)	0.20 (-2.40,2.79)	0.05 (-2.03,2.13)	**Inert treatment**			
0.68 (-0.96,2.31)	0.42 (-1.35,2.19)	0.31 (-1.62,2.23)	0.32 (-2.82,3.46)	0.17 (-1.33,1.67)	0.13 (-1.65,1.90)	**Exercise**		
0.86 (-1.47,3.19)	0.60 (-1.82,3.03)	0.49 (-2.09,3.07)	0.51 (-2.79,3.80)	0.36 (-2.06,2.77)	0.31 (-1.72,2.34)	0.18 (-1.84,2.21)	**Physical agents**	
1.50 (0.32,2.68)	1.24 (-0.38,2.87)	1.13 (-0.56,2.82)	1.15 (-2.07,4.36)	1.00 (-0.64,2.63)	0.95 (-0.95,2.85)	0.82 (-0.75,2.40)	0.64 (-1.72,3.00)	**Passive control**

Abbreviation: CBT: Cognitive Behavioral Therapy.

Footnote: Results are presented as standardized mean difference and 95% confidence intervals. For each comparison (column vs. row) a difference > 0 indicates the intervention in the column is superior to the comparator in the row. Numbers in bold represent statistically significant results.

Appendix 28. Meta-regression in Chapter 7

Table S5.50. Meta-regression for sleep quality

Variable	Immediate post-intervention		Short-term		Mid-term		Long-term	
	Coef. (SE)	*P*	Coef. (SE)	*P*	Coef. (SE)	*P*	Coef. (SE)	*P*
Sample size	0.000 (0.006)	0.99	0.025 (0.028)	0.40	0.019 (0.014)	0.18	-0.133 (0.095)	0.26
Age	-0.002 (0.037)	0.96	0.088 (0.151)	0.57	-0.041 (0.127)	0.75	1.992 (1.525)	0.28
Percentage of female	0.038 (0.019)	0.05	0.019 (0.063)	0.77	0.014 (0.054)	0.80	0.124 (0.160)	0.58
Baseline sleep quality	-0.030 (0.031)	0.32	-0.094 (0.076)	0.24	-0.104 (0.091)	0.27	0.095 (0.208)	0.68
Baseline pain severity	0.032 (0.033)	0.33	0.019 (0.085)	0.83	0.062 (0.097)	0.53	0.375 (0.328)	0.34
Treatment length	-0.050 (0.073)	0.49	-0.217 (0.225)	0.36	-0.109 (0.199)	0.59	1.118 (1.093)	0.38

Appendix 29. Grading the evidence of the network meta-analysis in Chapter 7

We used the CINeMA (Confidence in Network Meta-Analysis) framework, implemented in the web application CINeMA (https://cinema.ispm.unibe.ch/), to assess the certainty of evidence for sleep quality [445, 446]. The CINeMA framework consists of six domains that affect the level of evidence in the estimates of NMA: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.

To evaluate each network estimate, we used the following criteria:

(1) Within-study bias: We assessed overall risk of bias using the Cochrane risk of bias tool 2. Within-study bias for each pairwise comparison was classified as “no concerns”, “some concerns”, or “major concerns” based on the weighted average overall risk of bias according to the contribution matrix.

(2) Reporting bias: We used comparison-adjusted funnel plots and Egger test results to assess publication bias. Our network did not show any publication bias, and we conducted a comprehensive search across seven databases. We assumed as “no concerns” for reporting bias. We assumed “some concerns” for long-term sleep quality due to the unavailability of comparison-adjusted funnel plots with less than 10 studies.

(3) Indirectness: We evaluated whether populations, interventions, outcomes, and study settings represented the specific research questions. We used the PICOs framework to develop inclusion and exclusion criteria. We found no clear evidence of violations of the transitivity assumption, and meta-regression showed that potential modifiers did not significantly impact the primary results. Therefore, these characteristics were directly relevant to the research questions, and indirectness was not downgraded.

(4) Imprecision: We set a cutoff threshold of SMD 0.5 for clinical effectiveness [614] and assessed precision using treatment effects included in the 95% confidence interval relative to potentially clinically important differences for each pairwise comparison.

(5) Heterogeneity: We considered heterogeneity based on the relationship between the 95% confidence intervals (CI) and the 95% prediction intervals (PrI) with the clinically important differences defined above in the domain of imprecision.

(6) Incoherence: We used the design-by-treatment model and did not detect any global inconsistency in each NMA ($p>0.10$). Only direct evidence or indirect evidence was rated as “no concerns”. The mixed estimate (when both direct and indirect evidence was available) was downgraded when the results of local node side-splitting showed important inconsistency ($p<0.10$).

We classified the overall judgment on the confidence in the NMA estimate for each comparison as "very low," "low," "moderate," and "high." The starting point for certainty was high, and it could be downgraded to one level for a rating of "some concerns" and two levels for a rating of "major concerns." It is recommended to consider judgments on different domains jointly rather than in isolation, as imprecision, incoherence, and heterogeneity are interconnected [446].

Table S5.51. CINEMA Assessments for Sleep quality

a) At immediate post-intervention

Comparison	N of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Acupuncture:Inert treatment	3	Major concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Very low
Acupuncture:Passive control	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Assistive technique:Inert treatment	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Assistive technique:Passive control	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
CBT:Education	7	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
CBT:Exercise	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
CBT:Inert treatment	2	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
CBT:Mindful psychotherapy	3	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
CBT:Passive control	13	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Education:Exercise	3	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Education:Mind-body exercise	4	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Education:Nutritional therapy	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Relaxation	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Education:Passive control	2	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Exercise:Inert treatment	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Exercise:Mind-body exercise	7	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Exercise:Mindful psychotherapy	2	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low

Exercise:Physical agents	3	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Exercise:Relaxation	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Exercise:Passive control	6	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Inert treatment:Manual therapy	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Inert treatment:Mind-body exercise	2	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Inert treatment:Mindful psychotherapy	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Inert treatment:Non-invasive brain stimulation	11	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Inert treatment:Nutritional therapy	3	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Inert treatment:Physical agents	6	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Inert treatment:Relaxation	3	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Low
Inert treatment:Passive control	2	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Manual therapy:Mind-body exercise	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Manual therapy:Relaxation	2	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Manual therapy:Passive control	4	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Mind-body exercise:Passive control	7	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Mindful psychotherapy:Relaxation	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Mindful psychotherapy:Passive control	6	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Physical agents:Passive control	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Relaxation:Passive control	3	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Low

Acupuncture:Assistive technique	0	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Very low
Acupuncture:CBT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Education	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Acupuncture:Exercise	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Manual therapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Mind-body exercise	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Mindful psychotherapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Nutritional therapy	0	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Very low
Acupuncture:Physical agents	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Relaxation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Assistive technique:CBT	0	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Very low
Assistive technique:Education	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Assistive technique:Exercise	0	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Very low
Assistive technique:Manual therapy	0	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Very low
Assistive technique:Mind-body exercise	0	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Very low
Assistive technique:Mindful psychotherapy	0	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Very low
Assistive technique:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Assistive technique:Nutritional therapy	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low

Assistive technique:Physical agents	0	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Very low
Assistive technique:Relaxation	0	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Very low
CBT:Manual therapy	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
CBT:Mind-body exercise	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
CBT:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
CBT:Nutritional therapy	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
CBT:Physical agents	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
CBT:Relaxation	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Education:Inert treatment	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Education:Manual therapy	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Education:Mindful psychotherapy	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Education:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Education:Physical agents	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Exercise:Manual therapy	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Exercise:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Exercise:Nutritional therapy	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Manual therapy:Mindful psychotherapy	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Manual therapy:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Manual therapy:Nutritional therapy	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low

Manual therapy:Physical agents	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Mind-body exercise:Mindful psychotherapy	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Mind-body exercise:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Mind-body exercise:Nutritional therapy	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Mind-body exercise:Physical agents	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Mind-body exercise:Relaxation	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Mindful psychotherapy:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Mindful psychotherapy:Nutritional therapy	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Mindful psychotherapy:Physical agents	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Non-invasive brain stimulation:Nutritional therapy	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Non-invasive brain stimulation:Physical agents	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Non-invasive brain stimulation:Relaxation	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Non-invasive brain stimulation:Passive control	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Nutritional therapy:Physical agents	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Nutritional therapy:Relaxation	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Nutritional therapy:Passive control	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Physical agents:Relaxation	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low

b) At short-term follow-up

Comparison	N of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Acupuncture:Inert treatment	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
CBT:Education	2	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
CBT:Inert treatment	2	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
CBT:Mindful psychotherapy	1	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Very low
CBT:Passive control	4	Major concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Very low
Education:Mind-body exercise	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Mind-body exercise	3	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Exercise:Physical agents	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Inert treatment:Non-invasive brain stimulation	3	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Inert treatment:Nutritional therapy	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Inert treatment:Physical agents	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Mind-body exercise:Passive control	1	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Mindful psychotherapy:Passive control	4	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Acupuncture:CBT	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Education	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Exercise	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Mind-body exercise	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low

Acupuncture:Mindful psychotherapy	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Non-invasive brain stimulation	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Nutritional therapy	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Physical agents	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Passive control	0	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
CBT:Exercise	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
CBT:Mind-body exercise	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
CBT:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
CBT:Nutritional therapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
CBT:Physical agents	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Exercise	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Inert treatment	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Mindful psychotherapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Nutritional therapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Physical agents	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Passive control	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Exercise:Inert treatment	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Mindful psychotherapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low

Exercise:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Nutritional therapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Passive control	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Inert treatment:Mind-body exercise	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Inert treatment:Mindful psychotherapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Inert treatment:Passive control	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Mind-body exercise:Mindful psychotherapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Mind-body exercise:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Mind-body exercise:Nutritional therapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Mind-body exercise:Physical agents	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Mindful psychotherapy:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Mindful psychotherapy:Nutritional therapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Mindful psychotherapy:Physical agents	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Non-invasive brain stimulation:Nutritional therapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Non-invasive brain stimulation:Physical agents	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Non-invasive brain stimulation:Passive control	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Nutritional therapy:Physical agents	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Nutritional therapy:Passive control	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low

Physical agents:Passive control	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low

c) At mid-term follow-up

Comparison	N of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
CBT:Education	5	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
CBT:Exercise	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
CBT:Inert treatment	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
CBT:Mindful psychotherapy	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
CBT:Passive control	6	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
Education:Mind-body exercise	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Passive control	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Exercise:Inert treatment	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Mind-body exercise	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Mindful psychotherapy	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Physical agents	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Passive control	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low
Inert treatment:Mindful psychotherapy	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Inert treatment:Non-invasive brain stimulation	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Inert treatment:Physical agents	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Mind-body exercise:Passive control	1	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Very low

Mindful psychotherapy:Passive control	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
CBT:Mind-body exercise	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
CBT:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
CBT:Physical agents	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Education:Exercise	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Inert treatment	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Mindful psychotherapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Physical agents	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Inert treatment:Mind-body exercise	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Inert treatment:Passive control	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Mind-body exercise:Mindful psychotherapy	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Mind-body exercise:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Mind-body exercise:Physical agents	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Mindful psychotherapy:Non-invasive brain stimulation	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Mindful psychotherapy:Physical agents	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
Non-invasive brain stimulation:Physical agents	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low

Non-invasive brain stimulation:Passive control	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Physical agents:Passive control	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low

d) At long-term follow-up

Comparison	N of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
CBT:Education	1	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Very low
CBT:Exercise	1	Major concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Inert treatment	1	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low
Exercise:Mind-body exercise	1	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low
Exercise:Mindful psychotherapy	2	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Very low
Exercise:Passive control	2	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low
Inert treatment:Mindful psychotherapy	1	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Very low
Mindful psychotherapy:Passive control	1	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low
CBT:Inert treatment	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low
CBT:Mind-body exercise	0	Major concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low
CBT:Mindful psychotherapy	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low
CBT:Passive control	0	Major concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Exercise	0	Major concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Very low
Education:Inert treatment	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low
Education:Mind-body exercise	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Very low
Education:Mindful psychotherapy	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low
Education:Passive control	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low

Inert treatment:Mind-body exercise	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low
Inert treatment:Passive control	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low
Mind-body exercise:Mindful psychotherapy	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low
Mind-body exercise:Passive control	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low

Appendix 30. Adverse events of rTMS in Chapter 8

Table S6.52. Adverse events during treatments

	Sham-rTMS	M1-rTMS	DLPFC-rTMS
Headache	1 (2)	2 (2)	3 (6)
Dizziness	-	2 (5)	-
Scalp pain	1 (2)	-	1 (2)
Nocturnal arousal	-	1 (4)	-
Burning sensation	1 (3)	-	-
Total adverse events	3 (7)	5 (11)	4 (8)

Abbreviation: DLPFC: Dorsolateral prefrontal cortex; M1: Primary motor cortex; rTMS: Repetitive transcranial magnetic stimulation.
Footnote: Values are presented as the number of participants and the number of adverse events (number in the brackets).

Appendix 31. Exploratory association between outcome measures in Chapter 8

Table S6.53. Association analyses among clinical outcomes

	NPRS post	ISI post	WASO post	CPM post	TSP post	NPRS follow-up	ISI follow-up
NPRS post	-	**r=0.51, p=0.002**	r=0.23, p=0.178	**r=-0.46, p=0.005**	r=0.17, p=0.326	-	-
ISI post	**r=0.51, p=0.002**	-	r=0.32, p=0.054	r=-0.05, p=0.777	r=-0.03, p=0.847	-	-
WASO post	r=0.23, p=0.178	r=0.32, p=0.054	-	r=-0.31, p=0.067	r=0.08, p=0.646	-	-
CPM post	**r=-0.46, p=0.005**	r=-0.05, p=0.777	r=-0.31, p=0.067	-	**r=-0.41, p=0.012**	-	-
TSP post	r=0.17, p=0.326	r=-0.03, p=0.847	r=0.08, p=0.646	**r=-0.41, p=0.012**	-	-	-
NPRS follow-up	-	-	-	-	-	-	**r=0.38, p=0.022**
ISI follow-up	-	-	-	-	-	**r=0.38, p=0.022**	-

Abbreviation: CPM: conditioned pain modulation; ISI: Insomnia Severity Index; NPRS: 11-point Numerical Pain Rating Scale; TSP: Temporal summation of pain; WASO: Wake after sleep onset measured by Actigraphy

Footnote: P value was calculated by Pearson's correlation. The p-value in bold indicates a statistically significant correlation ($p < 0.05$).

References

[1] James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392(10159):1789-858.
[2] Cohen S, Vase L, Hooten W. Chronic pain: an update on burden, best practices, and new advances. Lancet (London, England). 2021;397(10289):2082-97. doi: 10.1016/s0140-6736(21)00393-7. PubMed PMID: 34062143.
[3] Licciardone JC. The epidemiology and medical management of low back pain during ambulatory medical care visits in the United States. Osteopathic Medicine and Primary Care. 2008;2(1):1-17.
[4] Mills SE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. British journal of anaesthesia. 2019;123(2):e273-e83.
[5] Aaron RV, Ravyts SG, Carnahan ND, Bhattiprolu K, Harte N, McCaulley CC, et al. Prevalence of Depression and Anxiety Among Adults With Chronic Pain: A Systematic Review and Meta-Analysis. JAMA Network Open. 2025;8(3):e250268-e. doi: 10.1001/jamanetworkopen.2025.0268.
[6] Yong RJ, Mullins PM, Bhattacharyya N. Prevalence of chronic pain among adults in the United States. Pain. 2022;163(2):e328-e32.
[7] Breivik H, Eisenberg E, O'Brien T. The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care. BMC public health. 2013;13:1-14.
[8] Sun Y, Laksono I, Selvanathan J, Saripella A, Nagappa M, Pham C, et al. Prevalence of sleep disturbances in patients with chronic non-cancer pain: A systematic review and meta-analysis. Sleep medicine reviews. 2021;57:101467. doi: 10.1016/j.smrv.2021.101467. PubMed PMID: 33827029.
[9] Generaal E, Vogelzangs N, Penninx BW, Dekker J. Insomnia, sleep duration, depressive symptoms, and the onset of chronic multisite musculoskeletal pain. Sleep. 2017;40(1):zsw030.
[10] Bilterys T, Siffain C, De Maeyer I, Van Looveren E, Mairesse O, Nijs J, et al. Associates of Insomnia in People with Chronic Spinal Pain: A Systematic Review and Meta-Analysis. Journal of clinical medicine. 2021;10(14). doi: 10.3390/jcm10143175. PubMed PMID: 34300341.
[11] Van Looveren E, Bilterys T, Munneke W, Cagnie B, Ickmans K, Mairesse O, et al. The Association between Sleep and Chronic Spinal Pain: A Systematic Review from the Last Decade. Journal of Clinical Medicine. 2021;10(17). doi: 10.3390/jcm10173836. PubMed PMID: WOS:000694313900001.
[12] Chang JR, Kwan RLC, Sun ER, Li SX, Liang P, Liu JQJ, et al. Differential pain perception among females with or without nonspecific chronic low back pain and comorbid insomnia: a quantitative sensory testing analysis. PAIN. 2025. doi: 10.1097/j.pain.0000000000003591. PubMed PMID: 00006396-990000000-00863.
[13] Rabey M, Slater H, O'Sullivan P, Beales D, Smith A. Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: a cluster analysis. Pain. 2015;156(10):1874-84.
[14] Kaila-Kangas L, Kivimäki M, Hämä M, Riihimäki H, Luukkonen R, Kirjonen J, et al. Sleep disturbances as predictors of hospitalization for back disorders-a 28-year follow-up of industrial employees. Spine (03622436). 2006;31(1):51-6. PubMed PMID: 106400671. Language: English. Entry Date: 20060224. Revision Date: 20190819. Publication Type: journal article.
[15] Babiloni AH, De Koninck BP, Beetz G, De Beaumont L, Martel MO, Lavigne GJ. Sleep and pain: recent insights, mechanisms, and future directions in the investigation of this relationship. Journal of neural transmission. 2020;127(4):647-60.
[16] Haack M, Simpson N, Sethna N, Kaur S, Mullington J. Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2020;45(1):205-16. doi: 10.1038/s41386-019-0439-z. PubMed PMID: 31207606.
[17] Herrero Babiloni A, Beetz G, Tang NKY, Heinzer R, Nijs J, Martel MO, et al. Towards the endotyping of the sleep-pain interaction: a topical review on multitarget strategies based on phenotypic vulnerabilities and

putative pathways. Pain. 2021;162(5):1281-8. Epub 2020/10/27. doi: 10.1097/j.pain.0000000000002124. PubMed PMID: 33105436.
[18] Selvanathan J, Tang NK, Peng PW, Chung F. Sleep and pain: relationship, mechanisms, and managing sleep disturbance in the chronic pain population. International Anesthesiology Clinics. 2022;60(2):27-34.
[19] Krause AJ, Prather AA, Wager ED, Lindquist MA, Walker MP. The Pain of Sleep Loss: A Brain Characterization in Humans. Journal of Neuroscience. 2019;39(12):2291-300. doi: 10.1523/jneurosci.2408-18.2018. PubMed PMID: WOS:000461756300011.
[20] Staffe AT, Bech MW, Clemmensen SLK, Nielsen HT, Larsen DB, Petersen KK. Total sleep deprivation increases pain sensitivity, impairs conditioned pain modulation and facilitates temporal summation of pain in healthy participants. PLoS ONE. 2019;14(12). doi: 10.1371/journal.pone.0225849.
[21] Kamiyama H, Iida T, Nishimori H, Kubo H, Uchiyama M, De Laat A, et al. Effect of sleep restriction on somatosensory sensitivity in the oro-facial area: An experimental controlled study. Journal of Oral Rehabilitation. 2019;46(4):303-9. doi: 10.1111/joor.12758. PubMed PMID: 135260230. Language: English. Entry Date: 20190315. Revision Date: 20200331. Publication Type: Article.
[22] Simpson NS, Scott-Sutherland J, Gautam S, Sethna N, Haack M. Chronic exposure to insufficient sleep alters processes of pain habituation and sensitization. Pain. 2018;159(1):33-40. doi: 10.1097/j.pain.0000000000001053.
[23] Arima T, Svensson P, Rasmussen C, Nielsen KD, Drewes AM, Arendt-Nielsen L. The relationship between selective sleep deprivation, nocturnal jaw-muscle activity and pain in healthy men. Journal of oral rehabilitation. 2001;28(2):140-8.
[24] Drewes AM, Nielsen KD, Rasmussen C, Arima T, Svensson P, Rossel P, et al. The effects of controlled delta sleep deprivation on experimental pain in healthy subjects. Journal of Musculoskeletal Pain. 2000;8(3):49-67. doi: 10.1300/J094v08n03_05.
[25] Smith MT, Remeniuk B, Finan PH, Speed TJ, Tompkins DA, Robinson M, et al. Sex differences in measures of central sensitization and pain sensitivity to experimental sleep disruption: Implications for sex differences in chronic pain. Sleep. 2019;42(2). doi: 10.1093/sleep/zsy209.
[26] Schrimpf M, Liegl G, Boeckle M, Leitner A, Geisler P, Pieh C. The effect of sleep deprivation on pain perception in healthy subjects: a meta-analysis. Sleep medicine. 2015;16(11):1313-20. doi: 10.1016/j.sleep.2015.07.022. PubMed PMID: 26498229.
[27] Chang JR, Fu S-N, Li X, Li SX, Wang X, Zhou Z, et al. The differential effects of sleep deprivation on pain perception in individuals with or without chronic pain: A systematic review and meta-analysis. Sleep Medicine Reviews. 2022:101695.
[28] Abeler K, Friborg O, Engstrøm M, Sand T, Bergvik S. Sleep characteristics in adults with and without chronic musculoskeletal pain: the role of mental distress and pain catastrophizing. Clin J Pain. 2020;36(9):707-15.
[29] Bjurstrom MF, Irwin MR. Polysomnographic characteristics in nonmalignant chronic pain populations: a review of controlled studies. Sleep medicine reviews. 2016;26:74-86.
[30] Van Someren EJ. Brain mechanisms of insomnia: new perspectives on causes and consequences. Physiological reviews. 2021;101(3):995-1046.
[31] Nijs J, George SZ, Clauw DJ, Fernández-de-las-Peñas C, Kosek E, Ickmans K, et al. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. The Lancet Rheumatology. 2021;3(5):e383-e92.
[32] Zebhauser PT, Hohn VD, Ploner M. Resting-state electroencephalography and magnetoencephalography as biomarkers of chronic pain: a systematic review. Pain. 2023;164(6):1200-21. doi: 10.1097/j.pain.0000000000002825. PubMed PMID: 00006396-202306000-00003.
[33] Schouppe S, Van Oosterwijck S, Danneels L, Van Damme S, Van Oosterwijck J. Are Functional Brain Alterations Present in Low Back Pain? A Systematic Review of EEG Studies. J Pain. 2020;21(1-2):25-43. Epub 2019/07/02. doi: 10.1016/j.jpain.2019.06.010. PubMed PMID: 31260806.
[34] Simpson N, Scott-Sutherland J, Gautam S, Sethna N, Haack M. Chronic exposure to insufficient sleep alters processes of pain habituation and sensitization. Pain. 2018;159(1):33-40. doi: 10.1097/j.pain.0000000000001053. PubMed PMID: 28891869.

[35] Kamiyama H, Iida T, Nishimori H, Kubo H, Uchiyama M, De Laat A, et al. Effect of sleep restriction on somatosensory sensitivity in the oro-facial area: An experimental controlled study. Journal of oral rehabilitation. 2019;46(4):303-9. doi: 10.1111/joor.12758. PubMed PMID: 30570153.
[36] Stroemel-Scheder C, Kundermann B, Lautenbacher S. The effects of recovery sleep on pain perception: A systematic review. Neuroscience and biobehavioral reviews. 2020;113:408-25. doi: 10.1016/j.neubiorev.2020.03.028. PubMed PMID: 32275917.
[37] Afolalu E, Ramlee F, Tang N. Effects of sleep changes on pain-related health outcomes in the general population: A systematic review of longitudinal studies with exploratory meta-analysis. Sleep medicine reviews. 2018;39:82-97. doi: 10.1016/j.smrv.2017.08.001. PubMed PMID: 29056414.
[38] Chang JR, Wang X, Lin G, Samartzis D, Pinto SM, Wong AY. Are changes in sleep quality/quantity or baseline sleep parameters related to changes in clinical outcomes in patients with nonspecific chronic low back pain?: a systematic review. Clin J Pain. 2022;38(4):292-307.
[39] Runge N, Ahmed I, Saueressig T, Perea J, Labie C, Mairesse O, et al. The bidirectional relationship between sleep problems and chronic musculoskeletal pain: a systematic review with meta-analysis. PAIN. 2024;165(11).
[40] Ho K, Ferreira P, Pinheiro M, Aquino Silva D, Miller C, Grunstein R, et al. Sleep interventions for osteoarthritis and spinal pain: a systematic review and meta-analysis of randomized controlled trials. Osteoarthritis Cartilage. 2019;27(2):196-218. doi: 10.1016/j.joca.2018.09.014. PubMed PMID: 30342087.
[41] Selvanathan J, Pham C, Nagappa M, Peng PWH, Englesakis M, Espie CA, et al. Cognitive behavioral therapy for insomnia in patients with chronic pain-A systematic review and meta-analysis of randomized controlled trials. Sleep Medicine Reviews. 2021;60. doi: 10.1016/j.smrv.2021.101460. PubMed PMID: WOS:000744231300010.
[42] Whale K, Dennis J, Wylde V, Beswick A, Gooberman-Hill R. The effectiveness of non-pharmacological sleep interventions for people with chronic pain: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2022;23(1):1-33.
[43] Tang NKY, Lereya ST, Boulton H, Miller MA, Wolke D, Cappuccio FP. Nonpharmacological Treatments of Insomnia for Long-Term Painful Conditions: A Systematic Review and Meta-analysis of Patient-Reported Outcomes in Randomized Controlled Trials. Sleep. 2015;38(11):1751-64. doi: 10.5665/sleep.5158.
[44] Bohra MH, Espie CA. Is cognitive behavioural therapy for insomnia effective in treating insomnia and pain in individuals with chronic non-malignant pain? British Journal of Pain. 2013;7(3):138-51.
[45] Craige EA, Memon AR, Belavy DL, Vincent GE, Owen PJ. Effects of non-pharmacological interventions on sleep in chronic low back pain: A systematic review and meta-analysis of randomised controlled trials. Sleep Medicine Reviews. 2023:101761.
[46] Chang JR, Cheung YK, Sharma S, Li SX, Tao RR, Lee JLC, et al. Comparative effectiveness of non-pharmacological interventions on sleep in individuals with chronic musculoskeletal pain: A systematic review with network meta-analysis. Sleep Medicine Reviews. 2023:101867.
[47] Matthews EE, Arnedt JT, McCarthy MS, Cuddihy LJ, Aloia MS. Adherence to cognitive behavioral therapy for insomnia: a systematic review. Sleep medicine reviews. 2013;17(6):453-64.
[48] Morin CM, Drake CL, Harvey AG, Krystal AD, Manber R, Riemann D, et al. Insomnia disorder. Nature reviews Disease primers. 2015;1(1):1-18.
[49] Herrero Babiloni A, Brazeau D, Jodoin M, Theis-Mahon N, Martel MO, Lavigne GJ, et al. The Impact of Sleep Disturbances on Endogenous Pain Modulation: A Systematic Review and Meta-Analysis. The Journal of Pain. 2024;25(4):875-901. doi: 10.1016/j.jpain.2023.10.023.
[50] Lefaucheur J, André-Obadia N, Antal A, Ayache S, Baeken C, Benninger D, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2014;125(11):2150-206. doi: 10.1016/j.clinph.2014.05.021. PubMed PMID: 25034472.
[51] Lefaucheur J-P, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). Clinical neurophysiology. 2020;131(2):474-528.
[52] Babiloni AH, Bellemare A, Beetz G, Vinet S-A, Martel MO, Lavigne GJ, et al. The effects of non-invasive brain stimulation on sleep disturbances among different neurological and neuropsychiatric conditions: A systematic review. Sleep Medicine Reviews. 2021;55:101381.

[53] Lanza G, Fisicaro F, Cantone M, Pennisi M, Ilaria Cosentino FI, Lanuzza B, et al. Repetitive transcranial magnetic stimulation in primary sleep disorders. Sleep Medicine Reviews. 2022:101735. doi: https://doi.org/10.1016/j.smrv.2022.101735.
[54] O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. Cochrane database of systematic reviews. 2018(3).
[55] Giannoni-Luza S, Pacheco-Barrios K, Cardenas-Rojas A, Mejia-Pando PF, Luna-Cuadros MA, Barouh JL, et al. Non-invasive motor cortex stimulation effects on quantitative sensory testing (QST) in healthy and chronic pain subjects: a systematic review and meta-analysis. Pain. 2020;161(9):1955.
[56] Cruccu G, Garcia-Larrea L, Hansson P, Keindl M, Lefaucheur JP, Paulus W, et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. European Journal of Neurology. 2016;23(10):1489-99.
[57] Sun N, He Y, Wang Z, Zou W, Liu X. The effect of repetitive transcranial magnetic stimulation for insomnia: a systematic review and meta-analysis. Sleep Med. 2021;77:226-37.
[58] Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2019;160(1):19-27.
[59] Aziz Q, Giamberardino MA, Barke A, Korwisi B, Baranowski AP, Wesselmann U, et al. The IASP classification of chronic pain for ICD-11: chronic secondary visceral pain. PAIN. 2019;160(1).
[60] Bennett MI, Kaasa S, Barke A, Korwisi B, Rief W, Treede R-D, et al. The IASP classification of chronic pain for ICD-11: chronic cancer-related pain. PAIN. 2019;160(1).
[61] Benoliel R, Svensson P, Evers S, Wang S-J, Barke A, Korwisi B, et al. The IASP classification of chronic pain for ICD-11: chronic secondary headache or orofacial pain. PAIN. 2019;160(1).
[62] Nicholas M, Vlaeyen JWS, Rief W, Barke A, Aziz Q, Benoliel R, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. PAIN. 2019;160(1):28-37. doi: 10.1097/j.pain.0000000000001390. PubMed PMID: 00006396-201901000-00004.
[63] Perrot S, Cohen M, Barke A, Korwisi B, Rief W, Treede R-D, et al. The IASP classification of chronic pain for ICD-11: chronic secondary musculoskeletal pain. PAIN. 2019;160(1):77-82. doi: 10.1097/j.pain.0000000000001389. PubMed PMID: 00006396-201901000-00010.
[64] Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain. 2019;160(1):53-9. Epub 2018/12/27. doi: 10.1097/j.pain.0000000000001365. PubMed PMID: 30586071; PubMed Central PMCID: PMCPMC6310153.
[65] Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede R-D, et al. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. PAIN. 2019;160(1).
[66] Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, et al. Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. Morbidity and Mortality Weekly Report. 2018;67(36):1001.
[67] Fayaz A, Croft P, Langford R, Donaldson L, Jones G. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ open. 2016;6(6):e010364.
[68] Yongjun Z, Tingjie Z, Xiaoqiu Y, Zhiying F, Feng Q, Guangke X, et al. A survey of chronic pain in China. Libyan Journal of Medicine. 2020;15(1).
[69] Jackson T, Thomas S, Stabile V, Han X, Shotwell M, McQueen K. Prevalence of chronic pain in low-income and middle-income countries: a systematic review and meta-analysis. The Lancet. 2015;385:S10.
[70] Mokdad AH, Ballestros K, Echko M, Glenn S, Olsen HE, Mullany E, et al. The state of US health, 1990-2016: burden of diseases, injuries, and risk factors among US states. Jama. 2018;319(14):1444-72.
[71] Gaskin DJ, Richard P. The economic costs of pain in the United States. The journal of pain. 2012;13(8):715-24.
[72] Meints S, Edwards R. Evaluating psychosocial contributions to chronic pain outcomes. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018;87:168-82.
[73] Melzack R, Casey KL. Sensory, motivational, and central control determinants of pain: a new conceptual model. The skin senses. 1968;1:423-43.
[74] Wang L-H, Ding W-Q, Sun Y-G. Spinal ascending pathways for somatosensory information processing. Trends in Neurosciences. 2022.

[75] Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell. 2009;139(2):267-84.
[76] St. John Smith E. Advances in understanding nociception and neuropathic pain. Journal of neurology. 2018;265(2):231-8.
[77] Peirs C, Seal RP. Neural circuits for pain: recent advances and current views. Science. 2016;354(6312):578-84.
[78] Dubin AE, Patapoutian A. Nociceptors: the sensors of the pain pathway. The Journal of clinical investigation. 2010;120(11):3760-72.
[79] De Ridder D, Adhia D, Vanneste S. The anatomy of pain and suffering in the brain and its clinical implications. Neuroscience & Biobehavioral Reviews. 2021;130:125-46.
[80] Steeds CE. The anatomy and physiology of pain. Surgery (Oxford). 2009;27(12):507-11.
[81] Apkarian AV, Bushnell MC, Treede R-D, Zubieta J-K. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain. 2005;9(4):463-84.
[82] Tan LL, Kuner R. Neocortical circuits in pain and pain relief. Nature Reviews Neuroscience. 2021;22(8):458-71.
[83] Xu A, Larsen B, Henn A, Baller EB, Scott JC, Sharma V, et al. Brain responses to noxious stimuli in patients with chronic pain: a systematic review and meta-analysis. JAMA network open. 2021;4(1):e2032236-e.
[84] Jensen KB, Regenbogen C, Ohse MC, Frasnelli J, Freiherr J, Lundström JN. Brain activations during pain: a neuroimaging meta-analysis of patients with pain and healthy controls. Pain. 2016;157(6):1279-86.
[85] Iannetti GD, Mouraux A. From the neuromatrix to the pain matrix (and back). Experimental brain research. 2010;205(1):1-12.
[86] Kucyi A, Davis KD. The dynamic pain connectome. Trends in neurosciences. 2015;38(2):86-95.
[87] Kucyi A, Davis KD. The neural code for pain: from single-cell electrophysiology to the dynamic pain connectome. The Neuroscientist. 2017;23(4):397-414.
[88] Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. Current opinion in supportive and palliative care. 2014;8(2):143.
[89] Fields H. State-dependent opioid control of pain. Nature Reviews Neuroscience. 2004;5(7):565-75.
[90] Linnman C, Moulton EA, Barmettler G, Becerra L, Borsook D. Neuroimaging of the periaqueductal gray: state of the field. Neuroimage. 2012;60(1):505-22.
[91] Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annual review of neuroscience. 1984;7(1):309-38.
[92] Fields H, Malick A, Burstein R. Dorsal horn projection targets of ON and OFF cells in the rostral ventromedial medulla. Journal of neurophysiology. 1995;74(4):1742-59.
[93] Barbaro NM, Heinricher MM, Fields HL. Putative pain modulating neurons in the rostral ventral medulla: reflex-related activity predicts effects of morphine. Brain research. 1986;366(1-2):203-10.
[94] Fields H, Heinricher MM. Anatomy and physiology of a nociceptive modulatory system. Philosophical Transactions of the Royal Society of London B, Biological Sciences. 1985;308(1136):361-74.
[95] Fillingim RB, Loeser JD, Baron R, Edwards RR. Assessment of chronic pain: domains, methods, and mechanisms. The journal of pain. 2016;17(9):T10-T20.
[96] Tracey I, Woolf CJ, Andrews NA. Composite pain biomarker signatures for objective assessment and effective treatment. Neuron. 2019;101(5):783-800.
[97] Rolke R, Baron R, Maier C, Tölle TR, Treede DR, Beyer A, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. Pain. 2006;123(3):231-43. doi: 10.1016/j.pain.2006.01.041.
[98] Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain. 2006;10(1):77-88.
[99] Attal N, Baron R, Bouhassira D, Drangholt M, Dyck PJ, Edwards RR, et al. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. PAIN®. 2013;154(9):1807-19.
[100] Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. The Journal of Pain. 2009;10(6):556-72.

[101] Georgopoulos V, Akin-Akinyosoye K, Zhang W, McWilliams DF, Hendrick P, Walsh DA. Quantitative Sensory Testing (QST) and predicting outcomes for musculoskeletal pain, disability and negative affect: a systematic review and meta-analysis. Pain. 2019;160(9):1920.
[102] Treede R-D. The role of quantitative sensory testing in the prediction of chronic pain. Pain. 2019;160:S66-S9.
[103] Cardoso JS, Riley 3rd JL, Glover T, Sibille KT, Bartley EJ, Goodin BR, et al. Experimental pain phenotyping in community-dwelling individuals with knee osteoarthritis. Pain. 2016;157(9):2104.
[104] Smith SM, Dworkin RH, Turk DC, Baron R, Polydefkis M, Tracey I, et al. The potential role of sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials: IMMPACT considerations. The Journal of Pain. 2017;18(7):757-77.
[105] Marcuzzi A, Dean CM, Wrigley PJ, Chakiath RJ, Hush JM. Prognostic value of quantitative sensory testing in low back pain: a systematic review of the literature. Journal of pain research. 2016;9:599.
[106] Arendt-Nielsen L, Morlion B, Perrot S, Dahan A, Dickenson A, Kress H, et al. Assessment and manifestation of central sensitisation across different chronic pain conditions. Eur J Pain. 2018;22(2):216-41. doi: 10.1002/ejp.1140. PubMed PMID: 29105941.
[107] Weaver KR, Griffioen MA, Klinedinst NJ, Galik E, Duarte AC, Colloca L, et al. Quantitative sensory testing across chronic pain conditions and use in special populations. Frontiers in Pain Research. 2022:124.
[108] Marcuzzi A, Wrigley PJ, Dean CM, Adams R, Hush JM. The long-term reliability of static and dynamic quantitative sensory testing in healthy individuals. Pain. 2017;158(7):1217-23.
[109] Uddin Z, MacDermid JC. Quantitative sensory testing in chronic musculoskeletal pain. Pain Medicine. 2016;17(9):1694-703.
[110] Arant K, Katz J, Neogi T. Quantitative sensory testing: identifying pain characteristics in patients with osteoarthritis. Osteoarthritis Cartilage. 2022;30(1):17-31.
[111] Bannister K, Hughes S. One size does not fit all: towards optimising the therapeutic potential of endogenous pain modulatory systems. PAIN. 2023;164(1):e5-e9. doi: 10.1097/j.pain.0000000000002697. PubMed PMID: 00006396-202301000-00004.
[112] den Bandt HL, Ickmans K, Leemans L, Nijs J, Voogt L. Differences in Quantitative Sensory Testing Outcomes Between Patients With Low Back Pain in Primary Care and Pain-free Controls. Clin J Pain. 2022;38(6):381-7.
[113] Neziri AY, Curatolo M, Limacher A, Nüesch E, Radanov B, Andersen OK, et al. Ranking of parameters of pain hypersensitivity according to their discriminative ability in chronic low back pain. PAIN®. 2012;153(10):2083-91.
[114] Fernandes C, Pidal-Miranda M, Samartin-Veiga N, Carrillo-de-la-Peña MT. Conditioned pain modulation as a biomarker of chronic pain: a systematic review of its concurrent validity. PAIN. 2019;160(12):2679-90. doi: 10.1097/j.pain.0000000000001664. PubMed PMID: 00006396-201912000-00003.
[115] McPhee ME, Vaegter HB, Graven-Nielsen T. Alterations in pronociceptive and antinociceptive mechanisms in patients with low back pain: a systematic review with meta-analysis. Pain. 2020;161(3):464-75.
[116] den Bandt HL, Paulis WD, Beckwée D, Ickmans K, Nijs J, Voogt L. Pain Mechanisms in Low Back Pain: A Systematic Review With Meta-analysis of Mechanical Quantitative Sensory Testing Outcomes in People With Nonspecific Low Back Pain. J Orthop Sports Phys Ther. 2019;49(10):698-715. doi: 10.2519/jospt.2019.8876.
[117] Morone NE, Karp JF, Lynch CS, Bost JE, El Khoudary SR, Weiner DK. Impact of chronic musculoskeletal pathology on older adults: a study of differences between knee OA and low back pain. Pain Medicine. 2009;10(4):693-701.
[118] Mibu A, Nishigami T, Tanaka K, Manfuku M, Yono S. Difference in the impact of central sensitization on pain-related symptoms between patients with chronic low back pain and knee osteoarthritis. Journal of Pain Research. 2019;12:1757.
[119] Blumenstiel K, Gerhardt A, Rolke R, Bieber C, Tesarz J, Friederich H-C, et al. Quantitative sensory testing profiles in chronic back pain are distinct from those in fibromyalgia. Clin J Pain. 2011;27(8):682-90.
[120] Baliki MN, Apkarian AV. Nociception, pain, negative moods, and behavior selection. Neuron. 2015;87(3):474-91.
[121] Kuner R, Flor H. Structural plasticity and reorganisation in chronic pain. Nature reviews Neuroscience. 2017;18(2):113. doi: 10.1038/nrn.2017.5. PubMed PMID: 28704354.

[122] Henn AT, Larsen B, Frahm L, Xu A, Adebimpe A, Scott JC, et al. Structural imaging studies of patients with chronic pain: an anatomical likelihood estimate meta-analysis. PAIN. 2023;164(1):e10-e24. doi: 10.1097/j.pain.0000000000002681. PubMed PMID: 00006396-202301000-00005.
[123] Ng S, Urquhart D, Fitzgerald P, Cicuttini F, Hussain S, Fitzgibbon B. The Relationship Between Structural and Functional Brain Changes and Altered Emotion and Cognition in Chronic Low Back Pain Brain Changes: A Systematic Review of MRI and fMRI Studies. Clin J Pain. 2018;34(3):237-61. doi: 10.1097/ajp.0000000000000534. PubMed PMID: 28719509.
[124] Mansour AR, Baliki MN, Huang L, Torbey S, Herrmann KM, Schnitzer TJ, et al. Brain white matter structural properties predict transition to chronic pain. PAIN®. 2013;154(10):2160-8.
[125] Vachon-Presseau E, Tétreault P, Petre B, Huang L, Berger SE, Torbey S, et al. Corticolimbic anatomical characteristics predetermine risk for chronic pain. Brain. 2016;139(7):1958-70.
[126] Bautin P, Fortier M-A, Sean M, Little G, Martel M, Descoteaux M, et al. What has brain diffusion magnetic resonance imaging taught us about chronic primary pain: a narrative review. PAIN. 2025;166(2).
[127] Friebel U, Eickhoff SB, Lotze M. Coordinate-based meta-analysis of experimentally induced and chronic persistent neuropathic pain. Neuroimage. 2011;58(4):1070-80.
[128] Ploner M, May ES. Electroencephalography and magnetoencephalography in pain research—current state and future perspectives. Pain. 2018;159(2):206-11.
[129] Davis KD. Imaging vs quantitative sensory testing to predict chronic pain treatment outcomes. Pain. 2019;160:S59-S65.
[130] Savignac C, Ocay DD, Mahdid Y, Blain-Moraes S, Ferland CE. Clinical use of electroencephalography in the assessment of acute thermal pain: a narrative review based on articles from 2009 to 2019. Clinical EEG and Neuroscience. 2022;53(2):124-32.
[131] Peng W, Tang D. Pain related cortical oscillations: methodological advances and potential applications. Frontiers in computational neuroscience. 2016;10:9.
[132] Granovsky Y, Granot M, Nir R-R, Yarnitsky D. Objective correlate of subjective pain perception by contact heat-evoked potentials. The Journal of Pain. 2008;9(1):53-63.
[133] Lenoir D, Willaert W, Coppieters I, Malfliet A, Ickmans K, Nijs J, et al. Electroencephalography during nociceptive stimulation in chronic pain patients: a systematic review. Pain Medicine. 2020;21(12):3413-27.
[134] Pinheiro E, de Queirós F, Montoya P, Santos C, do Nascimento M, Ito C, et al. Electroencephalographic Patterns in Chronic Pain: A Systematic Review of the Literature. PloS one. 2016;11(2):e0149085. doi: 10.1371/journal.pone.0149085. PubMed PMID: 26914356.
[135] Mathew J, Perez TM, Adhia DB, De Ridder D, Mani R. Is There a Difference in EEG Characteristics in Acute, Chronic, and Experimentally Induced Musculoskeletal Pain States? a Systematic Review. Clin EEG Neurosci. 2022:15500594221138292. Epub 2022/11/16. doi: 10.1177/15500594221138292. PubMed PMID: 36377346.
[136] Kane N, Acharya J, Beniczky S, Caboclo L, Finnigan S, Kaplan PW, et al. A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017. Clinical neurophysiology practice. 2017;2:170.
[137] Al-Fahoum AS, Al-Fraihat AA. Methods of EEG signal features extraction using linear analysis in frequency and time-frequency domains. International Scholarly Research Notices. 2014;2014.
[138] Li Z, Zhang L, Zhang F, Gu R, Peng W, Hu L. Demystifying signal processing techniques to extract resting-state EEG features for psychologists. Brain Science Advances. 2020;6(3):189-209.
[139] Kim JA, Davis KD. Neural oscillations: understanding a neural code of pain. The Neuroscientist. 2021;27(5):544-70.
[140] Li Z, Zhang L, Zeng Y, Zhao Q, Hu L. Gamma-Band Oscillations of Pain and Nociception: A systematic review and meta-analysis of human and rodent studies. Neuroscience & Biobehavioral Reviews. 2023:105062.
[141] Ploner M, Sorg C, Gross J. Brain rhythms of pain. Trends in cognitive sciences. 2017;21(2):100-10.
[142] Ronga I, Valentini E, Mouraux A, Iannetti G. Novelty is not enough: laser-evoked potentials are determined by stimulus saliency, not absolute novelty. Journal of Neurophysiology. 2013;109(3):692-701.
[143] Moayedi M, Liang M, Sim A, Hu L, Haggard P, Iannetti G. Laser-evoked vertex potentials predict defensive motor actions. Cerebral Cortex. 2015;25(12):4789-98.

[144] Nir R-R, Sinai A, Moont R, Harari E, Yarnitsky D. Tonic pain and continuous EEG: prediction of subjective pain perception by alpha-1 power during stimulation and at rest. Clinical Neurophysiology. 2012;123(3):605-12.
[145] Nir R-R, Sinai A, Raz E, Sprecher E, Yarnitsky D. Pain assessment by continuous EEG: association between subjective perception of tonic pain and peak frequency of alpha oscillations during stimulation and at rest. Brain research. 2010;1344:77-86.
[146] Nickel MM, May ES, Tiemann L, Schmidt P, Postorino M, Dinh ST, et al. Brain oscillations differentially encode noxious stimulus intensity and pain intensity. Neuroimage. 2017;148:141-7.
[147] Nickel MM, Ta Dinh S, May ES, Tiemann L, Hohn VD, Gross J, et al. Neural oscillations and connectivity characterizing the state of tonic experimental pain in humans. Human brain mapping. 2020;41(1):17-29.
[148] Schulz E, May ES, Postorino M, Tiemann L, Nickel MM, Witkovsky V, et al. Prefrontal gamma oscillations encode tonic pain in humans. Cerebral cortex. 2015;25(11):4407-14.
[149] Peng W, Hu L, Zhang Z, Hu Y. Changes of spontaneous oscillatory activity to tonic heat pain. PloS one. 2014;9(3):e91052.
[150] Gram M, Graversen C, Olesen S, Drewes A. Dynamic spectral indices of the electroencephalogram provide new insights into tonic pain. Clinical Neurophysiology. 2015;126(4):763-71.
[151] Huishi Zhang C, Sohrabpour A, Lu Y, He B. Spectral and spatial changes of brain rhythmic activity in response to the sustained thermal pain stimulation. Human brain mapping. 2016;37(8):2976-91.
[152] Zhao W, Van Someren EJ, Li C, Chen X, Gui W, Tian Y, et al. EEG spectral analysis in insomnia disorder: a systematic review and meta-analysis. Sleep medicine reviews. 2021;59:101457.
[153] Fallon N, Chiu Y, Nurmikko T, Stancak A. Altered theta oscillations in resting EEG of fibromyalgia syndrome patients. Eur J Pain. 2018;22(1):49-57.
[154] Meneses FM, Queirós FC, Montoya P, Miranda JG, Dubois-Mendes SM, Sá KN, et al. Patients with rheumatoid arthritis and chronic pain display enhanced alpha power density at rest. Frontiers in human neuroscience. 2016;10:395.
[155] González-Roldán AM, Cifre I, Sitges C, Montoya P. Altered dynamic of EEG oscillations in fibromyalgia patients at rest. Pain Medicine. 2016;17(6):1058-68.
[156] Furman AJ, Thapa T, Summers SJ, Cavaleri R, Fogarty JS, Steiner GZ, et al. Cerebral peak alpha frequency reflects average pain severity in a human model of sustained, musculoskeletal pain. Journal of neurophysiology. 2019;122(4):1784-93.
[157] May ES, Nickel MM, Ta Dinh S, Tiemann L, Heitmann H, Voth I, et al. Prefrontal gamma oscillations reflect ongoing pain intensity in chronic back pain patients. Human brain mapping. 2019;40(1):293-305.
[158] Vanneste S, Song J-J, De Ridder D. Thalamocortical dysrhythmia detected by machine learning. Nature communications. 2018;9(1):1-13.
[159] Mussigmann T, Bardel B, Lefaucheur J-P. Resting-state electroencephalography (EEG) biomarkers of chronic neuropathic pain. A systematic review. NeuroImage. 2022:119351.
[160] Hirshkowitz M, Whiton K, Albert S, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. Sleep health. 2015;1(1):40-3. doi: 10.1016/j.sleh.2014.12.010. PubMed PMID: 29073412.
[161] Tomaso CC, Johnson AB, Nelson TD. The effect of sleep deprivation and restriction on mood, emotion, and emotion regulation: Three meta-analyses in one. Sleep. 2021;44(6):zsaa289.
[162] Pires GN, Bezerra AG, Tufik S, Andersen ML. Effects of acute sleep deprivation on state anxiety levels: a systematic review and meta-analysis. Sleep Med. 2016;24:109-18.
[163] Wickens CD, Hutchins SD, Laux L, Sebok A. The impact of sleep disruption on complex cognitive tasks: a meta-analysis. Human factors. 2015;57(6):930-46.
[164] Krause AJ, Simon EB, Mander BA, Greer SM, Saletin JM, Goldstein-Piekarski AN, et al. The sleep-deprived human brain. Nature Reviews Neuroscience. 2017;18(7):404-18.
[165] Sigurdson K, Ayas NT. The public health and safety consequences of sleep disorders. Canadian journal of physiology and pharmacology. 2007;85(1):179-83.
[166] Hublin C, Partinen M, Koskenvuo M, Kaprio J. Sleep and mortality: a population-based 22-year follow-up study. Sleep. 2007;30(10):1245-53.

[167] American Psychiatric Association. Diagnostic and statistical manual of mental disorders teAAP, Association.
[168] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep medicine reviews. 2002;6(2):97-111.
[169] Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res. 2017;26(6):675-700.
[170] Pigeon WR, Bishop TM, Krueger KM. Insomnia as a precipitating factor in new onset mental illness: a systematic review of recent findings. Current psychiatry reports. 2017;19:1-11.
[171] Khan MS, Aouad R. The effects of insomnia and sleep loss on cardiovascular disease. Sleep medicine clinics. 2017;12(2):167-77.
[172] Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler EO. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. Diabetes care. 2009;32(11):1980-5.
[173] Kyle SD, Morgan K, Espie CA. Insomnia and health-related quality of life. Sleep medicine reviews. 2010;14(1):69-82.
[174] Roth T. Insomnia: definition, prevalence, etiology, and consequences. Journal of clinical sleep medicine. 2007;3(5 suppl):S7-S10.
[175] Léger D, Bayon V. Societal costs of insomnia. Sleep medicine reviews. 2010;14(6):379-89.
[176] Daley M, Morin CM, LeBlanc M, Grégoire J-P, Savard J. The economic burden of insomnia: direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms, and good sleepers. Sleep. 2009;32(1):55-64.
[177] Riemann D, Nissen C, Palagini L, Otte A, Perlis ML, Spiegelhalder K. The neurobiology, investigation, and treatment of chronic insomnia. The Lancet Neurology. 2015;14(5):547-58.
[178] Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep medicine reviews. 2010;14(1):19-31.
[179] Krone L, Frase L, Piosczyk H, Selhausen P, Zittel S, Jahn F, et al. Top-down control of arousal and sleep: Fundamentals and clinical implications. Sleep medicine reviews. 2017;31:17-24.
[180] Farina B, Dittoni S, Colicchio S, Testani E, Losurdo A, Gnoni V, et al. Heart rate and heart rate variability modification in chronic insomnia patients. Behavioral sleep medicine. 2014;12(4):290-306.
[181] Xia L, Chen G-H, Li Z-H, Jiang S, Shen J. Alterations in hypothalamus-pituitary-adrenal/thyroid axes and gonadotropin-releasing hormone in the patients with primary insomnia: a clinical research. PloS one. 2013;8(8):e71065.
[182] Fasiello E, Gorgoni M, Scarpelli S, Alfonsi V, Strambi LF, De Gennaro L. Functional connectivity changes in insomnia disorder: A systematic review. Sleep medicine reviews. 2022;61:101569.
[183] Andersen M, Araujo P, Frange C, Tufik S. Sleep Disturbance and Pain: A Tale of Two Common Problems. Chest. 2018;154(5):1249-59. doi: 10.1016/j.chest.2018.07.019. PubMed PMID: 30059677.
[184] Goossens Z, Van Stallen A, Vermuyten J, Rice D, Runge N, Huysmans E, et al. Day-to-day associations between pain intensity and sleep outcomes in an adult chronic musculoskeletal pain population: A systematic review. Sleep Medicine Reviews. 2024:102013.
[185] Agmon M, Armon G. Increased insomnia symptoms predict the onset of back pain among employed adults. PloS one. 2014;9(8):e103591. doi: 10.1371/journal.pone.0103591. PubMed PMID: 25084165.
[186] Mork PJ, Vik KL, Moe B, Lier R, Bardal EM, Nilsen TIL. Sleep problems, exercise and obesity and risk of chronic musculoskeletal pain: the Norwegian HUNT study. European journal of public health. 2014;24(6):924-9. doi: 10.1093/eurpub/ckt198. PubMed PMID: 24293504.
[187] Skarpsno E, Nilsen T, Mork P. The effect of long-term poor sleep quality on risk of back-related disability and the modifying role of physical activity. Scientific reports. 2021;11(1):15386. doi: 10.1038/s41598-021-94845-7. PubMed PMID: 34321561.
[188] Silva S, Hayden JA, Mendes G, Verhagen A, Pinto RZ, Silva A. Sleep as a prognostic factor in low back pain: a systematic review of prospective cohort studies and secondary analyses of randomized controlled trials. Sleep. 2024. doi: 10.1093/sleep/zsae023.
[189] Sivertsen B, Lallukka T, Petrie KJ, Steingrímsdóttir ÓA, Stubhaug A, Nielsen CS. Sleep and pain sensitivity in adults. Pain. 2015;156(8):1433-9.

[190] Campbell CM, Buenaver LF, Finan P, Bounds SC, Redding M, McCauley L, et al. Sleep, pain catastrophizing, and central sensitization in knee osteoarthritis patients with and without insomnia. Arthritis care & research. 2015;67(10):1387-96.
[191] Letzen JE, Remeniuk B, Smith MT, Irwin MR, Finan PH, Seminowicz DA. Individual differences in pain sensitivity are associated with cognitive network functional connectivity following one night of experimental sleep disruption. Human Brain Mapping. 2020;41(3):581-93. doi: 10.1002/hbm.24824.
[192] Vanneste S, De Ridder D. Chronic pain as a brain imbalance between pain input and pain suppression. Brain Communications. 2021;3(1):fcab014.
[193] Azevedo E, Manzano GM, Silva A, Martins R, Andersen ML, Tufik S, et al. The effects of total and REM sleep deprivation on laser-evoked potential threshold and pain perception. PAIN. 2011;152(9):2052-8. doi: 10.1016/j.pain.2011.04.032. PubMed PMID: 104577304. Language: English. Entry Date: 20120615. Revision Date: 20210115. Publication Type: journal article.
[194] Tiede W, Magerl W, Baumgärtner U, Durrer B, Ehlert U, Treede RD, et al. Sleep restriction attenuates amplitudes and attentional modulation of pain-related evoked potentials, but augments pain ratings in healthy volunteers. PAIN. 2010;148(1):36-42. doi: 10.1016/j.pain.2009.08.029. PubMed PMID: 105314469. Language: English. Entry Date: 20100423. Revision Date: 20210115. Publication Type: journal article.
[195] Odegard SS, Omland PM, Nilsen KB, Stjern M, Gravdahl GB, Sand T. The effect of sleep restriction on laser evoked potentials, thermal sensory and pain thresholds and suprathreshold pain in healthy subjects. Clinical Neurophysiology. 2015;126(10):1979-87. doi: 10.1016/j.clinph.2014.12.011.
[196] Matre D, Hu L, Viken LA, Hjelle IB, Wigemyr M, Knardahl S, et al. Experimental sleep restriction facilitates pain and electrically induced cortical responses. Sleep. 2015;38(10):1607-17. doi: 10.5665/sleep.5058.
[197] Ree A, Nilsen KB, Knardahl S, Sand T, Matre D. Sleep restriction does not potentiate nocebo-induced changes in pain and cortical potentials. European Journal of Pain. 2020;24(1):110-21. doi: 10.1002/ejp.1466. PubMed PMID: 140250382. Language: English. Entry Date: In Process. Revision Date: 20201231. Publication Type: journal article.
[198] Puterflam JM, Comis JJ, Lan Q, Liu C, Lipschitz AJ, Grunstein RR, et al. The short-term effects of opioid and non-opioid pharmacotherapies on sleep in people with chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. Sleep Medicine Reviews. 2022:101672. doi: https://doi.org/10.1016/j.smrv.2022.101672.
[199] Husak AJ, Bair MJ. Chronic pain and sleep disturbances: a pragmatic review of their relationships, comorbidities, and treatments. Pain Medicine. 2020;21(6):1142-52.
[200] Craige EA, Tagliaferri SD, Ferguson SA, Scott H, Belavy DL, Easton DF, et al. Effects of pharmacotherapy on sleep-related outcomes in adults with chronic low back pain: A systematic review and meta-analysis of randomised controlled trials. EClinicalMedicine. 2023;55:101749. Epub 2022/11/26. doi: 10.1016/j.eclinm.2022.101749. PubMed PMID: 36425870; PubMed Central PMCID: PMCPMC9678954.
[201] Goforth HW, Preud'homme XA, Krystal AD. A randomized, double-blind, placebo-controlled trial of eszopiclone for the treatment of insomnia in patients with chronic low back pain. Sleep. 2014;37(6):1053-60. doi: 10.5665/sleep.3760. PubMed PMID: 24882900.
[202] Proctor A, Bianchi MT. Clinical pharmacology in sleep medicine. International Scholarly Research Notices. 2012;2012.
[203] Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. Journal of Clinical Sleep Medicine. 2021;17(2):255-62.
[204] Morin CM, Bei B, Bjorvatn B, Poyares D, Spiegelhalder K, Wing YK. World sleep society international sleep medicine guidelines position statement endorsement of “behavioral and psychological treatments for chronic insomnia disorder in adults: An American Academy of sleep medicine clinical practice guidelines”. Sleep Med. 2023. doi: https://doi.org/10.1016/j.sleep.2023.07.001.
[205] Climent-Sanz C, Valenzuela-Pascual F, Martinez-Navarro O, Blanco-Blanco J, Rubi-Carnacea F, Garcia-Martinez E, et al. Cognitive behavioral therapy for insomnia (CBT-i) in patients with fibromyalgia: a systematic review and meta-analysis. Disability and Rehabilitation. 2022;44(20):5770-83. doi: 10.1080/09638288.2021.1954706. PubMed PMID: WOS:000676044200001.

[206] Enomoto K, Adachi T, Fujino H, Kugo M, Tatsumi S, Sasaki J. Comparison of the effectiveness of cognitive behavioral therapy for insomnia, cognitive behavioral therapy for pain, and hybrid cognitive behavioral therapy for insomnia and pain in individuals with comorbid insomnia and chronic pain: A systematic review and network meta-analysis. Sleep Medicine Reviews. 2022:101693. doi: https://doi.org/10.1016/j.smrv.2022.101693.
[207] Kundakci B, Kaur J, Goh SL, Hall M, Doherty M, Zhang W, et al. Efficacy of nonpharmacological interventions for individual features of fibromyalgia: A systematic review and meta-analysis of randomised controlled trials. Pain. 2022;163(8):1432-45.
[208] Estévez-López F, Maestre-Cascales C, Russell D, Álvarez-Gallardo IC, Rodriguez-Ayllon M, Hughes CM, et al. Effectiveness of Exercise on Fatigue and Sleep Quality in Fibromyalgia: A Systematic Review and Meta-analysis of Randomized Trials. Archives of Physical Medicine and Rehabilitation. 2021;102(4):752-61. doi: 10.1016/j.apmr.2020.06.019.
[209] Hou W-H, Wang T-Y, Kang J-H. The effects of add-on non-invasive brain stimulation in fibromyalgia: a meta-analysis and meta-regression of randomized controlled trials. Rheumatology. 2016;55(8):1507-17.
[210] Glombiewski JA, Sawyer AT, Gutermann J, Koenig K, Rief W, Hofmann SG. Psychological treatments for fibromyalgia: a meta-analysis. PAIN®. 2010;151(2):280-95.
[211] Pinto SM, Cheung JP, Samartzis D, Karppinen J, Zheng Y-p, Pang MY, et al. Are Morphometric and Biomechanical Characteristics of Lumbar Multifidus Related to Pain Intensity or Disability in People With Chronic Low Back Pain After Considering Psychological Factors or Insomnia? Frontiers in psychiatry. 2022:611.
[212] Gerhart J, Burns J, Post K, Smith D, Porter L, Burgess H, et al. Relationships Between Sleep Quality and Pain-Related Factors for People with Chronic Low Back Pain: Tests of Reciprocal and Time of Day Effects. Ann Behav Med. 2017;51(3):365-75. doi: 10.1007/s12160-016-9860-2. PubMed PMID: 123190778. Language: English. Entry Date: 20180330. Revision Date: 20190712. Publication Type: journal article.
[213] Tang NK, Goodchild CE, Sanborn AN, Howard J, Salkovskis PM. Deciphering the temporal link between pain and sleep in a heterogeneous chronic pain patient sample: a multilevel daily process study. Sleep. 2012;35(5):675-87.
[214] Skarpsno ES, Mork PJ, Nilsen TIL, Nordstoga AL. Influence of sleep problems and co-occurring musculoskeletal pain on long-term prognosis of chronic low back pain: the HUNT Study. Journal of epidemiology and community health. 2020;74(3):283-9. doi: 10.1136/jech-2019-212734. PubMed PMID: 31801790.
[215] Liberati A, Altman D, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clinical research ed). 2009;339:b2700. doi: 10.1136/bmj.b2700. PubMed PMID: 19622552.
[216] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021;372.
[217] Portney L, Watkins M. Foundations of clinical research. Applications to practice. 3rd, editor. Upper Saddle River: NJ: Prentice Hall; 2009.
[218] Sterne J, Savović J, Page M, Elbers R, Blencowe N, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2019;366:l4898. doi: 10.1136/bmj.l4898. PubMed PMID: 31462531.
[219] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. bmj. 2016;355.
[220] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis: John Wiley & Sons; 2021.
[221] Morris SB, DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. Psychol Methods. 2002;7(1):105.
[222] Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. Biological psychiatry. 2016;80(1):40-52.
[223] Cohen J. Statistical power analysis for the behavioral sciences 2nd ed Hillsdale NJ Erlbaum. 1988.

[224] Higgins J. Cochrane handbook for systematic reviews of interventions. Version 5.1. 0 [updated March 2011]. The Cochrane Collaboration. www cochrane-handbook org. 2011.
[225] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315(7109):629-34.
[226] Van Tulder M, Furlan A, Bombardier C, Bouter L. Updated Method Guidelines for Systematic Reviews in the Cochrane Collaboration Back Review Group. Spine. 2003;28(12):1290-9. doi: 10.1097/01.BRS.0000065484.95996.AF.
[227] Busch V, Haas J, Crönlein T, Pieh C, Geisler P, Hajak G, et al. Sleep deprivation in chronic somatoform pain-effects on mood and pain regulation. Psychiatry Research. 2012;195(3):134-43. doi: 10.1016/j.psychres.2011.07.021.
[228] Irwin MR, Olmstead R, Carrillo C, Sadeghi N, Fitzgerald JD, Ranganath VK, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. Sleep. 2012;35(4):537-43. doi: 10.5665/sleep.1742. PubMed PMID: 108178952. Language: English. Entry Date: 20121109. Revision Date: 20150712. Publication Type: Journal Article.
[229] Ablin JN, Clauw DJ, Lyden AK, Ambrose K, Williams DA, Gracely RH, et al. Effects of sleep restriction and exercise deprivation on somatic symptoms and mood in healthy adults. Clinical and Experimental Rheumatology. 2013;31(6):S53-S9. PubMed PMID: WOS:000329769800009.
[230] Kristiansen ES, Nielsen LS, Christensen SS, Botvid SHC, Nørgaard Poulsen J, Gazerani P. Sleep deprivation sensitizes human craniofacial muscles. Somatosensory & motor research. 2017;34(2):116-22. doi: 10.1080/08990220.2017.1317241.
[231] Matre D, Andersen MR, Knardahl S, Nilsen KB. Conditioned pain modulation is not decreased after partial sleep restriction. Eur J Pain. 2016;20(3):408-16. doi: 10.1002/ejp.741. PubMed PMID: 112968679. Language: English. Entry Date: 20161001. Revision Date: 20180629. Publication Type: journal article.
[232] Eichhorn N, Treede RD, Schuh-Hofer S. The Role of Sex in Sleep Deprivation Related Changes of Nociception and Conditioned Pain Modulation. Neuroscience. 2018;387:191-200. doi: 10.1016/j.neuroscience.2017.09.044. PubMed PMID: WOS:000445102800019.
[233] Haack M, Lee E, Cohen DA, Mullington JM. Activation of the prostaglandin system in response to sleep loss in healthy humans: potential mediator of increased spontaneous pain. Pain. 2009;145(1-2):136-41. doi: 10.1016/j.pain.2009.05.029. PubMed PMID: 19560866.
[234] Hakkionen S, Alloui A, Gross A, Eschallier A, Dubray C. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. J Sleep Res. 2001;10(1):35-42. doi: http://dx.doi.org/10.1046/j.1365-2869.2001.00240.x. PubMed PMID: 619765093; 2002-04257-004.
[235] Kundermann B, Spernal J, Huber MT, Krieg J, Lautenbacher S. Sleep deprivation affects thermal pain thresholds but not somatosensory thresholds in healthy volunteers. Psychosom Med. 2004;66(6):932-7. doi: 10.1097/01.psy.0000145912.24553.c0. PubMed PMID: 106570963. Language: English. Entry Date: 20050128. Revision Date: 20200624. Publication Type: Journal Article.
[236] Larson RA, Carter JR. Total sleep deprivation and pain perception during cold noxious stimuli in humans. Scandinavian Journal of Pain. 2016;13:12-6. doi: 10.1016/j.sjpain.2016.05.037.
[237] Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. Sleep. 2006;29(2):145-51. PubMed PMID: 106451099. Language: English. Entry Date: 20060602. Revision Date: 20150711. Publication Type: Journal Article.
[238] Schuh-Hofer S, Baumgartner U, Treede RD. Effect of sleep deprivation on the electrophysiological signature of habituation to noxious laser stimuli. European Journal of Pain. 2015;19(8):1197-209. doi: 10.1002/ejp.698. PubMed PMID: WOS:000360180300018.
[239] Schuh-Hofer S, Wodarski R, Pfau DB, Caspani O, Magerl W, Kennedy JD, et al. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. PAIN. 2013;154(9):1613-21. doi: 10.1016/j.pain.2013.04.046. PubMed PMID: 104088811. Language: English. Entry Date: 20140404. Revision Date: 20210115. Publication Type: journal article.
[240] Faraut B, Léger D, Medkour T, Dubois A, Bayon V, Chennaoui M, et al. Napping reverses increased pain sensitivity due to sleep restriction. PLoS ONE. 2015;10(2). doi: 10.1371/journal.pone.0117425.

[241] Haack M, Mullington JM. Sustained sleep restriction reduces emotional and physical well-being. PAIN. 2005;119(1-3):56-64. doi: 10.1016/j.pain.2005.09.011. PubMed PMID: 104743265. Language: English. Entry Date: 20110610. Revision Date: 20210113. Publication Type: journal article.
[242] Neverdahl JP, Uglem M, Matre D, Hansen JO, Engstrøm M, Tronvik E, et al. Pain thresholds and suprathreshold pain after sleep restriction in migraine - A blinded crossover study. Cephalalgia : an international journal of headache. 2021:3331024211056565. doi: 10.1177/03331024211056565. PubMed PMID: 34786965.
[243] Smith MT, Edwards RR, McCann UD, Haythomthwaite JA. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. Sleep. 2007;30(4):494-505. PubMed PMID: 106176201. Language: English. Entry Date: 20071026. Revision Date: 20150711. Publication Type: Journal Article.
[244] Moldofsky H, Scarisbrick P. Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. Psychosom Med. 1976;38(1):35-44. doi: 10.1097/00006842-197601000-00006. PubMed PMID: 176677.
[245] Lacovides S, George K, Kamerman P, Baker FC. Sleep Fragmentation Hypersensitizes Healthy Young Women to Deep and Superficial Experimental Pain. Journal of Pain. 2017;18(7):844-54. doi: 10.1016/j.jpain.2017.02.436. PubMed PMID: WOS:000404946200009.
[246] Reynolds A, Banks S. Total sleep deprivation, chronic sleep restriction and sleep disruption. Progress in brain research. 2010;185:91-103. doi: 10.1016/b978-0-444-53702-7.00006-3. PubMed PMID: 21075235.
[247] Short MA, Banks S. The functional impact of sleep deprivation, sleep restriction, and sleep fragmentation. Sleep deprivation and disease: Springer; 2014. p. 13-26.
[248] Sardi NE, Lazzarim MK, Guilhen VA, Marcilio RS, Natume PS, Watanabe TC, et al. Chronic sleep restriction increases pain sensitivity over time in a periaqueductal gray and nucleus accumbens dependent manner. Neuropharmacology. 2018;139:52-60. doi: 10.1016/j.neuropharm.2018.06.022. PubMed PMID: WOS:000441644800005.
[249] Nobue A, Kunimasa Y, Tsuneishi H, Sano K, Oda H, Ishikawa M. Limb-Specific Features and Asymmetry of Nerve Conduction Velocity and Nerve Trunk Size in Human. Frontiers in Physiology. 2020:1576.
[250] Algafly AA, George KP. The effect of cryotherapy on nerve conduction velocity, pain threshold and pain tolerance. Br J Sports Med. 2007;41(6):365-9.
[251] Herrera E, Sandoval MC, Camargo DM, Salvini TF. Motor and sensory nerve conduction are affected differently by ice pack, ice massage, and cold water immersion. Phys Ther. 2010;90(4):581-91.
[252] Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. British journal of anaesthesia. 2013;111(1):52-8.
[253] Rosen S, Ham B, Mogil JS. Sex differences in neuroimmunity and pain. Journal of neuroscience research. 2017;95(1-2):500-8.
[254] Lerman S, Mun C, Hunt C, Kunatharaju S, Buenaver L, Finan P, et al. Insomnia with objective short sleep duration in women with temporomandibular joint disorder: quantitative sensory testing, inflammation and clinical pain profiles. Sleep Med. 2022;90:26-35. doi: 10.1016/j.sleep.2022.01.004. PubMed PMID: 35091170.
[255] Lee Y, Lu B, Edwards R, Wasan A, Nassikas N, Clauw D, et al. The role of sleep problems in central pain processing in rheumatoid arthritis. Arthritis rheumatism 2013;65(1):59-68. doi: 10.1002/art.37733. PubMed PMID: 23124650.
[256] Tomim DH, Pontarolla FM, Bertolini JF, Arase M, Tobaldini G, Lima M, et al. The pronociceptive effect of paradoxical sleep deprivation in rats: evidence for a role of descending pain modulation mechanisms. Molecular neurobiology. 2016;53(3):1706-17.
[257] Javaheripour N, Shahdipour N, Noori K, Zarei M, Camilleri JA, Laird AR, et al. Functional brain alterations in acute sleep deprivation: An activation likelihood estimation meta-analysis. Sleep medicine reviews. 2019;46:64-73.
[258] Xu Y, Yu P, Zheng J, Wang C, Hu T, Yang Q, et al. Classifying vulnerability to sleep deprivation using resting-state functional MRI graph theory metrics. Frontiers in neuroscience. 2021;15.
[259] Ma N, Dinges DF, Basner M, Rao H. How acute total sleep loss affects the attending brain: a meta-analysis of neuroimaging studies. Sleep. 2015;38(2):233-40.

[260] van Ettinger-Veenstra H, Lundberg P, Alfoldi P, Sodermark M, Graven-Nielsen T, Sjors A, et al. Chronic widespread pain patients show disrupted cortical connectivity in default mode and salience networks, modulated by pain sensitivity. Journal of Pain Research. 2019;12:1743.
[261] Hemington KS, Rogachov A, Cheng JC, Bosma RL, Kim JA, Osborne NR, et al. Patients with chronic pain exhibit a complex relationship triad between pain, resilience, and within-and cross-network functional connectivity of the default mode network. Pain. 2018;159(8):1621-30.
[262] Irwin M, Cole S. Reciprocal regulation of the neural and innate immune systems. Nature reviews Immunology. 2011;11(9):625-32. doi: 10.1038/nri3042. PubMed PMID: 21818124.
[263] de Goeij M, van Eijk LT, Vanelderen P, Wilder-Smith OH, Vissers KC, van der Hoeven JG, et al. Systemic inflammation decreases pain threshold in humans in vivo. PLoS One. 2013;8(12):e84159.
[264] Berna C, Leknes S, Holmes EA, Edwards RR, Goodwin GM, Tracey I. Induction of depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness. Biological psychiatry. 2010;67(11):1083-90.
[265] Bushnell MC, Čeko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. Nature Reviews Neuroscience. 2013;14(7):502-11.
[266] Legrain V, Van Damme S, Eccleston C, Davis KD, Seminowicz DA, Crombez G. A neurocognitive model of attention to pain: behavioral and neuroimaging evidence. Pain. 2009;144(3):230-2.
[267] Ferreira ML, de Luca K, Haile LM, Steinmetz JD, Culbreth GT, Cross M, et al. Global, regional, and national burden of low back pain, 1990–2020, its attributable risk factors, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology. 2023;5(6):e316-e29.
[268] Gore M, Sadosky A, Stacey BR, Tai K-S, Leslie D. The burden of chronic low back pain: clinical comorbidities, treatment patterns, and health care costs in usual care settings. Spine. 2012;37(11):E668-E77. doi: 10.1097/BRS.0b013e318241e5de. PubMed PMID: 22146287.
[269] Hoy D, Brooks P, Blyth F, Buchbinder R. The Epidemiology of low back pain. Best Pract Res Clin Rheumatol. 2010;24(6):769-81. doi: 10.1016/j.berh.2010.10.002.
[270] Maher C, Underwood M, Buchbinder R. Non-specific low back pain. The Lancet. 2017;389(10070):736-47. doi: https://doi.org/10.1016/S0140-6736(16)30970-9.
[271] Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. The Lancet. 2018;391(10137):2356-67. doi: 10.1016/S0140-6736(18)30480-X.
[272] Mathias J, Cant M, Burke A. Sleep disturbances and sleep disorders in adults living with chronic pain: a meta-analysis. Sleep Med. 2018;52:198-210. doi: 10.1016/j.sleep.2018.05.023. PubMed PMID: 30314881.
[273] Amiri S, Behnezhad S. Sleep disturbances and back pain : Systematic review and meta-analysis. Neuropsychiatrie : Klinik, Diagnostik, Therapie und Rehabilitation : Organ der Gesellschaft Osterreichischer Nervenarzte und Psychiater. 2020;34(2):74-84. doi: 10.1007/s40211-020-00339-9. PubMed PMID: 32166629.
[274] Stroemel-Scheder C, Karmann AJ, Ziegler E, Heesen M, Knippenberg-Bigge K, Lang PM, et al. Sleep, experimental pain and clinical pain in patients with chronic musculoskeletal pain and healthy controls. Journal of Pain Research. 2019;12:3381-93. doi: 10.2147/JPR.S211574.
[275] Haack M, Engert LC, Besedovsky L, Goldstein MR, Devine JK, Dang R, et al. Alterations of pain pathways by experimental sleep disturbances in humans: Central pain-inhibitory, cyclooxygenase, and endocannabinoid pathways. Sleep. 2023:zsad061.
[276] Othman R, Jayakaran P, Swain N, Dassanayake S, Tumilty S, Mani R. Relationships Between Psychological, Sleep, and Physical Activity Measures and Somatosensory Function in People With Peripheral Joint Pain: A Systematic Review and Meta-Analysis. Pain Practice. 2021;21(2):226-61.
[277] Starkweather AR, Heineman A, Storey S, Rubia G, Lyon DE, Greenspan J, et al. Methods to measure peripheral and central sensitization using quantitative sensory testing: A focus on individuals with low back pain. Applied nursing research : ANR. 2016;29:237-41. Epub 2016/02/10. doi: 10.1016/j.apnr.2015.03.013. PubMed PMID: 26856520.
[278] Zeng L-N, Zong Q-Q, Yang Y, Zhang L, Xiang Y-F, Ng CH, et al. Gender difference in the prevalence of insomnia: a meta-analysis of observational studies. Frontiers in Psychiatry. 2020;11:577429.
[279] Li JXL, Wang X, Henry A, Anderson CS, Hammond N, Harris K, et al. Sex differences in pain expressed by patients across diverse disease states: individual patient data meta-analysis of 33,957 participants

in 10 randomized controlled trials. PAIN. 2023;164(8):1666-76. doi: 10.1097/j.pain.0000000000002884. PubMed PMID: 00006396-202308000-00004.
[280] Matre D, Knardahl S, Nilsen KB. Night-shift work is associated with increased pain perception. Scandinavian Journal of Work, Environment & Health. 2017:260-8.
[281] Kwan Y, Baek C, Chung S, Kim TH, Choi S. Resting-state quantitative EEG characteristics of insomniac patients with depression. International Journal of Psychophysiology. 2018;124:26-32.
[282] Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011;34(5):601-8.
[283] Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test–retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. Journal of psychosomatic research. 2002;53(3):737-40.
[284] Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E, et al. Report of the NIH Task Force on research standards for chronic low back pain. Phys Ther. 2015;95(2):e1-e18.
[285] Jensen MP, Mendoza ME, Ehde DM, Patterson DR, Molton IR, Dillworth TM, et al. Effects of hypnosis, cognitive therapy, hypnotic cognitive therapy, and pain education in adults with chronic pain: a randomized clinical trial. Pain. 2020;161(10):2284.
[286] Pinto CB, Bielefeld J, Barroso J, Yip B, Huang L, Schnitzer T, et al. Chronic pain domains and their relationship to personality, abilities, and brain networks. PAIN. 2023;164(1):59-71. doi: 10.1097/j.pain.0000000000002657. PubMed PMID: 00006396-202301000-00012.
[287] Chung K-F, Yeung W-F, Ho FY-Y, Yung K-P, Yu Y-M, Kwok C-W. Cross-cultural and comparative epidemiology of insomnia: the Diagnostic and statistical manual (DSM), International classification of diseases (ICD) and International classification of sleep disorders (ICSD). Sleep Med. 2015;16(4):477-82.
[288] Babiloni C, Barry RJ, Başar E, Blinowska KJ, Cichocki A, Drinkenburg WH, et al. International Federation of Clinical Neurophysiology (IFCN)–EEG research workgroup: Recommendations on frequency and topographic analysis of resting state EEG rhythms. Part 1: Applications in clinical research studies. Clinical Neurophysiology. 2020;131(1):285-307.
[289] Iacovides S, Avidon I, Baker F. Does pain vary across the menstrual cycle? A review. Eur J Pain. 2015;19(10):1389-405.
[290] Chien C-W, Bagraith KS, Khan A, Deen M, Strong J. Comparative responsiveness of verbal and numerical rating scales to measure pain intensity in patients with chronic pain. The journal of pain. 2013;14(12):1653-62.
[291] Chiarotto A, Terwee CB, Ostelo RW. Choosing the right outcome measurement instruments for patients with low back pain. Best Pract Res Clin Rheumatol. 2016;30(6):1003-20. doi: 10.1016/j.berh.2017.07.001.
[292] Waddell G, Newton M, Henderson I, Somerville D, Main CJ. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. Pain. 1993;52(2):157-68.
[293] Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychological assessment. 1995;7(4):524.
[294] Lovibond PF, Lovibond SH. The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behaviour research and therapy. 1995;33(3):335-43.
[295] Tsai P-S, Wang S-Y, Wang M-Y, Su C-T, Yang T-T, Huang C-J, et al. Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. Qual Life Res. 2005;14(8):1943-52.
[296] Yu DS. Insomnia Severity Index: psychometric properties with Chinese community-dwelling older people. Journal of advanced nursing. 2010;66(10):2350-9.
[297] Yap JC, Lau J, Chen PP, Gin T, Wong T, Chan I, et al. Validation of the Chinese Pain Catastrophizing Scale (HK-PCS) in patients with chronic pain. Pain medicine. 2008;9(2):186-95.
[298] Cheung PWH, Wong CKH, Cheung JPY. Psychometric validation of the cross-culturally adapted traditional Chinese version of the Back Beliefs Questionnaire (BBQ) and Fear-Avoidance Beliefs Questionnaire (FABQ). European Spine Journal. 2018;27(8):1724-33.
[299] Tsang RC. Measurement properties of the Hong Kong Chinese version of the Roland-Morris disability questionnaire. Hong Kong Physiotherapy Journal. 2004;22(1):40-9.

[300] Leung C, Wing Y, Kwong P, Shum ALK. Validation of the Chinese-Cantonese version of the Hospital Anxiety and Depression Scale and comparison with the Hamilton Rating Scale of Depression. Acta Psychiatrica Scandinavica. 1999;100(6):456-61.
[301] Vuilleumier PH, Manresa JAB, Ghamri Y, Mlekusch S, Siegenthaler A, Arendt-Nielsen L, et al. Reliability of quantitative sensory tests in a low back pain population. Regional Anesthesia & Pain Medicine. 2015;40(6):665-73.
[302] Klyne DM, Moseley GL, Sterling M, Barbe MF, Hodges PW. Individual variation in pain sensitivity and conditioned pain modulation in acute low back pain: effect of stimulus type, sleep, and psychological and lifestyle factors. The Journal of Pain. 2018;19(8):942. e1-. e18.
[303] Meints SM, Mawla I, Napadow V, Kong J, Gerber J, Chan S-T, et al. The relationship between catastrophizing and altered pain sensitivity in patients with chronic low back pain. Pain. 2019;160(4):833.
[304] Tesarz J, Gerhardt A, Leisner S, Janke S, Treede R-D, Eich W. Distinct quantitative sensory testing profiles in nonspecific chronic back pain subjects with and without psychological trauma. PAIN. 2015;156(4):577-86. doi: 10.1097/01.j.pain.0000460350.30707.8d. PubMed PMID: 00006396-201504000-00004.
[305] Marcuzzi A, Wrigley PJ, Dean CM, Graham PL, Hush JM. From acute to persistent low back pain: a longitudinal investigation of somatosensory changes using quantitative sensory testing—an exploratory study. PAIN Reports. 2018;3(2):e641. doi: 10.1097/pr9.0000000000000641. PubMed PMID: 01938936-201804000-00006.
[306] Owens MA, Bulls HW, Trost Z, Terry SC, Gossett EW, Wesson-Sides KM, et al. An examination of pain catastrophizing and endogenous pain modulatory processes in adults with chronic low back pain. Pain Medicine. 2016;17(8):1452-64.
[307] Ribeiro-Dasilva MC, Goodin BR, Fillingim RB. Differences in suprathreshold heat pain responses and self-reported sleep quality between patients with temporomandibular joint disorder and healthy controls. Eur J Pain. 2012;16(7):983-93. doi: 10.1002/j.1532-2149.2011.00108.x. PubMed PMID: WOS:000305903800006.
[308] Sherman AL, Morris MC, Bruehl S, Westbrook TD, Walker LS. Heightened temporal summation of pain in patients with functional gastrointestinal disorders and history of trauma. Ann Behav Med. 2015;49(6):785-92.
[309] Klyne DM, Schmid AB, Moseley GL, Sterling M, Hodges PW. Effect of types and anatomic arrangement of painful stimuli on conditioned pain modulation. The Journal of Pain. 2015;16(2):176-85.
[310] Granovsky Y, Miller-Barmak A, Goldstein O, Sprecher E, Yarnitsky D. CPM test–retest reliability:“Standard” vs “single test-stimulus” protocols. Pain medicine. 2016;17(3):521-9.
[311] Yarnitsky D, Bouhassira D, Drewes A, Fillingim R, Granot M, Hansson P, et al. Recommendations on practice of conditioned pain modulation (CPM) testing. Eur J Pain. 2015;19(6):805-6.
[312] Yarnitsky D, Granot M, Granovsky Y. Pain modulation profile and pain therapy: Between pro- and antinociception. PAIN®. 2014;155(4):663-5. doi: https://doi.org/10.1016/j.pain.2013.11.005.
[313] Weir CB, Jan A. BMI classification percentile and cut off points. StatPearls, StatPearls Publishing, Treasure Island (FL), 2020. Copyright © 2020, StatPearls Publishing LLC. 2019.
[314] Park SJ, Yoon DM, Yoon KB, Moon JA, Kim SH. Factors associated with higher reported pain levels in patients with chronic musculoskeletal pain: a cross-sectional, correlational analysis. PLoS One. 2016;11(9):e0163132.
[315] Kim JH. Multicollinearity and misleading statistical results. Korean J Anesthesiol. 2019;72(6):558-69. Epub 2019/07/16. doi: 10.4097/kja.19087. PubMed PMID: 31304696; PubMed Central PMCID: PMCPMC6900425.
[316] Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. Pain. 2003;105(3):403-13.
[317] Haack M, Scott-Sutherland J, Santangelo G, Simpson NS, Sethna N, Mullington JM. Pain sensitivity and modulation in primary insomnia. Eur J Pain. 2012;16(4):522-33. doi: 10.1016/j.ejpain.2011.07.007.
[318] Nielsen CS, Stubhaug A, Price DD, Vassend O, Czajkowski N, Harris JR. Individual differences in pain sensitivity: genetic and environmental contributions. PAIN®. 2008;136(1-2):21-9.

[319] Petrov ME, Goodin BR, Cruz-Almeida Y, King C, Glover TL, Bulls HW, et al. Disrupted sleep is associated with altered pain processing by sex and ethnicity in knee osteoarthritis. The journal of pain. 2015;16(5):478-90.
[320] Edwards R, Grace E, Peterson S, Klick B, Haythornthwaite J, Smith M. Sleep continuity and architecture: associations with pain-inhibitory processes in patients with temporomandibular joint disorder. Eur J Pain. 2009;13(10):1043-7.
[321] Roberts MB, Drummond PD. Sleep problems are associated with chronic pain over and above mutual associations with depression and catastrophizing. Clin J Pain. 2016;32(9):792-9.
[322] Payne M, Kuhn B, Lannon E, Sturycz C, Palit S, Güereca Y, et al. Temporal habituation of heat pain? Parameters used for measuring temporal summation primarily lead to decreases in pain ratings. The Journal of Pain. 2016;17(4):S58.
[323] Vollset SE, Ababneh HS, Abate YH, Abbafati C, Abbasgholizadeh R, Abbasian M, et al. Burden of disease scenarios for 204 countries and territories, 2022–2050: a forecasting analysis for the Global Burden of Disease Study 2021. The Lancet. 2024;403(10440):2204-56.
[324] Llinás R, Urbano FJ, Leznik E, Ramírez RR, van Marle HJ. Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci. 2005;28(6):325-33. Epub 2005/06/02. doi: 10.1016/j.tins.2005.04.006. PubMed PMID: 15927689.
[325] Kim JA, Bosma RL, Hemington KS, Rogachov A, Osborne NR, Cheng JC, et al. Neuropathic pain and pain interference are linked to alpha-band slowing and reduced beta-band magnetoencephalography activity within the dynamic pain connectome in patients with multiple sclerosis. Pain. 2019;160(1):187-97.
[326] Ueno K, Yamada K, Ueda M, Naito Y, Ishii R. Current source density and functional connectivity extracted from resting-state electroencephalography as biomarkers for chronic low back pain. Pain Rep. 2025;10(1):e1233. Epub 20250113. doi: 10.1097/pr9.0000000000001233. PubMed PMID: 39816905; PubMed Central PMCID: PMCPMC11732644.
[327] Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses. Behav Res Methods. 2009;41(4):1149-60.
[328] Duan W, Chen X, Wang Y-J, Zhao W, Yuan H, Lei X. Reproducibility of power spectrum, functional connectivity and network construction in resting-state EEG. Journal of Neuroscience Methods. 2021;348:108985.
[329] Gil Ávila C, Bott FS, Tiemann L, Hohn VD, May ES, Nickel MM, et al. DISCOVER-EEG: an open, fully automated EEG pipeline for biomarker discovery in clinical neuroscience. Scientific Data. 2023;10(1):613. doi: 10.1038/s41597-023-02525-0.
[330] Hohn VD, Tiemann L, Bott FS, May ES, Fritzen C, Nickel MM, et al. Neurofeedback and attention modulate somatosensory alpha oscillations but not pain perception. PLoS biology. 2025;23(1):e3002972.
[331] Zebhauser PT, Bott F, Ávila CG, Heitmann H, May ES, Tiemann L, et al. Effects of Centrally Acting Analgesics on Resting-State Electroencephalography Biomarker Candidates of Chronic Pain. The Journal of Pain. 2025:104788.
[332] Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. Journal of neuroscience methods. 2004;134(1):9-21.
[333] Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Computational intelligence and neuroscience. 2011;2011:1-9.
[334] Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. Neuroimage. 2010;52(3):1059-69.
[335] Pernet C, Garrido MI, Gramfort A, Maurits N, Michel CM, Pang E, et al. Issues and recommendations from the OHBM COBIDAS MEEG committee for reproducible EEG and MEG research. Nature neuroscience. 2020;23(12):1473-83.
[336] Dinh ST, Nickel MM, Tiemann L, May ES, Heitmann H, Hohn VD, et al. Brain dysfunction in chronic pain patients assessed by resting-state electroencephalography. Pain. 2019;160(12):2751.
[337] Van Veen BD, Van Drongelen W, Yuchtman M, Suzuki A. Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. IEEE Transactions on biomedical engineering. 1997;44(9):867-80.

[338] Schaefer A, Kong R, Gordon EM, Laumann TO, Zuo X-N, Holmes AJ, et al. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. Cerebral cortex. 2018;28(9):3095-114.
[339] Engel AK, Gerloff C, Hilgetag CC, Nolte G. Intrinsic coupling modes: multiscale interactions in ongoing brain activity. Neuron. 2013;80(4):867-86.
[340] Siems M, Siegel M. Dissociated neuronal phase-and amplitude-coupling patterns in the human brain. NeuroImage. 2020;209:116538.
[341] Cea-Cañas B, Gomez-Pilar J, Núñez P, Rodríguez-Vázquez E, de Uribe N, Díez Á, et al. Connectivity strength of the EEG functional network in schizophrenia and bipolar disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2020;98:109801.
[342] Pourmotabbed H, de Jongh Curry AL, Clarke DF, Tyler-Kabara EC, Babajani-Feremi A. Reproducibility of graph measures derived from resting-state MEG functional connectivity metrics in sensor and source spaces. Human Brain Mapping. 2022;43(4):1342-57.
[343] Holm S. A simple sequentially rejective multiple test procedure. Scandinavian journal of statistics. 1979:65-70.
[344] Vanneste S, Ost J, Van Havenbergh T, De Ridder D. Resting state electrical brain activity and connectivity in fibromyalgia. PloS one. 2017;12(6):e0178516.
[345] Balestrieri E, Chalas N, Stier C, Fehring J, Gil Ávila C, Dannlowski U, et al. Beyond oscillations—Toward a richer characterization of brain states. Imaging Neuroscience. 2025;3. doi: 10.1162/imag_a_00499.
[346] Quidé Y, Jahanshad N, Andoh J, Antoniou G, Apkarian AV, Ashar YK, et al. ENIGMA-Chronic Pain: a worldwide initiative to identify brain correlates of chronic pain. Pain. 2022:10.1097.
[347] Bosma RL, Kim JA, Cheng JC, Rogachov A, Hemington KS, Osborne NR, et al. Dynamic pain connectome functional connectivity and oscillations reflect multiple sclerosis pain. PAIN. 2018;159(11).
[348] Åkerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. International journal of neuroscience. 1990;52(1-2):29-37.
[349] Cavanagh JF, Frank MJ. Frontal theta as a mechanism for cognitive control. Trends in cognitive sciences. 2014;18(8):414-21.
[350] Ferguson KA, Cardin JA. Mechanisms underlying gain modulation in the cortex. Nature Reviews Neuroscience. 2020;21(2):80-92.
[351] McCormick DA, Nestvogel DB, He BJ. Neuromodulation of brain state and behavior. Annual review of neuroscience. 2020;43:391-415.
[352] Northoff G, Tumati S. "Average is good, extremes are bad"–Non-linear inverted U-shaped relationship between neural mechanisms and functionality of mental features. Neuroscience & Biobehavioral Reviews. 2019;104:11-25.
[353] Talebi MN, Moradi A, Kazemi K, Khazaie H, Nami M, Fathi M, et al. The effect of sleep deprivation on brain network connectivity, as revealed by graph theory: a systematic review. Scandinavia Journal of Sleep Medicine. 2022;1(2).
[354] Meucci RD, Fassa AG, Faria NMX. Prevalence of chronic low back pain: systematic review. Revista de Saúde Pública. 2015;49(0). doi: 10.1590/S0034-8910.2015049005874.
[355] Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1545-602. doi: 10.1016/S0140-6736(16)31678-6.
[356] Gore M, Sadosky A, Stacey B, Tai K, Leslie D. The burden of chronic low back pain: clinical comorbidities, treatment patterns, and health care costs in usual care settings. Spine. 2012;37(11):E668-77. doi: 10.1097/BRS.0b013e318241e5de. PubMed PMID: 22146287.
[357] Wong C, Mak R, Kwok T, Tsang J, Leung M, Funabashi M, et al. Prevalence, incidence, and factors associated with non-specific chronic low back pain in community-dwelling older adults aged 60 years and older: A systematic review and meta-analysis. The journal of pain. 2021. doi: 10.1016/j.jpain.2021.07.012. PubMed PMID: 34450274.
[358] Torrado-Carvajal A, Toschi N, Albrecht D, Chang K, Akeju O, Kim M, et al. Thalamic neuroinflammation as a reproducible and discriminating signature for chronic low back pain. Pain. 2021;162(4):1241-9. doi: 10.1097/j.pain.0000000000002108. PubMed PMID: 33065737.

[359] Pinto SM, Cheung JP, Samartzis D, Karppinen J, Zheng Y-p, Pang MY, et al. Differences in proprioception between young and middle-aged adults with and without chronic low back pain. Frontiers in Neurology. 2020;11:1723.
[360] Saukkonen J, Määttä J, Oura P, Kyllönen E, Tervonen O, Niinimäki J, et al. Association Between Modic Changes and Low Back Pain in Middle Age: A Northern Finland Birth Cohort Study. Spine. 2020;45(19):1360-7. doi: 10.1097/brs.0000000000003529. PubMed PMID: 32341297.
[361] Hancock M, Maher C, Petocz P, Lin C, Steffens D, Luque-Suarez A, et al. Risk factors for a recurrence of low back pain. The spine journal : official journal of the North American Spine Society. 2015;15(11):2360-8. doi: 10.1016/j.spinee.2015.07.007. PubMed PMID: 26169027.
[362] Anwer S, Li H, Antwi-Afari MF, Wong AYL. Associations between physical or psychosocial risk factors and work-related musculoskeletal disorders in construction workers based on literature in the last 20 years: A systematic review. International Journal of Industrial Ergonomics. 2021;83:103113.
[363] Wong AY, Samartzis D, Cheung PW, Cheung JPY. How common is back pain and what biopsychosocial factors are associated with back pain in patients with adolescent idiopathic scoliosis? Clinical orthopaedics and related research. 2019;477(4):676.
[364] Axén I. Pain-related Sleep Disturbance: A Prospective Study With Repeated Measures. The Clinical journal of pain. 2016;32(3):254-9. doi: 10.1097/AJP.0000000000000249. PubMed PMID: 25968449.
[365] Kim SH, Sun JM, Yoon KB, Moon JH, An JR, Yoon DM. Risk factors associated with clinical insomnia in chronic low back pain: a retrospective analysis in a university hospital in Korea. Korean J Pain. 2015;28(2):137. doi: 10.3344/kjp.2015.28.2.137.
[366] Lusa S, Miranda H, Luukkonen R, Punakallio A. Sleep disturbances predict long-term changes in low back pain among Finnish firefighters: 13-year follow-up study. International archives of occupational and environmental health. 2015;88(3):369-79. doi: 10.1007/s00420-014-0968-z. PubMed PMID: 25085527.
[367] Pakpour AH, Yaghoubidoust M, Campbell P. Persistent and Developing Sleep Problems: A Prospective Cohort Study on the Relationship to Poor Outcome in Patients Attending a Pain Clinic with Chronic Low Back Pain. Pain practice : the official journal of World Institute of Pain. 2018;18(1):79-86. doi: 10.1111/papr.12584. PubMed PMID: 28423222.
[368] Abbasi M, Kazemifar AM, Fatorechi H, Yazdi Z. Sleep Quality, Quality of Life and Insomnia Among Patients with Chronic Low Back Pain Compared to Normal Individuals. Sleep & Hypnosis. 2018;20(3):184-9. doi: 10.5350/Sleep.Hypn.2017.19.0151. PubMed PMID: 131651464. Language: English. Entry Date: 20180912. Revision Date: 20181008. Publication Type: Article. Journal Subset: Biomedical.
[369] Sezgin M, Hasanefendioğlu EZ, Sungur MA, Incel NA, Çimen ÖB, Kanık A, et al. Sleep quality in patients with chronic low back pain: a cross-sectional study assesing its relations with pain, functional status and quality of life. J Back Musculoskelet Rehabil. 2015;28(3):433-41. doi: 10.3233/BMR-140537. PubMed PMID: 25322735.
[370] Heffner KL, France CR, Trost Z, Ng HM, Pigeon WR, Heffner KL, et al. Chronic low back pain, sleep disturbance, and interleukin-6. Clinical Journal of Pain. 2011;27(1):35-41. doi: 10.1097/AJP.0b013e3181eef761. PubMed PMID: 104976796. Language: English. Entry Date: 20110415. Revision Date: 20191030. Publication Type: journal article.
[371] Bahouq H, Allali F, Rkain H, Hmamouchi I, Hajjaj-Hassouni N. Prevalence and severity of insomnia in chronic low back pain patients. Rheumatol Int. 2013;33(5):1277-81. doi: 10.1007/s00296-012-2550-x. PubMed PMID: 23124732.
[372] Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med. 2007;3(5 Suppl):S7-10.
[373] Li W, Gong Y, Liu J, Guo Y, Tang H, Qin S, et al. Peripheral and Central Pathological Mechanisms of Chronic Low Back Pain: A Narrative Review. Journal of pain research. 2021;14:1483-94. doi: 10.2147/jpr.S306280. PubMed PMID: 34079363.
[374] Wadhwa M, Kumari P, Chauhan G, Roy K, Alam S, Kishore K, et al. Sleep deprivation induces spatial memory impairment by altered hippocampus neuroinflammatory responses and glial cells activation in rats. Journal of neuroimmunology. 2017;312:38-48. doi: 10.1016/j.jneuroim.2017.09.003. PubMed PMID: 28912034.

[375] Manchanda S, Singh H, Kaur T, Kaur G. Low-grade neuroinflammation due to chronic sleep deprivation results in anxiety and learning and memory impairments. Molecular and cellular biochemistry. 2018;449:63-72. doi: 10.1007/s11010-018-3343-7. PubMed PMID: 29549603.
[376] Marin R, Cyhan T, Miklos W. Sleep Disturbance in Patients With Chronic Low Back Pain. Am J Phys Med Rehabil. 2006;85(5):430-5. doi: 10.1097/01.phm.0000214259.06380.79.
[377] Kelly G, Blake C, Power C, O'keeffe D, Fullen B. The association between chronic low back pain and sleep: a systematic review. Clin J Pain. 2011;27(2):169-81. doi: 10.1097/AJP.0b013e3181f3bdd5. PubMed PMID: 20842008.
[378] Burgess HJ, Rizvydeen M, Kimura M, Pollack MH, Hobfoll SE, Rajan KB, et al. An Open Trial of Morning Bright Light Treatment Among US Military Veterans with Chronic Low Back Pain: A Pilot Study. Pain medicine (Malden, Mass). 2019;20(4):770-8. doi: 10.1093/pm/pny174. PubMed PMID: 30204903.
[379] Akodu AK, Akindutire OM. The effect of stabilization exercise on pain-related disability, sleep disturbance, and psychological status of patients with non-specific chronic low back pain. The Korean journal of pain. 2018;31(3):199-205. doi: 10.3344/kjp.2018.31.3.199. PubMed PMID: 30013734.
[380] Heapy AA, Higgins DM, Goulet JL, LaChappelle KM, Driscoll MA, Czlapinski RA, et al. Interactive Voice Response-Based Self-management for Chronic Back Pain: The COPES Noninferiority Randomized Trial. JAMA internal medicine. 2017;177(6):765-73. doi: 10.1001/jamainternmed.2017.0223. PubMed PMID: 28384682.
[381] Schuh-Hofer S, Wodarski R, Pfau D, Caspani O, Magerl W, Kennedy J, et al. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. Pain. 2013;154(9):1613-21. doi: 10.1016/j.pain.2013.04.046. PubMed PMID: 23707287.
[382] Staffe AT, Bech MW, Clemmensen SLK, Nielsen HT, Larsen DB, Petersen KK. Total sleep deprivation increases pain sensitivity, impairs conditioned pain modulation and facilitates temporal summation of pain in healthy participants. PloS one. 2019;14(12):e0225849. doi: 10.1371/journal.pone.0225849. PubMed PMID: 31800612.
[383] Sherman KJ, Wellman RD, Cook AJ, Cherkin DC, Ceballos RM. Mediators of yoga and stretching for chronic low back pain. Evidence-based complementary and alternative medicine : eCAM. 2013;2013:130818. doi: 10.1155/2013/130818. PubMed PMID: 23690832.
[384] Roseen EJ, Gerlovin H, Femia A, Cho J, Bertisch S, Redline S, et al. Yoga, Physical Therapy, and Back Pain Education for Sleep Quality in Low-Income Racially Diverse Adults with Chronic Low Back Pain: a Secondary Analysis of a Randomized Controlled Trial. Journal of general internal medicine. 2020;35(1):167-76. doi: 10.1007/s11606-019-05329-4. PubMed PMID: 31667747.
[385] Koffel E, Kats AM, Kroenke K, Bair MJ, Gravely A, DeRonne B, et al. Sleep Disturbance Predicts Less Improvement in Pain Outcomes: Secondary Analysis of the SPACE Randomized Clinical Trial. Pain medicine (Malden, Mass). 2019. doi: 10.1093/pm/pnz221. PubMed PMID: 31529104.
[386] Kovacs FM, Seco J, Royuela A, Betegon JN, Sánchez-Herráez S, Meli M, et al. The association between sleep quality, low back pain and disability: A prospective study in routine practice. European journal of pain (London, England). 2018;22(1):114-26. doi: 10.1002/ejp.1095. PubMed PMID: 28845556.
[387] Stroup D, Berlin J, Morton S, Olkin I, Williamson G. MOOSE guidelines for meta-analyses and systematic reviews of observational studies. Jama. 2000;283:2008-12.
[388] Wong AYL, Kawchuk G, Parent E, Prasad N. Within- and between-day reliability of spinal stiffness measurements obtained using a computer controlled mechanical indenter in individuals with and without low back pain. Man Ther. 2013;18(5):395-402. doi: 10.1016/j.math.2013.02.003.
[389] Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280. doi: 10.7326/0003-4819-158-4-201302190-00009.
[390] Jill AH, Pierre Ct, Claire B. Evaluation of the Quality of Prognosis Studies in Systematic Reviews. Ann Intern Med. 2006;144(6):427. doi: 10.7326/0003-4819-144-6-200603210-00010.
[391] Ubachs J, Ziemons J, Minis-Rutten I, Kruitwagen R, Kleijnen J, Lambrechts S, et al. Sarcopenia and ovarian cancer survival: a systematic review and meta-analysis. Journal of cachexia, sarcopenia and muscle. 2019;10(6):1165-74. doi: 10.1002/jcsm.12468. PubMed PMID: 31389674.
[392] Øverås CK, Villumsen M, Axén I, Cabrita M, Leboeuf-Yde C, Hartvigsen J, et al. Association between objectively measured physical behaviour and neck- and/or low back pain: A systematic review. Eur J Pain. 2020;24(6):1007-22. doi: 10.1002/ejp.1551.

[393] Huguet A, Hayden J, Stinson J, McGrath P, Chambers C, Tougas M, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. Systematic reviews. 2013;2:71. doi: 10.1186/2046-4053-2-71. PubMed PMID: 24007720.
[394] Nordeman L, Thorselius L, Gunnarsson R, Mannerkorpi K. Predictors for future activity limitation in women with chronic low back pain consulting primary care: a 2-year prospective longitudinal cohort study. BMJ open. 2017;7(6):e013974. doi: 10.1136/bmjopen-2016-013974. PubMed PMID: 28674128.
[395] Rabey M, Smith A, Beales D, Slater H, O'Sullivan P. Multidimensional prognostic modelling in people with chronic axial low back pain. The Clinical Journal of Pain. 2017;33(10):877-91. doi: http://dx.doi.org/10.1097/AJP.0000000000000478. PubMed PMID: 1966150657; 2017-40033-003.
[396] Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test–retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. J Psychosom Res. 2002;53(3):737-40. doi: 10.1016/S0022-3999(02)00330-6.
[397] Miller K, Yarlas A, Wen W, Kowalski M, Lynch SY, Dain B, et al. Correlates of improvement in physical quality of life and quality of sleep among chronic low back pain patients with treatment with buprenorphine transdermal system (BTDS). Value in Health. 2013;16(3):A122. doi: 10.1016/j.jval.2013.03.587.
[398] Yarlas A, Miller K, Wen W, Lynch SY, Ripa SR, Pergolizzi JV, et al. Buprenorphine transdermal system improves sleep quality and reduces sleep disturbance in patients with moderate-to-severe chronic low back pain: Results from two randomized controlled trials. Pain Practice. 2016;16(3):345-58. doi: http://dx.doi.org/10.1111/papr.12281. PubMed PMID: 1890134659; 2016-11448-013.
[399] Jungquist C, O'Brien C, Matteson-Rusby S, Smith M, Pigeon W, Xia Y, et al. The efficacy of cognitive-behavioral therapy for insomnia in patients with chronic pain. Sleep Med. 2010;11(3):302-9. doi: 10.1016/j.sleep.2009.05.018. PubMed PMID: 20133188.
[400] Hemphill J. Interpreting the magnitudes of correlation coefficients. The American psychologist. 2003;58(1):78-9. doi: 10.1037/0003-066x.58.1.78. PubMed PMID: 12674822.
[401] Wittig RM, Zorick FJ, Blumer D, Heilbronn M, Roth T. Disturbed sleep in patients complaining of chronic pain. The Journal of nervous and mental disease. 1982;170(7):429-31.
[402] Smith M, Remeniuk B, Finan P, Speed T, Tompkins D, Robinson M, et al. Sex differences in measures of central sensitization and pain sensitivity to experimental sleep disruption: implications for sex differences in chronic pain. Sleep. 2019;42(2). doi: 10.1093/sleep/zsy209. PubMed PMID: 30371854.
[403] Smith MT, Edwards RR, McCann UD, Haythornthwaite J. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. Sleep. 2007;30(4):494-505. doi: 10.1093/sleep/30.4.494. PubMed PMID: WOS:000245966600015.
[404] Krause A, Prather A, Wager T, Lindquist M, Walker M. The Pain of Sleep Loss: A Brain Characterization in Humans. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2019;39(12):2291-300. doi: 10.1523/jneurosci.2408-18.2018. PubMed PMID: 30692228.
[405] Alexandre C, Latremoliere A, Ferreira A, Miracca G, Yamamoto M, Scammell T, et al. Decreased alertness due to sleep loss increases pain sensitivity in mice. Nature medicine. 2017;23(6):768-74. doi: 10.1038/nm.4329. PubMed PMID: 28481358.
[406] Alsaadi MS, McAuley HJ, Hush MJ, Lo JS, Bartlett RD, Grunstein GR, et al. The Bidirectional Relationship Between Pain Intensity and Sleep Disturbance/Quality in Patients With Low Back Pain. Clin J Pain. 2014;30(9):755-65. doi: 10.1097/AJP.0000000000000055.
[407] Haack M, Sanchez E, Mullington JM. Elevated Inflammatory Markers in Response to Prolonged Sleep Restriction Are Associated With Increased Pain Experience in Healthy Volunteers. Sleep. 2007;30(9):1145-52. doi: 10.1093/sleep/30.9.1145.
[408] Irwin M, Olmstead R, Carroll J. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. Biological psychiatry. 2016;80(1):40-52. doi: 10.1016/j.biopsych.2015.05.014. PubMed PMID: 26140821.
[409] Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep Deprivation and Activation of Morning Levels of Cellular and Genomic Markers of Inflammation. Arch Intern Med. 2006;166(16):1756-62. doi: 10.1001/archinte.166.16.1756.

[410] Loggia M, Chonde D, Akeju O, Arabasz G, Catana C, Edwards R, et al. Evidence for brain glial activation in chronic pain patients. Brain : a journal of neurology. 2015;138:604-15. doi: 10.1093/brain/awu377. PubMed PMID: 25582579.
[411] Nijs J, Loggia ML, Polli A, Moens M, Huysmans E, Goudman L, et al. Sleep disturbances and severe stress as glial activators: key targets for treating central sensitization in chronic pain patients? Expert opinion on therapeutic targets. 2017;21(8):817-26.
[412] Pejovic S, Basta M, Vgontzas A, Kritikou I, Shaffer M, Tsaoussoglou M, et al. Effects of recovery sleep after one work week of mild sleep restriction on interleukin-6 and cortisol secretion and daytime sleepiness and performance. American journal of physiology Endocrinology and metabolism. 2013;305(7):E890-6. doi: 10.1152/ajpendo.00301.2013. PubMed PMID: 23941878.
[413] Chennaoui M, Drogou C, Sauvet F, Gomez-Merino D, Scofield D, Nindl B. Effect of acute sleep deprivation and recovery on Insulin-like Growth Factor-I responses and inflammatory gene expression in healthy men. European cytokine network. 2014;25(3):52-7. doi: 10.1684/ecn.2014.0356. PubMed PMID: 25373853.
[414] Irwin MR, Olmstead R, Breen EC, Witarama T, Carrillo C, Sadeghi N, et al. Cognitive Behavioral Therapy and Tai Chi Reverse Cellular and Genomic Markers of Inflammation in Late-Life Insomnia: A Randomized Controlled Trial. Biol Psychiatry. 2015;78(10):721-9. doi: 10.1016/j.biopsych.2015.01.010.
[415] Irwin M, Olmstead R, Carrillo C, Sadeghi N, Breen E, Witarama T, et al. Cognitive behavioral therapy vs. Tai Chi for late life insomnia and inflammatory risk: a randomized controlled comparative efficacy trial. Sleep. 2014;37(9):1543-52. doi: 10.5665/sleep.4008. PubMed PMID: 25142571.
[416] Steenstra I, Munhall C, Irvin E, Oranye N, Passmore S, Van Eerd D, et al. Systematic Review of Prognostic Factors for Return to Work in Workers with Sub Acute and Chronic Low Back Pain. Journal of occupational rehabilitation. 2017;27(3):369-81. doi: 10.1007/s10926-016-9666-x. PubMed PMID: 27647141.
[417] Wilkens P, Scheel IB, Grundnes O, Hellum C, Storheim K. Prognostic factors of prolonged disability in patients with chronic low back pain and lumbar degeneration in primary care: a cohort study. Spine (Phila Pa 1976). 2013;38(1):65-74. doi: 10.1097/BRS.0b013e318263bb7b.
[418] Oliveira C, Pinheiro M, Teixeira R, Franco M, Silva F, Hisamatsu T, et al. Physical activity as a prognostic factor of pain intensity and disability in patients with low back pain: A systematic review. European journal of pain (London, England). 2019;23(7):1251-63. doi: 10.1002/ejp.1395. PubMed PMID: 30920074.
[419] Jensen OK, Nielsen CV, Stengaard-Pedersen K. One-year prognosis in sick-listed low back pain patients with and without radiculopathy. Prognostic factors influencing pain and disability. Spine J. 2010;10(8):659-75. doi: 10.1016/j.spinee.2010.03.026.
[420] Nitter AK, Pripp AH, Forseth KØ. Are sleep problems and non-specific health complaints risk factors for chronic pain? A prospective population-based study with 17 year follow-up. Scandinavian journal of pain. 2012;3(4):210-7. doi: 10.1016/j.sjpain.2012.04.001. PubMed PMID: 29913872.
[421] Aili K, Nyman T, Hillert L, Svartengren M. Sleep disturbances predict future sickness absence among individuals with lower back or neck-shoulder pain: A 5-year prospective study. Scandinavian Journal of Public Health. 2015;43(3):315-23. doi: http://dx.doi.org/10.1177/1403494814567755. PubMed PMID: 1680459452; 2015-16708-013.
[422] Alsaadi SM, McAuley JH, Hush JM, Bartlett DJ, McKeough ZM, Grunstein RR, et al. Assessing Sleep Disturbance in Low Back Pain: The Validity of Portable Instruments. PLoS One. 2014;9(4):e95824-e. doi: 10.1371/journal.pone.0095824.
[423] Kushida C, Littner M, Morgenthaler T, Alessi C, Bailey D, Coleman J, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep. 2005;28(4):499-521. doi: 10.1093/sleep/28.4.499. PubMed PMID: 16171294.
[424] Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020;396(10258):1204-22.
[425] Sebbag E, Felten R, Sagez F, Sibilia J, Devilliers H, Arnaud L. The world-wide burden of musculoskeletal diseases: a systematic analysis of the World Health Organization Burden of Diseases Database. Ann Rheum Dis. 2019;78(6):844-8.

[426] Vitiello MV, McCurry SM, Shortreed SM, Baker LD, Rybarczyk BD, Keefe FJ, et al. Short-term improvement in insomnia symptoms predicts long-term improvements in sleep, pain, and fatigue in older adults with comorbid osteoarthritis and insomnia. Pain®. 2014;155(8):1547-54.
[427] Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. Internal and emergency medicine. 2017;12(1):103-11. Epub 2016/12/04. doi: 10.1007/s11739-016-1583-7. PubMed PMID: 27913917; PubMed Central PMCID: PMCPMC5247317.
[428] Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-84.
[429] Papaconstantinou E, Cancelliere C, Verville L, Wong JJ, Connell G, Yu HN, et al. Effectiveness of non-pharmacological interventions on sleep characteristics among adults with musculoskeletal pain and a comorbid sleep problem: a systematic review. Chiropr Man Therap. 2021;29(1). doi: 10.1186/s12998-021-00381-6. PubMed PMID: WOS:000671327500001.
[430] Dworkin RH, Bruehl S, Fillingim RB, Loeser JD, Terman GW, Turk DC. Multidimensional diagnostic criteria for chronic pain: introduction to the ACTTION–American pain society pain taxonomy (AAPT). The Journal of Pain. 2016;17(9):T1-T9.
[431] Qaseem A, Wilt TJ, McLean RM, Forciea MA, Physicians* CGCotACo. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Annals of internal medicine. 2017;166(7):514-30.
[432] Belavy DL, Diwan AD, Ford J, Miller CT, Hahne AJ, Mundell N, et al. Network meta-analysis for comparative effectiveness of treatments for chronic low back pain disorders: systematic review protocol. BMJ Open. 2021;11(11):e057112. Epub 2021/12/01. doi: 10.1136/bmjopen-2021-057112. PubMed PMID: 34845083; PubMed Central PMCID: PMCPMC8634013.
[433] Gianola S, Bargeri S, Del Castillo G, Corbetta D, Turolla A, Andreano A, et al. Effectiveness of treatments for acute and subacute mechanical non-specific low back pain: a systematic review with network meta-analysis. Br J Sports Med. 2022;56(1):41-50. doi: 10.1136/bjsports-2020-103596.
[434] Gianola S, Castellini G, Andreano A, Corbetta D, Frigerio P, Pecoraro V, et al. Effectiveness of treatments for acute and sub-acute mechanical non-specific low back pain: protocol for a systematic review and network meta-analysis. Syst Rev. 2019;8(1):196. Epub 2019/08/10. doi: 10.1186/s13643-019-1116-3. PubMed PMID: 31395091; PubMed Central PMCID: PMCPMC6688358.
[435] De Crescenzo F, D'Alò GL, Ostinelli EG, Ciabattini M, Di Franco V, Watanabe N, et al. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. The Lancet. 2022;400(10347):170-84.
[436] Ho EK, Chen L, Simic M, Ashton-James CE, Comachio J, Wang DXM, et al. Psychological interventions for chronic, non-specific low back pain: systematic review with network meta-analysis. BMJ. 2022;376:e067718. Epub 2022/04/01. doi: 10.1136/bmj-2021-067718. PubMed PMID: 35354560; PubMed Central PMCID: PMCPMC8965745 at www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.
[437] Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2019.
[438] White IR. Network meta-analysis. The Stata Journal. 2015;15(4):951-85.
[439] Chaimani A, Salanti G. Visualizing assumptions and results in network meta-analysis: the network graphs package. The Stata Journal. 2015;15(4):905-50.
[440] Shim SR, Kim S-J, Lee J, Rücker G. Network meta-analysis: application and practice using R software. Epidemiology and health. 2019;41.
[441] Higgins J, Jackson D, Barrett J, Lu G, Ades A, White I. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Research synthesis methods. 2012;3(2):98-110.
[442] Rhodes KM, Turner RM, Higgins JP. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. J Clin Epidemiol. 2015;68(1):52-60. Epub 2014/10/12. doi: 10.1016/j.jclinepi.2014.08.012. PubMed PMID: 25304503; PubMed Central PMCID: PMCPMC4270451.

[443] Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in medicine. 2015;34(6):984-98.
[444] Salanti G, Ades A, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64(2):163-71.
[445] Nikolakopoulou A, Higgins JP, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. CINeMA: an approach for assessing confidence in the results of a network meta-analysis. PLoS medicine. 2020;17(4):e1003082.
[446] Papakonstantinou T, Nikolakopoulou A, Higgins JP, Egger M, Salanti G. Cinema: software for semiautomated assessment of the confidence in the results of network meta-analysis. Campbell Systematic Reviews. 2020;16(1):e1080.
[447] Nijs J, Mairesse O, Neu D, Leysen L, Danneels L, Cagnie B, et al. Sleep disturbances in chronic pain: neurobiology, assessment, and treatment in physical therapist practice. Physical therapy. 2018;98(5):325-35.
[448] Morin CM, Benca R. Chronic insomnia. The Lancet. 2012;379(9821):1129-41.
[449] Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. American Psychologist. 2014;69(2):153.
[450] van der Zweerde T, Bisdounis L, Kyle SD, Lancee J, van Straten A. Cognitive behavioral therapy for insomnia: a meta-analysis of long-term effects in controlled studies. Sleep medicine reviews. 2019;48:101208.
[451] Mitchell LJ, Bisdounis L, Ballesio A, Omlin X, Kyle SD. The impact of cognitive behavioural therapy for insomnia on objective sleep parameters: A meta-analysis and systematic review. Sleep medicine reviews. 2019;47:90-102.
[452] Geiger-Brown JM, Rogers VE, Liu W, Ludeman EM, Downton KD, Diaz-Abad M. Cognitive behavioral therapy in persons with comorbid insomnia: a meta-analysis. Sleep medicine reviews. 2015;23:54-67.
[453] Lund HG, Rybarczyk BD, Perrin PB, Leszczyszyn D, Stepanski E. The discrepancy between subjective and objective measures of sleep in older adults receiving CBT for comorbid insomnia. Journal of clinical psychology. 2013;69(10):1108-20.
[454] Aili K, Åström-Paulsson S, Stoetzer U, Svartengren M, Hillert L. Reliability of actigraphy and subjective sleep measurements in adults: the design of sleep assessments. Journal of Clinical Sleep Medicine. 2017;13(1):39-47.
[455] Segura-Jiménez V, Camiletti-Moirón D, Munguía-Izquierdo D, Álvarez-Gallardo IC, Ruiz JR, Ortega FB, et al. Agreement between self-reported sleep patterns and actigraphy in fibromyalgia and healthy women. Clin Exp Rheumatol. 2015;33(1 Suppl 88):S58-S67.
[456] Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. American journal of preventive medicine. 2009;36(5):452-7.
[457] Wallman EJ, Segrave RA, Gordon MS, Fraser MJOB, Pavlou C, Melvin GA. Acceptability, safety and tolerability of antidepressant repetitive transcranial magnetic stimulation for adolescents: A mixed-methods investigation. Journal of Affective Disorders. 2022;310:43-51.
[458] Centorrino F, Hernán MA, Drago-Ferrante G, Rendall M, Apicella A, Längar G, et al. Factors associated with noncompliance with psychiatric outpatient visits. Psychiatric Services. 2001;52(3):378-80.
[459] Swift JK, Greenberg RP. Premature discontinuation in adult psychotherapy: a meta-analysis. Journal of consulting and clinical psychology. 2012;80(4):547.
[460] Ong JC, Kuo TF, Manber R. Who is at risk for dropout from group cognitive-behavior therapy for insomnia? Journal of psychosomatic research. 2008;64(4):419-25.
[461] Bighelli I, Rodolico A, García-Mieres H, Pitschel-Walz G, Hansen W-P, Schneider-Thoma J, et al. Psychosocial and psychological interventions for relapse prevention in schizophrenia: a systematic review and network meta-analysis. The Lancet Psychiatry. 2021;8(11):969-80. doi: 10.1016/s2215-0366(21)00243-1.
[462] Loymans RJ, Gemperli A, Cohen J, Rubinstein SM, Sterk PJ, Reddel HK, et al. Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis. BMJ. 2014;348.
[463] Nussbaumer-Streit B, Klerings I, Dobrescu A, Persad E, Stevens A, Garritty C, et al. Excluding non-English publications from evidence-syntheses did not change conclusions: a meta-epidemiological study. Journal of clinical epidemiology. 2020;118:42-54.

[464] Hopewell S, Chan A-W, Collins GS, Hróbjartsson A, Moher D, Schulz KF, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. The Lancet. 2025;405(10489):1633-40. doi: 10.1016/S0140-6736(25)00672-5.
[465] Eldridge S, Chan C, Campbell M, Bond C, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ (Clinical research ed). 2016;355:i5239. doi: 10.1136/bmj.i5239. PubMed PMID: 27777223.
[466] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213. doi: 10.1016/0165-1781(89)90047-4.
[467] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Screening questionnaire before TMS: an update. 2011.
[468] Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol. 2010;10:1-10.
[469] Whitehead A, Julious S, Cooper C, Campbell M. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Statistical methods in medical research. 2016;25(3):1057-73. doi: 10.1177/0962280215588241. PubMed PMID: 26092476.
[470] Attal N, Poindessous-Jazat F, De Chauvigny E, Quesada C, Mhalla A, Ayache SS, et al. Repetitive transcranial magnetic stimulation for neuropathic pain: a randomized multicentre sham-controlled trial. Brain. 2021;144(11):3328-39.
[471] Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biological psychiatry. 2012;72(7):595-603.
[472] Lefaucheur J-P, Nguyen J-P. A practical algorithm for using rTMS to treat patients with chronic pain. Neurophysiologie Clinique. 2019;49(4):301-7.
[473] Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen L, Mall V, et al. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. Clinical Neurophysiology. 2012;123(5):858-82.
[474] Mhalla A, Baudic S, de Andrade DC, Gautron M, Perrot S, Teixeira MJ, et al. Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. Pain. 2011;152(7):1478-85. doi: 10.1016/j.pain.2011.01.034. PubMed PMID: WOS:000291474000010.
[475] Zhang Y-p, Liao W-j, Xia W-g. Effect of acupuncture cooperated with low-frequency repetitive transcranial magnetic stimulation on chronic insomnia: a randomized clinical trial. Current Medical Science. 2018;38:491-8.
[476] Guo Y, Zhao X, Zhang X, Li M, Liu X, Lu L, et al. Effects on resting-state EEG phase-amplitude coupling in insomnia disorder patients following 1 Hz left dorsolateral prefrontal cortex rTMS. Human Brain Mapping. 2023.
[477] Liu JQJ, Mak YW, Tang ALY, Kwan C, Al Zoubi F, Wong TKT, et al. Effects of acceptance and commitment therapy plus exercise for older adults with chronic low back pain: A preliminary cluster randomized controlled trial with qualitative interviews. The Journal of Pain. 2025;30:105350. doi: https://doi.org/10.1016/j.jpain.2025.105350.
[478] Dumville JC, Torgerson DJ, Hewitt CE. Reporting attrition in randomised controlled trials. Bmj. 2006;332(7547):969-71.
[479] McCurry SM, Zhu W, Von Korff M, Wellman R, Morin CM, Thakral M, et al. Effect of Telephone Cognitive Behavioral Therapy for Insomnia in Older Adults with Osteoarthritis Pain: A Randomized Clinical Trial. JAMA Internal Medicine. 2021;181(4):530-8. doi: 10.1001/jamainternmed.2020.9049.
[480] Sharma S, Jensen MP, Moseley GL, Abbott JH. Pain education for patients with non-specific low back pain in Nepal: protocol of a feasibility randomised clinical trial (PEN-LBP Trial). BMJ open. 2018;8(8):e022423.
[481] Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012;35(2):287-302.

[482] Marino M, Li Y, Rueschman MN, Winkelman JW, Ellenbogen J, Solet JM, et al. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. Sleep. 2013;36(11):1747-55.
[483] McCrae CS, Williams J, Roditi D, Anderson R, Mundt JM, Miller MB, et al. Cognitive behavioral treatments for insomnia and pain in adults with comorbid chronic insomnia and fibromyalgia: clinical outcomes from the SPIN randomized controlled trial. Sleep. 2019;42(3). doi: 10.1093/sleep/zsy234. PubMed PMID: WOS:000467166400004.
[484] Vickers AJ, Altman DG. Analysing controlled trials with baseline and follow up measurements. Bmj. 2001;323(7321):1123-4.
[485] Stillianesis G, Cavaleri R, Summers SJ, Tang C. Exploring patient perceptions of repetitive transcranial magnetic stimulation as a treatment for chronic musculoskeletal pain: a qualitative study. BMJ open. 2022;12(8):e058928.
[486] Bishop MD, Bialosky JE, Cleland JA. Patient expectations of benefit from common interventions for low back pain and effects on outcome: secondary analysis of a clinical trial of manual therapy interventions. Journal of Manual & Manipulative Therapy. 2011;19(1):20-5.
[487] Ambriz-Tututi M, Alvarado-Reynoso B, Drucker-Colín R. Analgesic effect of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic low back pain. Bioelectromagnetics. 2016;37(8):527-35.
[488] Masoumbeigi M, Alam NR, Kordi R, Rostami M, Rahimiforoushani A, Jafari AH, et al. Altered Amplitude of Low-Frequency Fluctuations of rs-fMRI Signal followed by rTMS Analgesic Effects in Non-Specific Chronic Low Back Pain (CLBP) Patients. Journal of Biomedical Physics & Engineering. 2024;14(5):435.
[489] Zhou J, Wang Y, Luo X, Fitzgerald PB, Cash RF, Fitzgibbon BM, et al. Revisiting the effects of rTMS over the dorsolateral prefrontal cortex on pain: an updated systematic review and meta-analysis. Brain stimulation. 2024.
[490] Che X, Cash RF, Luo X, Luo H, Lu X, Xu F, et al. High-frequency rTMS over the dorsolateral prefrontal cortex on chronic and provoked pain: A systematic review and meta-analysis. Brain Stimulation. 2021;14(5):1135-46.
[491] Li X, Liu Z, Hu Y, Jin R, Lou W, Peng W. Analgesic effects of high-frequency rTMS on pain anticipation and perception. Communications Biology. 2024;7(1):1573. doi: 10.1038/s42003-024-07129-x.
[492] Seminowicz DA, Moayedi M. The Dorsolateral Prefrontal Cortex in Acute and Chronic Pain. The Journal of Pain. 2017;18(9):1027-35. doi: https://doi.org/10.1016/j.jpain.2017.03.008.
[493] Wang F, Tian Z-C, Ding H, Yang X-J, Wang F-D, Ji R-X, et al. A sensory-motor-sensory circuit underlies antinociception ignited by primary motor cortex in mice. Neuron. 2025.
[494] Muzur A, Pace-Schott EF, Hobson JA. The prefrontal cortex in sleep. Trends in cognitive sciences. 2002;6(11):475-81.
[495] Etkin A, Büchel C, Gross JJ. The neural bases of emotion regulation. Nature reviews neuroscience. 2015;16(11):693-700.
[496] Feeser M, Prehn K, Kazzer P, Mungee A, Bajbouj M. Transcranial direct current stimulation enhances cognitive control during emotion regulation. Brain stimulation. 2014;7(1):105-12.
[497] Siebner HR, Funke K, Aberra AS, Antal A, Bestmann S, Chen R, et al. Transcranial magnetic stimulation of the brain: What is stimulated? – A consensus and critical position paper. Clinical Neurophysiology. 2022;140:59-97. doi: https://doi.org/10.1016/j.clinph.2022.04.022.
[498] Badr MY, Ahmed Gk, Amer RA, Aref HM, Salem RM, Elmokadem HA, et al. Effects of Transcranial Magnetic Stimulation on Sleep Quality in Fibromyalgia: A Double-Blind Randomized Clinical Trial. Sleep Med. 2024. doi: https://doi.org/10.1016/j.sleep.2024.09.043.
[499] Faerman A, Bishop JH, Stimpson KH, Phillips A, Gülser M, Amin H, et al. Stanford Hypnosis Integrated with Functional Connectivity-targeted Transcranial Stimulation (SHIFT): a preregistered randomized controlled trial. Nature Mental Health. 2024;2(1):96-103. doi: 10.1038/s44220-023-00184-z.
[500] Kong Q, Li T, Reddy S, Hodges S, Kong J. Brain stimulation targets for chronic pain: Insights from meta-analysis, functional connectivity and literature review. Neurotherapeutics. 2024;21(1):e00297.
[501] De Baets L, Runge N, Labie C, Mairesse O, Malfliet A, Verschueren S, et al. The interplay between symptoms of insomnia and pain in people with osteoarthritis: A narrative review of the current evidence. Sleep Medicine Reviews. 2023;70:101793. doi: https://doi.org/10.1016/j.smrv.2023.101793.

[502] Safety ACo, Care QiH. Low back pain clinical care standard. Clinical Care Standards. 2022.
[503] Ploner M. Developing neuroimaging-based biomarkers of pain: systematic and coordinated approaches. PAIN. 2025;166(2):234-5. doi: 10.1097/j.pain.0000000000003393. PubMed PMID: 00006396-202502000-00003.
[504] Ho RLM, Park J, Wang W-e, Thomas JS, Cruz-Almeida Y, Coombes SA. Lower individual alpha frequency in individuals with chronic low back pain and fear of movement. PAIN. 2024;165(5).
[505] Alsaadi SM, McAuley JH, Hush JM, Bartlett DJ, Henschke N, Grunstein RR, et al. Detecting insomnia in patients with low back pain: accuracy of four self-report sleep measures. BMC Musculoskelet Disord. 2013;14(1):196-. doi: 10.1186/1471-2474-14-196.
[506] Runge N, Ahmed I, Perea J, Labie C, Roland A, Goossens Z, et al. Terminology and definitions of sleep problems and disorders used in chronic musculoskeletal pain research—a scoping review with recommendations for future research. PAIN. 2025.
[507] Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. Jama. 2016;315(15):1624-45.
[508] Reid MC, Eccleston C, Pillemer K. Management of chronic pain in older adults. Bmj. 2015;350.
[509] Akodu AK, Nwanne CA, Fapojuwo OA. Efficacy of neck stabilization and Pilates exercises on pain, sleep disturbance and kinesiophobia in patients with non-specific chronic neck pain: A randomized controlled trial. Journal of Bodywork and Movement Therapies. 2021;26:411-9. doi: 10.1016/j.jbmt.2020.09.008. PubMed PMID: WOS:000652679200006.
[510] Almeida TF, Roizenblatt S, Benedito-Silva AA, Tufik S. The effect of combined therapy (ultrasound and interferential current) on pain and sleep in fibromyalgia. Pain. 2003;104(3):665-72. doi: 10.1016/s0304-3959(03)00139-8. PubMed PMID: WOS:000185101600026.
[511] Alves CRR, Santiago BM, Lima FR, Otaduy MCG, Calich AL, Tritto ACC, et al. Creatine Supplementation in Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis Care & Research. 2013;65(9):1449-59. doi: 10.1002/acr.22020. PubMed PMID: WOS:000323480600008.
[512] Amirova A, Cropley M, Theadom A. The Effectiveness of the Mitchell Method Relaxation Technique for the Treatment of Fibromyalgia Symptoms: A Three-Arm Randomized Controlled Trial. International Journal of Stress Management. 2017;24(1):86-106. doi: 10.1037/str0000017. PubMed PMID: WOS:000397424100005.
[513] Amutio A, Franco C, Sánchez-Sánchez LC, Pérez-Fuentes MdC, Gázquez-Linares JJ, Van Gordon W, et al. Effects of mindfulness training on sleep problems in patients with fibromyalgia. Frontiers in Psychology. 2018;9:8. doi: https://doi.org/10.3389/fpsyg.2018.01365. PubMed PMID: 2383127365; 2018-41319-001.
[514] Bakir E, Baglama SS, Gursoy S. The effects of reflexology on pain and sleep deprivation in patients with rheumatoid arthritis: A randomized controlled trial. Complementary therapies in clinical practice. 2018;31:315-9. doi: 10.1016/j.ctcp.2018.02.017.
[515] Basler HD, Rehfisch HP. Cognitive-behavioral therapy in patients with ankylosing spondylitis in a German self-help organization. Journal of psychosomatic research. 1991;35(2-3):345-54. doi: 10.1016/0022-3999(91)90089-7. PubMed PMID: 1710669.
[516] Bestaş E, Dündar Ü, Köken T, Koca B, Yeşil H. The comparison of effects of balneotherapy, water-based and land-based exercises on disease activity, symptoms, sleep quality, quality of life and serum sclerostin level in patients with ankylosing spondylitis: A prospective, randomized study. Archives of Rheumatology. 2022;37(2):159-68. doi: 10.46497/ArchRheumatol.2022.9024. PubMed PMID: 157398838. Language: English. Entry Date: 20220630. Revision Date: 20220701. Publication Type: Article.
[517] Blödt S, Pach D, Kaster T, Lüdtke R, Icke K, Reisshauer A, et al. Qigong versus exercise therapy for chronic low back pain in adults - A randomized controlled non-inferiority trial. European journal of pain. 2015;19(1):123-31. doi: 10.1002/ejp.529.
[518] Bongi SM, Di Felice C, Del Rosso A, Galluccio F, Landi G, Tai G, et al. The efficacy of the Resseguier method in the treatment of fibromyalgia syndrome: a randomised controlled trial. Clinical and Experimental Rheumatology. 2010;28(6):S46-S50. PubMed PMID: WOS:000286779700008.
[519] Brattberg G. Connective tissue massage in the treatment of fibromyalgia. European journal of pain (London, England). 1999;3(3):235-44. doi: 10.1016/S1090-3801(99)90050-2. PubMed PMID: CN-00395413.
[520] Brietzke AP, Zortea M, Carvalho F, Sanches PRS, Silva DPJ, Torres ILDS, et al. Large Treatment Effect With Extended Home-Based Transcranial Direct Current Stimulation Over Dorsolateral Prefrontal Cortex in

Fibromyalgia: A Proof of Concept Sham-Randomized Clinical Study. Journal of Pain. 2020;21(1-2):212-24. doi: 10.1016/j.jpain.2019.06.013.
[521] Burns JW, Jensen MP, Thorn B, Lillis TA, Carmody J, Newman AK, et al. Cognitive therapy, mindfulness-based stress reduction, and behavior therapy for the treatment of chronic pain: Randomized controlled trial. Pain. 2022;163(2):376-89. doi: 10.1097/j.pain.0000000000002357.
[522] Calandre EP, Rodriguez-Claro ML, Rico-Villademoros F, Vilchez JS, Hidalgo J, Delgado-Rodriguez A. Effects of pool-based exercise in fibromyalgia symptomatology and sleep quality: a prospective randomised comparison between stretching and Ai Chi. Clinical and Experimental Rheumatology. 2009;27(5):S21-S8. PubMed PMID: WOS:000273701500005.
[523] Cánovas F, Abellán-Ruíz MS, García-Muñoz AM, Luque-Rubia AJ, Victoria-Montesinos D, Pérez-Piñero S, et al. Randomised Clinical Trial to Analyse the Efficacy of Eggshell Membrane to Improve Joint Functionality in Knee Osteoarthritis. Nutrients. 2022;14(11). doi: 10.3390/nu14112340.
[524] Carson JW, Carson KM, Jones KD, Bennett RM, Wright CL, Mist SD. A pilot randomized controlled trial of the Yoga of Awareness program in the management of fibromyalgia. Pain. 2010;151(2):530-9. doi: 10.1016/j.pain.2010.08.020. PubMed PMID: WOS:000282826100038.
[525] Cash E, Salmon P, Weissbecker I, Rebholz WN, Bayley-Veloso R, Zimmaro LA, et al. Mindfulness Meditation Alleviates Fibromyalgia Symptoms in Women: Results of a Randomized Clinical Trial. Annals of Behavioral Medicine. 2015;49(3):319-30. doi: 10.1007/s12160-014-9665-0. PubMed PMID: WOS:000354206300006.
[526] Castel A, Cascon R, Padrol A, Sala J, Rull M. Multicomponent Cognitive-Behavioral Group Therapy With Hypnosis for the Treatment of Fibromyalgia: Long-Term Outcome. Journal of Pain. 2012;13(3):255-65. doi: 10.1016/j.jpain.2011.11.005. PubMed PMID: WOS:000301612900006.
[527] Castro-Sánchez AM, Aguilar-Ferrándiz ME, Matarán-Peñarrocha GA, del Mar Sánchez-Joya M, Arroyo-Morales M, Fernández-de-las-Peñas C. Short-term effects of a manual therapy protocol on pain, physical function, quality of sleep, depressive symptoms, and pressure sensitivity in women and men with fibromyalgia syndrome: A randomized controlled trial. The Clinical Journal of Pain. 2014;30(7):589-97. PubMed PMID: 1586112381; 2014-24436-006.
[528] Caumo W, Alves RL, Vicuña P, Alves CFDS, Ramalho L, Sanches PRS, et al. Impact of Bifrontal Home-Based Transcranial Direct Current Stimulation in Pain Catastrophizing and Disability due to Pain in Fibromyalgia: A Randomized, Double-Blind Sham-Controlled Study. Journal of Pain. 2022;23(4):641-56. doi: 10.1016/j.jpain.2021.11.002. PubMed Central PMCID: PMCSanofi Aventis(Brazil).
[529] Cheung C, Wyman JF, Resnick B, Savik K. Yoga for managing knee osteoarthritis in older women: a pilot randomized controlled trial. Bmc Complementary and Alternative Medicine. 2014;14. doi: 10.1186/1472-6882-14-160. PubMed PMID: WOS:000336858200001.
[530] Colbert AP, Markov MS, Banerji M, Pilla AA. Magnetic mattress pad use in patients with fibromyalgia: a randomized double-blind pilot study. Journal of Back and Musculoskeletal Rehabilitation. 1999;13(1):19-31. doi: 10.3233/bmr-1999-13104. PubMed PMID: WOS:000085636800003.
[531] Currie SR, Wilson KG, Pontefract AJ, deLaplante L. Cognitive-behavioral treatment of insomnia secondary to chronic pain. Journal of Consulting and Clinical Psychology. 2000;68(3):407-16. doi: 10.1037//0022-006x.68.3.407. PubMed PMID: WOS:000087651500005.
[532] Dall'Agnol L, Medeiros LF, Torres ILS, Deitos A, Brietzke A, Laste G, et al. Repetitive transcranial magnetic stimulation increases the corticospinal inhibition and the brain-derived neurotrophic factor in chronic myofascial pain syndrome: An explanatory double-blinded, randomized, sham-controlled trial. Journal of Pain. 2014;15(8):845-55. doi: 10.1016/j.jpain.2014.05.001. PubMed Central PMCID: PMCSanofi Aventis(Brazil).
[533] Darnall BD, Roy A, Chen AL, Ziadni MS, Keane RT, You DS, et al. Comparison of a Single-Session Pain Management Skills Intervention With a Single-Session Health Education Intervention and 8 Sessions of Cognitive Behavioral Therapy in Adults With Chronic Low Back Pain: A Randomized Clinical Trial. JAMA network open. 2021;4(8):e2113401. doi: 10.1001/jamanetworkopen.2021.13401. PubMed PMID: 34398206.
[534] De Medeiros SA, De Almeida Silva HJ, Do Nascimento RM, Da Silva Maia JB, De Almeida Lins CA, De Souza MC. Mat Pilates is as effective as aquatic aerobic exercise in treating women with fibromyalgia: A clinical, randomized and blind trial. Advances in Rheumatology. 2020;60(1). doi: 10.1186/s42358-020-0124-2.
[535] Deluze C, Bosia L, Zirbs A, Chantraine A, Vischer TL. Electroacupuncture in fibromyalgia: Results of a controlled trial. British Medical Journal. 1992;305(6864):1249-52. doi: 10.1136/bmj.305.6864.1249.

[536] Durcan L, Wilson F, Cunnane G. The effect of exercise on sleep and fatigue in rheumatoid arthritis: a randomized controlled study. The Journal of rheumatology. 2014;41(10):1966-73. doi: 10.3899/jrheum.131282. PubMed PMID: 25128510.
[537] Edinger JD, Wohlgemuth WK, Krystal AD, Rice JR. Behavioral insomnia therapy for fibromyalgia patients - A randomized clinical trial. Archives of Internal Medicine. 2005;165(21):2527-35. doi: 10.1001/archinte.165.21.2527. PubMed PMID: WOS:000233510200014.
[538] Ekici G, Unal E, Akbayrak T, Vardar-Yagli N, Yakut Y, Karabulut E. Effects of active/passive interventions on pain, anxiety, and quality of life in women with fibromyalgia: Randomized controlled pilot trial. Women & Health. 2017;57(1):88-107. doi: 10.1080/03630242.2016.1153017. PubMed PMID: WOS:000390989300006.
[539] Ericsson A, Palstam A, Larsson A, Lofgren M, Bileviciute-Ljungar I, Bjersing J, et al. Resistance exercise improves physical fatigue in women with fibromyalgia: a randomized controlled trial. Arthritis Research & Therapy. 2016;18. doi: 10.1186/s13075-016-1073-3. PubMed PMID: WOS:000381728500002.
[540] Fernández García R, Suárez Holgado JD, Formieles Ortiz I, Zurita Ortega F, Valverde Cepeda M, Fernández Sánchez M. Using a laser based program in patients diagnosed with fibromyalgia. Reumatologia clinica. 2011;7(2):94-7. doi: 10.1016/j.reuma.2010.01.007. PubMed PMID: 21794791.
[541] Field T, Diego M, Gonzalez G, Funk CG. Knee arthritis pain is reduced and range of motion is increased following moderate pressure massage therapy. Complementary Therapies in Clinical Practice. 2015;21(4):233-7. doi: 10.1016/j.ctcp.2015.08.002. PubMed PMID: WOS:000368920200005.
[542] Field T, Hernandez-Reif M, Diego M, Fraser M. Lower back pain and sleep disturbance are reduced following massage therapy. Journal of bodywork and movement therapies. 2007;11(2):141-5.
[543] Fonseca ACS, Faria PC, Alcântara MA, Pinto WD, De Carvalho LG, Lopes FG, et al. Effects of aquatic physiotherapy or health education program in women with fibromyalgia: a randomized clinical trial. Physiotherapy theory and practice. 2021;37(5):620-32. doi: 10.1080/09593985.2019.1639229.
[544] Franco KFM, Miyamoto GC, Franco YRD, Santo Salvador EME, do Nascimento BCB, Menten LA, et al. Is Pilates more effective and cost-effective than aerobic exercise in the treatment of patients with fibromyalgia syndrome? A randomized controlled trial with economic evaluation. European Journal of Pain. 2022. doi: 10.1002/ejp.2039. PubMed PMID: WOS:000857024500001.
[545] Gillis ME, Lumley MA, Mosley-Williams A, Leisen JCC, Roehrs T. The health effects of at-home written emotional disclosure in fibromyalgia: A randomized trial. Annals of Behavioral Medicine. 2006;32(2):135-46. doi: 10.1207/s15324796abm3202_11.
[546] Goldway N, Ablin J, Lubin O, Zamir Y, Keynan JN, Or-Borichev A, et al. Volitional limbic neuromodulation exerts a beneficial clinical effect on Fibromyalgia. Neuroimage. 2019;186:758-70. doi: 10.1016/j.neuroimage.2018.11.001. PubMed PMID: WOS:000455968400067.
[547] Gur A, Karakoc M, Nas K, Cevik R, Sarac J, Demir E. Efficacy of low power laser therapy in fibromyalgia: A single-blind, placebo-controlled trial. Lasers in Medical Science. 2002;17(1):57-61. doi: 10.1007/s10103-002-8267-4. PubMed PMID: WOS:000174402500011.
[548] Haak T, Scott B. The effect of Qigong on Fibromyalgia (FMS): A controlled randomized study. Disability and Rehabilitation. 2008;30(8):625-33. doi: 10.1080/09638280701400540.
[549] Hagiwara Y, Yabe Y, Yamada H, Watanabe T, Kanazawa K, Koide M, et al. Effects of a wearable type lumbosacral support for low back pain among hospital workers: A randomized controlled trial. Journal of Occupational Health. 2017;59(2):201-9. doi: 10.1539/joh.16-0203-OA. PubMed PMID: WOS:000399129800014.
[550] Hargrove JB, Bennett RM, Simons DG, Smith SJ, Nagpal S, Deering DE. A randomized placebo-controlled study of noninvasive cortical electrostimulation in the treatment of fibromyalgia patients. Pain Med. 2012;13(1):115-24. doi: 10.1111/j.1526-4637.2011.01292.x. PubMed PMID: 22233397.
[551] Harvey M-P, Lorrain D, Martel M, Bergeron-Vezina K, Houde F, Séguin M, et al. Can we improve pain and sleep in elderly individuals with transcranial direct current stimulation? - Results from a randomized controlled pilot study. Clinical interventions in aging. 2017;12:937-47. doi: 10.2147/CIA.S133423. PubMed PMID: 28652716.
[552] Hedman-Lagerlof M, Hedman-Lagerlof E, Axelsson E, Ljotsson B, Engelbrektsson J, Hultkrantz S, et al. Internet-Delivered Exposure Therapy for Fibromyalgia A Randomized Controlled Trial. Clinical Journal of Pain. 2018;34(6):532-42. doi: 10.1097/ajp.0000000000000566. PubMed PMID: WOS:000432189500006.

[553] Heffner KL, France CR, Ashrafioun L, Quiñones M, Walsh P, Maloney MD, et al. Clinical Pain-related Outcomes and Inflammatory Cytokine Response to Pain Following Insomnia Improvement in Adults With Knee Osteoarthritis. Clin J Pain. 2018;34(12):1133-40. doi: 10.1097/AJP.0000000000000644. PubMed PMID: 30134281.
[554] Hernandez-Reif M, Field T, Krasnegor J, Theakston H. Lower back pain is reduced and range of motion increased after massage therapy. International Journal of Neuroscience. 2001;106(3-4):131-45. doi: 10.3109/00207450109149744. PubMed PMID: WOS:000168009100002.
[555] Innes KE, Selfe TK, Kandati S, Wen S, Huysmans Z. Effects of Mantra Meditation versus Music Listening on Knee Pain, Function, and Related Outcomes in Older Adults with Knee Osteoarthritis: An Exploratory Randomized Clinical Trial (RCT). Evidence-based Complementary and Alternative Medicine. 2018;2018. doi: 10.1155/2018/7683897.
[556] Jones KD, Sherman CA, Mist SD, Carson JW, Bennett RM, Li FZ. A randomized controlled trial of 8-form Tai chi improves symptoms and functional mobility in fibromyalgia patients. Clinical Rheumatology. 2012;31(8):1205-14. doi: 10.1007/s10067-012-1996-2. PubMed PMID: WOS:000307274000009.
[557] Jungquist CR, O'Brien C, Matteson-Rusby S, Smith MT, Pigeon WR, Xia Y, et al. The efficacy of cognitive-behavioral therapy for insomnia in patients with chronic pain. Sleep Med. 2010;11(3):302-9. doi: 10.1016/j.sleep.2009.05.018. PubMed PMID: 20133188.
[558] Kılıç N, Parlar Kılıç S. The effect of progressive muscle relaxation on sleep quality and fatigue in patients with rheumatoid arthritis: A randomized controlled trial. International journal of nursing practice. 2021:e13015. doi: 10.1111/ijn.13015.
[559] Lai CH, Leung TK, Peng CW, Chang KH, Lai MJ, Lai WF, et al. Effects of Far-Infrared Irradiation on Myofascial Neck Pain: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. Journal of Alternative and Complementary Medicine. 2014;20(2):123-9. doi: 10.1089/acm.2013.0122. PubMed PMID: WOS:000338346500009.
[560] Lami MJ, Martinez MP, Miro E, Sanchez AI, Prados G, Caliz R, et al. Efficacy of Combined Cognitive-Behavioral Therapy for Insomnia and Pain in Patients with Fibromyalgia: A Randomized Controlled Trial. Cognitive Therapy and Research. 2018;42(1):63-79. doi: 10.1007/s10608-017-9875-4. PubMed PMID: WOS:000422937800006.
[561] Latocha KM, Løppenthin KB, Østergaard M, Jennum PJ, Hetland ML, Røgind H, et al. The effect of group-based cognitive behavioural therapy for insomnia in patients with rheumatoid arthritis: A randomised controlled trial. Rheumatology (Oxford, England). 2022. doi: 10.1093/rheumatology/keac448.
[562] Lauche R, Spitzer J, Schwahn B, Ostermann T, Bernardy K, Cramer H, et al. Efficacy of cupping therapy in patients with the fibromyalgia syndrome-a randomised placebo controlled trial. Scientific Reports. 2016;6. doi: 10.1038/srep37316. PubMed PMID: WOS:000388269100001.
[563] Lee WJ, Park H. Effects of auricular acupressure on sleep and pain in elderly people who have osteoarthritis and live in nursing homes: A randomized, single-blind, placebo-controlled trial. Explore. 2022. doi: 10.1016/j.explore.2022.07.001.
[564] Lin AP, Chiu CC, Chen SC, Huang YJ, Lai CH, Kang JH. Using High-Definition Transcranial Alternating Current Stimulation to Treat Patients with Fibromyalgia: A Randomized Double-Blinded Controlled Study. Life-Basel. 2022;12(9). PubMed PMID: WOS:000856938900001.
[565] Liu W, Zahner L, Cornell M, Le T, Ratner J, Wang YX, et al. Benefit of Qigong Exercise in Patients With Fibromyalgia: A Pilot Study. International Journal of Neuroscience. 2012;122(11):657-64. doi: 10.3109/00207454.2012.707713. PubMed PMID: WOS:000309751600006.
[566] Loeppenthin K, Esbensen BA, Klausen JM, Ostergaard M, Christensen JF, Tolver A, et al. Efficacy and Acceptability of Intermittent Aerobic Exercise on Polysomnography-Measured Sleep in People With Rheumatoid Arthritis With Self-Reported Sleep Disturbance: A Randomized Controlled Trial. Acr Open Rheumatology. 2022;4(5):395-405. doi: 10.1002/acr2.11403. PubMed PMID: WOS:000747953800001.
[567] Lu JJ, Huang LY, Wu X, Fu WJ, Liu Y. Effect of Tai Ji Quan training on self-reported sleep quality in elderly Chinese women with knee osteoarthritis: a randomized controlled trail. Sleep Medicine. 2017;33:70-5. doi: 10.1016/j.sleep.2016.12.024. PubMed PMID: WOS:000401680000013.
[568] Lumley MA, Schubiner H, Lockhart NA, Kidwell KM, Harte SE, Clauw DJ, et al. Emotional awareness and expression therapy, cognitive behavioral therapy, and education for fibromyalgia: a cluster-randomized

controlled trial. Pain. 2017;158(12):2354-63. doi: 10.1097/j.pain.0000000000001036. PubMed PMID: WOS:000419133700010.
[569] Lynch M, Sawynok J, Hiew C, Marcon D. A randomized controlled trial of qigong for fibromyalgia. Arthritis Research & Therapy. 2012;14(4). doi: 10.1186/ar3931. PubMed PMID: WOS:000314974600022.
[570] Macian N, Dualé C, Voute M, Leray V, Courrent M, Bodé P, et al. Short-Term Magnesium Therapy Alleviates Moderate Stress in Patients with Fibromyalgia: a Randomized Double-Blind Clinical Trial. Nutrients. 2022;14(10). doi: 10.3390/nu14102088. PubMed PMID: CN-02401023.
[571] Maddali Bongi S, Paoletti G, Calà M, Del Rosso A, El Aoufy K, Mikhaylova S. Efficacy of rehabilitation with Tai Ji Quan in an Italian cohort of patients with Fibromyalgia Syndrome. Complementary therapies in clinical practice. 2016;24:109-15. doi: 10.1016/j.ctcp.2016.05.010. PubMed PMID: 27502810.
[572] Maestu C, Blanco M, Nevado A, Romero J, Rodriguez-Rubio P, Galindo J, et al. Reduction of pain thresholds in fibromyalgia after very low-intensity magnetic stimulation: A double-blinded, randomized placebo-controlled clinical trial. Pain Research & Management. 2013;18(6):E101-E6. doi: 10.1155/2013/270183. PubMed PMID: WOS:000329575500001.
[573] Martínez M, Miró E, Sánchez A, Díaz-Piedra C, Cáliz R, Vlaeyen J, et al. Cognitive-behavioral therapy for insomnia and sleep hygiene in fibromyalgia: a randomized controlled trial. Journal of Behavioral Medicine. 2014;37(4):683-97. doi: 10.1007/s10865-013-9520-y. PubMed PMID: 103916179. Language: English. Entry Date: 20141113. Revision Date: 20200708. Publication Type: Journal Article.
[574] McKenna SG, Donnelly A, Esbensen BA, Comber L, Ng WL, Anjum AM, et al. The feasibility of an exercise intervention to improve sleep (time, quality and disturbance) in people with rheumatoid arthritis: a pilot RCT. Rheumatol Int. 2021;41(2):297-310. doi: 10.1007/s00296-020-04760-9. PubMed PMID: WOS:000604148000003.
[575] Miro E, Lupianez J, Martinez MP, Sanchez AI, Diaz-Piedra C, Guzman MA, et al. Cognitive-behavioral therapy for insomnia improves attentional function in fibromyalgia syndrome: A pilot, randomized controlled trial. Journal of Health Psychology. 2011;16(5):770-82. doi: 10.1177/1359105310390544. PubMed PMID: WOS:000291676700008.
[576] Munguia-Izquierdo D, Legaz-Arrese A. Assessment of the Effects of Aquatic Therapy on Global Symptomatology in Patients With Fibromyalgia Syndrome: A Randomized Controlled Trial. Archives of Physical Medicine and Rehabilitation. 2008;89(12):2250-7. doi: 10.1016/j.apmr.2008.03.026. PubMed PMID: WOS:000261803900003.
[577] Murphy SL, Harris RE, Keshavarzi NR, Zick SM. Self-Administered Acupressure for Chronic Low Back Pain: A Randomized Controlled Pilot Trial. Pain Medicine. 2019;20(12):2588-97. doi: 10.1093/pm/pnz138. PubMed PMID: WOS:000504318000025.
[578] Nadal-Nicolás Y, Rubio-Arias J, Martínez-Olcina M, Reche-García C, Hernández-García M, Martínez-Rodríguez A. Effects of Manual Therapy on Fatigue, Pain, and Psychological Aspects in Women with Fibromyalgia. International journal of environmental research and public health. 2020;17(12). doi: 10.3390/ijerph17124611. PubMed PMID: CN-02160610.
[579] Nelson DV, Bennett RM, Barkhuizen A, Sexton GJ, Jones KD, Esty ML, et al. Neurotherapy of Fibromyalgia? Pain Medicine. 2010;11(6):912-9. doi: 10.1111/j.1526-4637.2010.00862.x. PubMed PMID: WOS:000278314200015.
[580] Nia NG, Afrasiabifar A, Behnammoghadam M, Cooper RZ. The Effect of EMDR Versus Guided Imagery on Insomnia Severity in Patients With Rheumatoid Arthritis. Journal of Emdr Practice and Research. 2019;13(1):2-9. doi: 10.1891/1933-3196.13.1.2. PubMed PMID: WOS:000460808600001.
[581] Norregaard J, Lykkegaard JJ, Mehlsen J, DanneskioldSamsoe B. Exercise training in treatment of fibromyalgia. Journal of Musculoskeletal Pain. 1997;5(1):71-9. doi: 10.1300/J094v05n01_05. PubMed PMID: WOS:A1997XF26900005.
[582] Passard A, Attal N, Benadhira R, Brasseur L, Saba G, Sichere P, et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain. 2007;130:2661-70. doi: 10.1093/brain/awm189. PubMed PMID: WOS:000250039500018.
[583] Peng MS, Wang R, Wang YZ, Chen CC, Wang J, Liu XC, et al. Efficacy of Therapeutic Aquatic Exercise vs Physical Therapy Modalities for Patients With Chronic Low Back Pain A Randomized Clinical Trial. Jama Network Open. 2022;5(1). doi: 10.1001/jamanetworkopen.2021.42069. PubMed PMID: WOS:000739974000002.

[584] Pigeon WR, Moynihan J, Matteson-Rusby S, Jungquist CR, Xia Y, Tu X, et al. Comparative effectiveness of CBT interventions for co-morbid chronic pain & insomnia: a pilot study. Behaviour research and therapy. 2012;50(11):685-9. doi: 10.1016/j.brat.2012.07.005. PubMed PMID: 22982083.
[585] Racine M, Jensen MP, Harth M, Morley-Forster P, Nielson WR. Operant Learning Versus Energy Conservation Activity Pacing Treatments in a Sample of Patients With Fibromyalgia Syndrome: A Pilot Randomized Controlled Trial. Journal of Pain. 2019;20(4):420-39. doi: 10.1016/j.jpain.2018.09.013. PubMed PMID: WOS:000462807000004.
[586] Redondo JR, Justo CM, Moraleda FV, Velayos YG, Puche JJO, Zubero JR, et al. Long-term efficacy of therapy in patients with fibromyalgia: A physical exercise-based program and a cognitive-behavioral approach. Arthritis & Rheumatism-Arthritis Care & Research. 2004;51(2):184-92. doi: 10.1002/art.20252. PubMed PMID: WOS:000220764600006.
[587] Ribeiro VGC, Lacerda ACR, Santos JM, Coelho-Oliveira AC, Fonseca SF, Prates ACN, et al. Efficacy of Whole-Body Vibration Training on Brain-Derived Neurotrophic Factor, Clinical and Functional Outcomes, and Quality of Life in Women with Fibromyalgia Syndrome: A Randomized Controlled Trial. Journal of Healthcare Engineering. 2021;2021. doi: 10.1155/2021/7593802.
[588] Roizenblatt S, Fregni F, Gimenez R, Wetzel T, Rigonatti SP, Tufik S, et al. Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study. Pain practice : the official journal of World Institute of Pain. 2007;7(4):297-306. doi: 10.1111/j.1533-2500.2007.00152.x. PubMed PMID: 17986164.
[589] Samartin-Veiga N, Pidal-Miranda M, Gonzalez-Villar AJ, Bradley C, Garcia-Larrea L, O'Brien AT, et al. Transcranial direct current stimulation of 3 cortical targets is no more effective than placebo as treatment for fibromyalgia: a double-blind sham-controlled clinical trial. Pain. 2022;163(7):E850-E61. doi: 10.1097/j.pain.0000000000002493. PubMed PMID: WOS:000811723900005.
[590] Sánchez AI, Díaz-Piedra C, Miró E, Martínez MP, Gálvez R, Buela-Casal G. Effects of cognitive-behavioral therapy for insomnia on polisomnographic parameters in fibromyalgia patients. International Journal of Clinical and Health Psychology. 2012;12(1):39-53. PubMed PMID: 1013495755; 2011-29900-003.
[591] Sanudo B, Carrasco L, de Hoyo M, Figueroa A, Saxton JM. Vagal modulation and symptomatology following a 6-month aerobic exercise programme for women with fibromyalgia. Clinical and Experimental Rheumatology. 2015;33(1):S41-S5. PubMed PMID: WOS:000352829200007.
[592] Sarmento CVM, Moon S, Pfeifer T, Smirnova IV, Colgrove Y, Lai SM, et al. The therapeutic efficacy of Qigong exercise on the main symptoms of fibromyalgia: A pilot randomized clinical trial. Integrative Medicine Research. 2020;9(4). doi: 10.1016/j.imr.2020.100416. PubMed PMID: WOS:000600140200017.
[593] Schmidt S, Grossman P, Schwarzer B, Jena S, Naumann J, Walach H. Treating fibromyalgia with mindfulness-based stress reduction: Results from a 3-armed randomized controlled trial. Pain. 2011;152(2):361-9. doi: 10.1016/j.pain.2010.10.043. PubMed PMID: WOS:000286192000022.
[594] Silva AR, Bernardo A, de Mesquita MF, Vaz-Patto J, Moreira P, Silva ML, et al. An anti-inflammatory and low fermentable oligo, di, and monosaccharides and polyols diet improved patient reported outcomes in fibromyalgia: A randomized controlled trial. Frontiers in Nutrition. 2022;9. doi: 10.3389/fnut.2022.856216. PubMed PMID: WOS:000850823600001.
[595] Smith MT, Finan PH, Buenaver LF, Robinson M, Haque U, Quain A, et al. Cognitive-behavioral therapy for insomnia in knee osteoarthritis: A randomized, double-blind, active placebo-controlled clinical trial. Arthritis and Rheumatology. 2015;67(5):1221-33. doi: 10.1002/art.39048.
[596] Soares JJ, Grossi G. A randomized, controlled comparison of educational and behavioural interventions for women with fibromyalgia. Scandinavian Journal of Occupational Therapy. 2002;9(1):35-45.
[597] Song J, Wei L, Cheng K, Lin Q, Xia P, Wang X, et al. The effect of modified Tai Chi exercises on the physical function and quality of life in elderly women with knee osteoarthritis. Frontiers in Aging Neuroscience. 2022;14:10. doi: https://doi.org/10.3389/fnagi.2022.860762. PubMed PMID: 2682435787; 2022-75141-001.
[598] Stegner AJ, Almassi NE, Dougherty RJ, Ellingson LD, Gretzon NP, Lindheimer JB, et al. Safety and efficacy of short-term structured resistance exercise in Gulf War Veterans with chronic unexplained muscle pain: A randomized controlled trial. Life Sciences. 2021;282. doi: 10.1016/j.lfs.2021.119810. PubMed PMID: WOS:000681715900001.

[599] Tang H-Y, McCurry SM, Pike KC, Riegel B, Vitiello MV. Open-loop Audio-Visual Stimulation for sleep promotion in older adults with comorbid insomnia and osteoarthritis pain: results of a pilot randomized controlled trial. Sleep Med. 2021;82:37-42. doi: 10.1016/j.sleep.2021.03.025. PubMed PMID: 150412505. Language: English. Entry Date: 20211018. Revision Date: 20220717. Publication Type: journal article.
[600] Udina-Cortes C, Fernandez-Carnero J, Romano AA, Cuenca-Zaldivar JN, Villafane JH, Castro-Marrero J, et al. Effects of neuro-adaptive electrostimulation therapy on pain and disability in fibromyalgia A prospective, randomized, double-blind study. Medicine. 2020;99(51). doi: 10.1097/md.0000000000023785. PubMed PMID: WOS:000612839600096.
[601] Van Gordon W, Shonin E, Dunn TJ, Garcia-Campayo J, Griffiths MD. Meditation awareness training for the treatment of fibromyalgia syndrome: A randomized controlled trial. British Journal of Health Psychology. 2017;22(1):186-206. doi: 10.1111/bjhp.12224. PubMed PMID: WOS:000397298800012.
[602] Vitiello MV, McCurry SM, Shortreed SM, Balderson BH, Baker LD, Keefe FJ, et al. Cognitive-Behavioral Treatment for Comorbid Insomnia and Osteoarthritis Pain in Primary Care: The Lifestyles Randomized Controlled Trial. Journal of the American Geriatrics Society. 2013;61(6):947-56. doi: 10.1111/jgs.12275. PubMed PMID: 104183434. Language: English. Entry Date: 20130622. Revision Date: 20200708. Publication Type: Journal Article.
[603] Vitiello MV, Rybarczyk B, Von Korff M, Stepanski EJ. Cognitive Behavioral Therapy for Insomnia Improves Sleep and Decreases Pain in Older Adults with Co-Morbid Insomnia and Osteoarthritis. Journal of Clinical Sleep Medicine. 2009;5(4):355-62. PubMed PMID: WOS:000270263300011.
[604] Wang CC, Schmid CH, Fielding RA, Harvey WF, Reid KF, Price LL, et al. Effect of tai chi versus aerobic exercise for fibromyalgia: comparative effectiveness randomized controlled trial. Bmj-British Medical Journal. 2018;360. doi: 10.1136/bmj.k851. PubMed PMID: WOS:000428811700027.
[605] Ward L, Stebbings S, Athens J, Cherkin D, Baxter GD. Yoga for the management of pain and sleep in rheumatoid arthritis: a pilot randomized controlled trial. Musculoskeletal Care. 2018;16(1):39-47. doi: 10.1002/msc.1201. PubMed PMID: WOS:000426869800006.
[606] Wigers SH, Stiles TC, Vogel PA. Effects of aerobic exercise versus stress management treatment in fibromyalgia. A 4.5 year prospective study. Scandinavian journal of rheumatology. 1996;25(2):77-86. doi: 10.3109/03009749609069212. PubMed PMID: 8614771.
[607] Wiklund T, Linton SJ, Alfoldi P, Gerdle B. Is sleep disturbance in patients with chronic pain affected by physical exercise or ACT-based stress management? - A randomized controlled study. Bmc Musculoskeletal Disorders. 2018;19. doi: 10.1186/s12891-018-2020-z. PubMed PMID: WOS:000429815900002.
[608] Wong A, Figueroa A, Sanchez-Gonzalez MA, Son WM, Chernykh O, Park SY. Effectiveness of Tai Chi on Cardiac Autonomic Function and Symptomatology in Women With Fibromyalgia: A Randomized Controlled Trial. Journal of Aging and Physical Activity. 2018;26(2):214-21. doi: 10.1123/japa.2017-0038. PubMed PMID: WOS:000435081600007.
[609] Wu Y-L, Fang S-C, Chen S-C, Tai C-J, Tsai P-S. Effects of neurofeedback on fibromyalgia: A randomized controlled trial. Pain Management Nursing. 2021;22(6):755-63. doi: https://doi.org/10.1016/j.pmn.2021.01.004. PubMed PMID: 2645545043; 2022-12817-014.
[610] Yao CJ, Li ZR, Zhang SP, Wu ZW, Zhu QG, Fang L. Effects of Wuqinxi in the Patients with Chronic Low Back Pain: A Randomized Controlled Trial. Evidence-Based Complementary and Alternative Medicine. 2020;2020. doi: 10.1155/2020/1428246. PubMed PMID: WOS:000567142000001.
[611] Yeh CH, Suen LK-P, Shen J, Chien L-C, Liang Z, Glick RM, et al. Changes in Sleep With Auricular Point Acupressure for Chronic Low Back Pain. Behavioral sleep medicine. 2016;14(3):279-94. doi: 10.1080/15402002.2014.981820. PubMed PMID: 26244591.
[612] Yousefi S, Zanjani Z, Omidi A, Zamani B, Sayyah M. Comparison of mindfulness-based stress reduction therapy and cognitive-behavioral therapy of chronic fatigue, sleep quality, executive function and disease activity in patients with rheumatoid arthritis. Journal of Contemporary Psychotherapy: On the Cutting Edge of Modern Developments in Psychotherapy. 2022. doi: https://doi.org/10.1007/s10879-022-09558-3. PubMed PMID: 2712882457; 2023-00814-001.
[613] Ge L, Sadeghirad B, Ball GD, da Costa BR, Hitchcock CL, Svendrovski A, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials. BMJ. 2020;369.

[614] Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. Journal of clinical epidemiology. 2011;64(12):1283-93.