SAHLGRENSKA ACADEMY

EVIDENCE FOR PHYSICAL ACTIVITY IN TREATMENT OF ADULT PATIENTS WITH CHRONIC LOW BACK OR NECK PAIN – A SYSTEMATIC LITERATURE STUDY

Degree Project in Medicine
Charlotte Ankarborg
Programme in Medicine,
Gothenburg, Sweden, 2021

Main Supervisor: Paulin Andréll, MD, Ass Prof. adjunct senior lecturer in pain medicine,
Department of Anesthesiology and Intensive Care Medicine/Pain Centre,
Sahlgrenska University Hospital/ University of Gothenburg, Gothenburg
Co-Supervisor: Emma Varkey, MSc, RPT, Sahlgrenska University Hospital/Östra, Department of Occupational Therapy and Physiotherapy/the University of Gothenburg, Gothenburg.
Co-Supervisor: Margit Vikström, Msc, RPT, Pain Centre,
Department of Rehabilitation Medicine, Danderyd Hospital, Stockholm

CONTENTS

ABSTRACT

Degree project, Programme in Medicine*, Evidence for physical activity in treatment of adult patients with chronic low back or neck pain- A systematic literature study*, Charlotte Ankarborg, 2021, the Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

BACKGROUND. Chronic primary pain has been recognized as a disease by WHO (World Health Organization). The definition of chronic pain is pain that lasts or recurs for longer than three months. In Sweden physical exercise has a major part in the rehabilitation of chronic pain. **AIM**. To investigate the current evidence for physical activity as treatment in adult patients with chronic low back or neck pain. **METHODS** A systematic search in five databases for systematic reviews with or without meta-analysis, published between 2017- January 2021, was conducted. A systematic screening strategy, the PICO model, was used to limit the search. **RESULTS.** Out of 781 articles, 8 systematic reviews were selected for synthesis (chronic low back pain n=5; chronic neck pain n= 3). There is low to moderate evidence that physical exercise (both mindful exercises and aerobic exercises) improves disability and gives pain relief in patients with low back pain at <3-6 months follow-up. There is limited to low evidence that physical exercise improves disability and gives pain relief in patients with chronic neck pain at <3-6 months follow-up. There is moderate evidence that physical exercise compared to non-active control had no effect on pain relief or disability at long-term follow-up (≥12 months) in neither of the patient groups. No serious adverse events from using the physical interventions investigated were found. **CONCLUSION**. Physical exercise is effective for pain relief and disability in the rehabilitation of patients with chronic low back pain and chronic neck pain in <3-6 months. However, at ≥12 months of follow-up, there was no difference between the exercise intervention group and the non-active group in neither pain relief nor disability. Physical exercise is not associated with any serious adverse events.

KEYWORDS. Chronic pain, Disability, Low Back Pain, Neck pain, Physical activity, Systematic review.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Examensarbete, Läkarprogrammet, *Evidensen för fysisk aktivitet i behandlingen av vuxna med långvarig rygg- och nacksmärta --en systematisk litteraturöversikt*. av Charlotte Ankarborg, 2021, Sahlgrenska akademin, Göteborgs universitet; Göteborg, Sverige.

BAKGRUND. Sedan juni år 2019 har långvarig primär smärta erkänts som en sjukdom av WHO (World Health Organization). Definitionen av långvarig smärta är smärta som varar eller återkommer under tre månaders tid eller längre. I rehabiliteringen av långvarig smärta används i Sverige idag en kombination av flera olika metoder, där fysisk träning har en betydande roll. **SYFTE.** Att utröna den aktuella evidensen för fysisk aktivitet i behandlingen av vuxna patienter med långvarig ländryggs- eller nacksmärta. **METOD.** Insamlandet av material skedde genom en systematisk sökning i fem olika databaser, enkom innehållande systematiska översikter med eller utan metaanalyser. Materialet begränsades genom publikationsår: år 2017-januari 2021, samt användandet av PICO modellen som står för **P**opulation: vuxna med långvarig smärta. **I**ntervention = behandling: Fysisk träning. **C**omparison = Jämförelse: Ingen träning alls eller andra ''passiva'' behandlingsformer så som t.ex. utbildning eller stretching. I **O**utcome= Utfall intresserade vi oss för mätbar smärta eller fysisk funktion. **RESULTAT.** Av 781 artiklar valdes slutligen 8 systematiska översikter ut för sammanställning (långvarig ländryggsmärta n=5; långvarig nacksmärta n= 3). Vid <3–6 månaders uppföljning sågs låg till medelstark evidens för att fysisk träning (både för mindfulness- och konditionsträning) lindrar långvarig smärta samt förbättrar fysisk funktion hos patienter med ländryggsmärta. För patienter med långvarig nacksmärta finns begränsad till låg evidens för att fysisk träning ger smärtlindring och förbättrad fysisk funktion efter <3–6 månader. Vid uppföljning ≥12 månader sågs dock ingen skillnad mellan fysiskt aktiv grupp och inaktiv behandlingsgrupp vid mätning av smärtintensitet eller fysisk funktion. Inga allvarliga sidoeffekter av de fysiska träningsformerna som ingick rapporterades. **SLUTSATS.** Vid rehabilitering av patienter med långvarig ländryggssmärta eller nacksmärta sågs svaga till medelstarka bevis på att fysisk träning under >3–6 månaders tid gav en smärtlindrande effekt och en ökad fysisk funktion. Medelstarka bevis sågs dock för att det vid 12 månaders uppföljning, inte fanns någon skillnad mellan aktiv- och inaktiv behandlingsgrupp, vid mätning av samma värden. Fysisk träning är inte förknippat med några allvarliga biverkningar.

Nyckelord. Fysisk Funktion, Långvarig smärta, Ländryggsmärta, Nacksmärta, Fysisk aktivitet, Systematisk översikt.

ABBREVIATIONS AND ACRONYMS

*ABPS = Aberdeen Back Pain Scale. Score (0-100)
CLBP = Chronic Low Back Pain
CNP = Chronic Neck Pain
COX inhibitors = Cyclooxygenase inhibitor (anti-inflammatory drugs)
GP= General Practitioner
GRADE = Grading of Recommendations, Assessment, Development and Evaluation
HRR = Heart rate reserve
IASP = International Association for the Study of Pain
LBP = Low Back Pain
*LBPRS = Low Back Pain Rating Scale. Score (0-100)
MA= Meta-analysis
MeSH = Medical Subject Headings
NA = Not Available
NDI = Neck Disability Index
NMA = Network Meta-analysis
*NPAD = Neck Pain and Disability scale. Score (0-100) including 20 sections with 0-5 points.
*NPNPQ = Northwick Park Neck Pain Questionnaire (0-36). Include 9 sections with 4 points on each. Maximum: 9*4 = 36 points. Points if 9 sections are applicable: (score/ 36) * 100%.
*NRS = Numeric Rating Scale. Score (0-10)
NSAIDs = Nonsteroidal Anti-Inflammatory Drugs
NSLBP = Non-Specific Low Back Pain
*ODI = Oswestry Disability Index. Score (0-100)
PICO model = systematic screening strategy selecting material to include or exclude by: Population, Intervention, Comparison and Outcome.
PPA= Prescribed physical activity
RCT(s) = Randomized Controlled Trial(s)
*RMDQ = Roland–Morris Disability Questionnaire: Score (0-24)
ROM= Range of motion
RPT = Registered Physical Therapist
SR= Systematic Review
TENS = Transcutaneous Electric Nerve Stimulation
*VAS = Visual Analog Scale. Score (0-10).
WHO = World Health Organization
WMA = The World Medical Association
YPTCQ = Yoga/Pilates/ Tai Chi /Qigong

*As for all used scales 0 = no pain/ disability. Higher score = worse health condition

1 INTRODUCTION

1.1 DEFINITION OF PAIN

The **definition** of pain in the year 2020 is, according to the International Association for the Study of Pain (IASP*), "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."* Further, IASP state that pain may have adverse effects on function and social and mental well-being. IASP also clarifies that pain is an individual state and varies depending on biological, psychological, and social factors. The inability to communicate can never diminish the possibility that a human or a non-human animal experiences pain, and there are many behaviors in how to express pain (IASP, 2020).

1.2 CHRONIC PAIN

Pain can either be defined as acute, cancer-related, or chronic (persistent). **Acute pain** is often a reaction to tissue damage, whereas the body's regular pain system is working as a protective function (1). The definition of **chronic pain** is pain that lasts or recurs for longer than three months (2). The intent is stated by IASP and occurs in the World Health Organization (WHO) International Classification of Diseases (ICD) 11th version ICD-11. Chronic primary pain has been recognized as a disease by WHO since June year 2019 (3). In Sweden, clinicians use ICD-10, and it is still uncertain when the transfer from ICD- 10 to ICD- 11 will happen.

1.3 CLASSIFICATION OF PAIN

Clinically **pain is divided into three or four categories** based on their pathophysiological mechanisms and clinical signs and symptoms in the body. Nociceptive pain (I) is typically the result of actual or threatened damage to non-neural tissue. It is due to nociceptors' activation, which is the normal function of an intact pain system. Neuropathic pain (II) is caused by a lesion or a disease in the nervous system. Even if the cause of the pain can easily be identified, the treatment can be less successive in neuropathic pain, and the body's pain system can also react differently to physical activity (1, 4). Nociplastic pain (III) is described and defined by Kosek et al., p. 1383 (4) as "*pain that arises from altered nociception, despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain*". The nervous system itself can be undamaged but has a malfunctioning regulation of the pain signals, causing increased sensitivity (central sensitization) and a changed reaction to physical activity. Central sensitization is due to an increased response to nociceptive stimuli and involves a combination of physiological and psychological mechanisms. Therefore, patients with central sensitization

are in need of a complex treatment approach (4). Pain of unknown origin (IV) (previously idiopathic pain) is where cause and origin cannot be classified as neuropathic, nociceptive, or nociplastic (1).

1.4 Epidemiology and Co-Morbidity

Chronic pain is a frequent condition that's more complex in treatment than acute pain (5). The global population-estimated prevalence of chronic pain among adults in earlier dated studies is 20% (6, 7). Women have a higher prevalence of chronic pain than men. Women, compared to men, also tended to refrain from physical activity due to pain (6). There is a close connection between pain and depression (7). Those who report chronic pain commonly suffer from ill health and limitations in their daily life activities compared to individuals not suffering from chronic pain (6). Chronic pain patients attending treatment at a multidisciplinary pain center scored their health-related quality of life similar to patients with advanced cancer admitted to palliative care at the same hospital (8).

2 Conditions of Interest

The conditions of interest in this thesis are **chronic low back pain (CLBP) and chronic neck pain (CNP)**. Both common conditions among patients seeking professional help and guidance in primary care and specialized care at hospitals.

2.1 Chronic Low Back Pain (CLBP)

Defined as "pain in the area on the posterior aspect of the body from the lower margin of the twelfth rib to the lower gluteal folds with or without pain referred into one, or both lower limbs" Hoy et al., p 968 (9). CLBP is one of the leading causes of disability worldwide (10). **Epidemiology and its consequences.** Considering the years lived with disability (YLDs), CLBP ranked highest out of all 291 conditions studied in the Global Burden of Disease 2010 Study, in terms of disability and its prevalence is increasing with an aging population. The global point prevalence of CLBP was 9.4% (95% CI 9.0 to 9.8) in 2010, with the highest age-standardized majority in western Europe (mean: 15.0%; 95% CI 14.1 to 16.0) (9). CLBP is associated with poor quality of life, absenteeism from work, and high medical expenses. All of which can lead to a substantial economic burden both for the individual and the society (11). Low to moderate evidence shows that aerobic exercise and strengthening exercises prevents reoccurring of back pain compared to no exercise (12). In earlier studies by Gerdle et. al. 2018 (13) it's described a strong evidence that for CLBP patients, exercise gives pain relief, improve disability and is superior inactive treatments.

2.2 CHRONIC NECK PAIN (CNP)

Chronic neck pain is defined as "an often widespread sensation with hyperalgesia in the skin, ligaments, and muscles on palpation and in both passive and active movements in neck and shoulder area." Misailidou et al., p 51 (14). Cervical spinal pain being "pain perceived anywhere in the posterior region of the cervical spine, from the superior nuchal line to the first thoracic spinous process" Misailidou et al., p 50 (14). **Epidemiology and its consequences.** Neck pain is calculated to affect between 12.1% and 71.5% of the general world population and is disabling, preventing patients from working in more than 10% of the cases. During a five-year follow-up period, 50%-85% of the investigated participants also experienced recurring neck problems. As it appears, the prognosis for neck pain is multifactorial. Younger age and a coping mechanism involving self-assurance and greater optimism were associated with a better prognosis. Also, being more introverted, having less need for socializing promoted a better prognosis. Whereas poor general health, having previous neck pain episodes, and a more anxious mind or poor psychological health were all associated with a poorer prognosis (15).

3 TREATMENT

3.1 PHARMACOLOGICAL TREATMENT

The management of acute pain does not usually lead to any clinical problems. Acute pain responds well to pharmacological treatment and/or eliminating the cause of the pain (5). Since chronic pain is multifactorial pharmacological treatment in managing chronic pain is more complex compared to acute pain. Traditional analgesics like paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids are well used and successful in treating acute nociceptive pain but less effective for chronic pain patients (16). According to Breivik et al. (7) many patients with chronic pain, not treated by a specialist, use "over the counter" drugs. Only 2% of those 4839 Europeans who responded that they had chronic pain had ongoing treatment by a pain specialist; 70% were treated in primary care. About 40 % were not satisfied with their treatment, and 50% of these (n= 968) took non-prescription analgesics, such as NSAIDs, paracetamol and weak opioids on their own initiative (7). Pharmacology treatment has side effects, NSAIDs increases the risk for cardiovascular heart and kidney failure and gastric ulcers. Opioids, antiepileptic, muscle relaxants and antidepressant medication used for their analgetic effect cause tiredness and nausea. These side effects can counteract the beneficial effects from each painkiller. Clinical treatment of chronic pain includes antidepressants and/or antiepileptic medication combined with non-pharmacological methods as physiotherapy, psychological

treatments and TENS; Transcutaneous Electric Nerve Stimulation (18). Physical exercise, TENS, duloxetine and COX inhibitors all inhibit the descending pain path from the brain to the spinal cord (18). Many patients with chronic pain change their behaviour and avoid physical activity due to pain (6). With a decreased pain intensity, the patient is more easily able to participate in physical activity and use the prolonged benefits found in using physical exercise as a part of treatment. For the prognosis of recovery, time is vital, as prolonged pain may lead to central sensitization. The prognosis is better the earlier the patient can resume daily activities (5, 19).

3.2 MULTIMODAL PAIN REHABILITATION

Multimodal rehabilitation (MMR) is a method used in primary care as well as in hospitals. It consists of a group of specialists (i.e., physician, nurse, physiotherapist, psychologist) specialized in rehabilitation that constructs an individual treatment plan with and for the individual patient. The team combines different physical, psychological, and other non-exercise interventions for those patients accepted for multimodal rehabilitation. The patients are limited in daily activity and the goal is usually an increased daily physical function. The method (compared to no treatment) is proven to be successful in reducing sick leave and increasing work capacity among patients suffering from chronic back pain (20). A combination of several methods of training (i.e., Yoga, Pilates, Stretching, and Strengthening exercises) was preferred compared to a single method in the treatment of CLBP (12).

3.3 PHYSIOTHERAPY

There is high-quality evidence that exercise conducted with the help of professional physiotherapists has a positive effect on pain, disability, general health, and work capacity, compared to without professional help, on both short-term and long-term follow-up (13, 20). Prescribed physical exercise interventions are often used to treat chronic pain conditions and performed with the physiotherapist's expertise in Sweden. Methods used in the treatment of CLBP and CNP are, i.e., individual physical exercise program, isometric exercises, TENS, acupuncture and manual therapy, defined as using the physiotherapists' hands on the patient to treat pain (21). For those 38% of 701 patients that have had physiotherapy as treatment felt that it had been extremely or very helpful (7)

3.4 PHYSICAL EXERCISE AND ITS BENEFITS

The World Health Organization (WHO) recommends all adults to engage in physical activity (3). Physical activity is defined by Caspersen et al. p. 126 (22) as *"Any bodily movement produced by skeletal muscles that results in energy expenditure*.". Exercise is defined by Caspersen et al., p. 126 as *"A subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness"* (22). In the literature, exercise is sometimes divided into Aerobic exercise, Strengthening exercise, and Mindful exercise (23, 24).

Physical activity gives pain relief by the production of endogenous opioids and activating the descendent pain inhibition from the brain to the spinal cord (18, 25). It has also been shown in studies that the levels of noradrenaline, dopamine and serotonin increase in the brain after an exercise session. Noradrenaline regulates, i.e., the feeling of being more alert, the attention level, and the heart rate. Dopamine gives a feeling of reward, happiness and affects motivation. Serotonin gives a feeling of tranquility and satisfaction (25).

With exercising a volume and response reduction in risk occurs for a variety of diseases and health conditions as hypertension, cardiovascular disease and mortality, type- 2 diabetes and all-cause mortality (3, 25), and decreasing mental health (25). Some physical activity is better than none, and more is better than some. Even light-intensity activity appears to provide benefit and is superior to behave inactively (3, 25, 26).

Different types of activity promote various types of physiologic changes and various health outcomes (25). We today know that aerobic exercise can give us new brain cells in an area called the hippocampus, and by that, better memory. By exercising aerobics and strength training, it has been shown in studies that the short-term memory can be improved and also by that get an increased ability to remember words and the placing of objects (25). Exercise has shown to be low to moderately effective as a treatment to reduce pain and increase physical function in patients with chronic non-specific low back pain (10, 12). In animal studies, exercise has been evaluated as an equally effective treatment for depression and anxiety as antidepressants. For mild to moderate depression, the recommendation is that 30-45 minutes of walking or running at least 2-3 times a week for two months can be equally effective as medication (25).

In a study comparing pharmacologic treatment to exercise in patients with low back pain, the exercise was the only intervention that demonstrated sustained benefit after the intervention

ended (11) An overview of 21 high-quality Cochrane Reviews published 2017, including adults with chronic pain (covering ten different diagnoses i.e., arthritis, back and neck pain, patello-femoral pain, and fibromyalgia) investigated the impact of different types of physical activity and exercise on pain severity, disability, quality of life and healthcare use. The evidence for any adverse events associated with exercise interventions or physical activity was also covered; 25% of included reviews reported adverse events. With low evidence value, the most common adverse event was increased soreness or muscle pain, which subsided after a couple of weeks. Mostly small- to moderate improvements in pain and disability could be seen, but the result was inconsistent across the reviews. There is little evidence to be found regarding long-term follow-up (≥ 12 months) (12, 24).

3.4.1 AEROBIC EXERCISE

Aerobic activities such as walking, team sports, or dancing typically use large muscle groups in rhythmic, repetitive movements at a pace that can be continued for more than a few minutes. There is moderate evidence that **aerobic exercise** improves the efficiency and capacity of the cardiorespiratory system (3, 26). Walking improved pain, disability, and fear-avoidance behavior likewise for patients with CLBP. Walking is an easily accessed type of exercise (27). The global recommendation for adults of 150–300 minutes of moderate-intensity aerobic physical activity; or at least 75–150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week, reduced symptoms of anxiety and depression (3, 28). Aerobic exercise for 45 minutes three times a week at 70% intensity of maximum VO2 capacity increased except for endurance capacity and memory also sleep quality (3, 25).

3.4.2 STRENGTHENING EXERCISES

Strength training indicates activities meant to improve the strength, power, endurance, and size of skeletal muscles. Benefits counts as pain relief, increased muscle mass, physical function, and endurance (5, 26). Adults are strongly recommended to do muscle-strengthening activities involving all major muscle groups at moderate or greater intensity on two or more days a week (3). With moderate evidence, core stabilization/ motor- control exercise interventions showed a small impact on pain and disability for CLBP patients at short-,medium- and long-term follow-up (13). In a previous review over systematic reviews, motor-control exercises showed god effect improving disability for chronic low back patients in short- and medium-term follow-up (12). Core stability is achieved by a global strengthening of the core muscles,

whereas Motor- control exercises are defined as an isolated strengthening exercise for the deep spinal muscles (29).

3.4.3 MINDFUL EXERCISES- YOGA /PILATES/ TAI CHI/ QIGONG

Mindful exercises (Yoga, Pilates, Tai Chi, and Qigong) combine the training of muscles, proprioception, balance, mental focus, meditation, and rhythmic abdominal diaphragmatic breathing. Mindful exercises are proven beneficial for symptomatic management in a variety of diseases, such as fibromyalgia, multiple sclerosis, knee osteoarthritis, ankylosing spondylitis, balance disorder, cerebrovascular disease, and mental illness. Tai Chi and Qigong share characteristics of soft, whole-body movements focusing on relaxation, posture, and breathing (30-32). Mindfulness-based stress reduction has, with moderate quality evidence, proven effective for patients with chronic pain (33).

4 WHY THIS THESIS IS OF VALUE

Previous systematic reviews indicate that multimodal rehabilitation (MMR) is a helpful approach in treating patients with chronic pain. The last report was published in 2018 and were based on literature searches in 2011, 2013 and 2017. It describes evidence for non-pharmacological interventions used in Sweden, as part of pain rehabilitation programs for patients suffering musculoskeletal chronic pain. The report concluded with **strong evidence** for physical activity regarding the treatment of both CLBP and CNP separate at <3- 6 months follow-up. Exercise was superior to inactive treatment, regarding pain relief and improved physical function (13).

This thesis aims to help fulfilling the important task of ensuring that the best treatment is given to chronic pain patients. This thesis is part of an important quality work, keeping clinicians updated with new research. Doing so by updating the previous findings for physical activity with an open mind. No particular expectations of finding very different new data or improvements were made. This since a) the time- frame is limited and b) physical activity has been used and proven effective in pain treatment for a long time. Compared to previous searches, this thesis reflects the increased acknowledgement to Yoga, Pilates, Tai Chi and Qigong as useful treatment tools for chronic pain. These exercise forms also referred to as ‘’Mindful exercises’’. This form of training has a pain reliving effect above other beneficial effects.

5 AIM

This thesis finally aim was to investigate contemporary evidence for physical activity as treatment in adult patients with chronic low back or neck pain, published between the year 2017 to January 2021.

5.1 RESEARCH QUESTION

What is the evidence for physical activity as an intervention in treating adult patients with chronic low back pain or neck pain?

6 MATERIAL AND METHODS

6.1 DESIGN

The approach to answering this thesis' research question is made by conducting a systematic literature review of systematic reviews (with or without meta-analysis of included articles), published between 2017 – January 2021.

6.2 ETHICAL STATEMENT

As all analyses are based on previously published articles, no ethical approval or patient consent is required.

According to The World Medical Association (WMA) that developed the Declaration of Helsinki, ethical approval is needed for research in order to protect and preserve the best interest of the participants in the research project. Informed consent must always be gathered from persons participating in research. The safety, integrity, and human rights of the patients must always be considered of greater value than the value of science and society (34).

6.3 THE PICO- MODEL

To answer the scientific question of this thesis, the PICO model, consisting of Population, Intervention, Comparison, and Outcome, was used (35) to limit the search. The search started wide to be narrowed in the end of the selection-process. The included systematic reviews and meta-analysis met the following eligibility criteria according to PICO:

6.3.1 POPULATION

The study sample consisted of adult patients (≥18 years) with chronic musculoskeletal pain, defined as pain persisting for longer than three months and perceived in the musculoskeletal system (i.e., bones, joints, tendons, or muscles). Inflammatory pain (as rheumatoid arthritis) or pain secondary to cancer or/ and neurological symptoms or conditions were excluded. Reviews

that included both chronic and acute musculoskeletal pain were approved if the results for the chronic pain population were reported separately.

Early in the process of this thesis all adult patients with chronic musculoskeletal pain were included and as the thesis took form it was narrowed down to only including adults with chronic low back or neck pain.

6.3.2 INTERVENTION

Physical activity and or any form of physical exercise intervention. Manual therapy, stretching, or the McKenzie method was not considered as exercise.

6.3.3 COMPARISON

The control group consisted of either another treatment/intervention other than physical exercise or no treatment. Hence articles comparing exercise to another exercise intervention and not including results for exercise vs. no treatment or non-exercise intervention were excluded.

6.3.4 OUTCOME REPORTING AND DATA SYNTHESIS

The outcomes included were effects on pain intensity, physical function, daily life activity, disability, quality of life, sick leave/ ability to work, psychological function, or health in general. The included articles did not have to cover all outcomes, but at least one of these outcomes. When synthetizing the result of the final selection of systematic reviews we focused on the outcomes pain intensity and physical function.

6.4 CRITERIA FOR CONSIDERING REVIEWS FOR INCLUSION

Table 1. Details of Inclusion and Exclusion criteria.

Inclusion	**Exclusion**
Systematic review or meta-analysis	Narrative review, scoping review, guidelines
Written in English, Danish, Norwegian, or Swedish	Any other language than chosen for inclusion
published in the year 2017-2021	
Agreeing with the PICO format	Not agreeing with the PICO format

The search was set up in 2017 since the most recent review of the national evidence group that this work will update was done in October 2017. Systematic reviews and meta-analyses were selected since the national evidence group for pain rehabilitation had determined that if there are good systematic reviews of high quality, these reports should be used primarily to assess the current evidence. See the criteria above in Table 1.

6.5 Data Collection and Analysis

6.5.1 Search method for identification of reviews

The five electronic databases AMED, Cinahl, Cochrane Library, PubMed and Scopus were all searched for eligible articles published in the year 2017 to January 2021. The search was done at the end of January 2021. The search string was designed in collaboration with a librarian at the University Library of Medicine in Gothenburg. The search contained a combination of thesaurus terms and free text words. The PubMed search algorithm and descriptors were constructed first and were adapted for the other databases as appropriate (see Appendix S1).

Search string used in PubMed: *(Exercise OR "Exercise Therapy" OR "Physical Activity" AND Pain AND (Chronic OR persistent) AND Adult AND (Meta-Analysis OR Review OR Systematic Review)* Filters: Danish, English, Norwegian, Swedish, from 2017/1/1 - 2021/1/31.

Furthermore, reference lists of included articles were screened for possible inclusion of supplementary systematic reviews of interest.

6.5.2 Study selection

The reviews identified from the five databases were uploaded into the software program Endnote. Found duplicates in Endnote were manually removed before the reviews were being transferred to Rayyan (https://www.rayyan.ai/). Rayyan (36) is an online screening tool developed for research groups doing systematic literature overviews to simplify collaboration, since the selection can be done blinded, voting YES, NO or MABY separately to include or exclude the review in the next step. (The selection steps being a) Title- b) Abstract- and c) Full-text-screening). The screening of the reviews was done first separately by each co-author participating in that step and later discussed together during online meetings. Only the co-authors participating in the final step/ Full-text- screening, did the quality evaluation of the included full-texts in the end. The full-texts were evaluated by their individual result and importance depending on quality and size, which were considered in the summarized result of the thesis. The eight included full-texts were divided between me (Charlotte) n= 8, Dr Andréll n= 4 and Registered Physical Therapist (RPT) Varkey n= 4.

When done voting separately in Rayyan, the blind- mode was turned off to see how all the collaborators had voted. All discrepancies along the whole process were solved by consensus. Since we were four collaborators, and all participated during the Title- screening and Abstract-screening we decided to include/ exclude all off the articles were three of us voted YES/ NO

and discuss those were it was 2/2 conflict results. If three of us voted MABY we also discussed these.

During Full-text screening the result were divided between the author (me) were I read all 53 reviews, Dr Paulin Andréll read 27 reviews and RPT Emma Varkey read 26 reviews. In this step every inclusion /exclusion of a review were discussed. Even if 2/3 of us voted YES/NO, or if one of us voted MABY and two YES or NO we discussed why about these reviews. No Scandinavian articles were found. Only publications written in English were evaluated.

6.5.3 QUALITY OF INCLUDED REVIEWS AND RESULTS

For the assessment of the quality of included reviews, the same quality measures as the evidence group at NRS used in the previous evaluation of physical exercise done by Gerdle et al. This quality assessment is based on a simplification of the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system and was taken from an article by Pollock et al. (2016). The GRADE approach is an internationally used tool to systematically rate the certainty of evidence in systematic reviews and meta-analyses (37)

Table 2. The quality of evidence according to GRADE.

High	A high confidence in that the true effect lies close to that of the estimated effect.
Moderate	A moderate confidence in that the true effect lies close to that of the estimated effect, with a possibility that it is substantially different.
Low	Limited confidence in the estimated effect. The true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the estimated effect: The true effect is likely to be substantially different from the estimated effect.

7 RESULTS

7.1 STUDY SELECTION

Title- and abstract-screening, the full-text reading as well as the evaluating and summarizing of the individual result, and then the overall result of the finally included reviews were completed first independently by the lead author and co-authors and then discussed together. The screening process described above.

The primary search yielded 781 articles. Initially, 62 duplicates were removed in Endnote before 719 articles were transferred to Rayyan. In the screening tool, three titles were discovered to be books from the year 1993 and subsequently directly removed before the 716 titles were

screened. In Rayyan additional 42 duplicates were found and excluded. In total, 104 duplicates were removed.

A total of 534 records were excluded after Title screening, according to inclusion and exclusion criteria, with the exception that included articles also compared any physical exercise intervention to other types of exercise in C (comparison). A total of 140 abstracts were screened, 77 articles were then removed regarding PICO with C (comparison) defined as no other treatment or other non-exercise intervention. Since many included articles still remained after the abstract screening, P (population) was first narrowed down from musculoskeletal pain to fibromyalgia, neck pain, and low back pain, hence removing additional ten articles. In total, 53 full-text articles were assessed for eligibility. From these, 38 full-text articles were excluded with reason; see Table 6 in the supplementary information.

Remaining were 15 systematic reviews with or without meta-analysis. Since chronic low back pain or neck pain both are more common diagnoses than fibromyalgia in those patients seeking treatment for chronic pain in Gothenburg the Population of fibromyalgia was excluded (n=7). Please see Table 7 in the supplementary information for articles concerning Fibromyalgia. The remaining eight reviews was divided accordingly: CLBP (n=5) and CNP (n=3).

The flowchart of the literature search and study selection is presented in Fig 1.

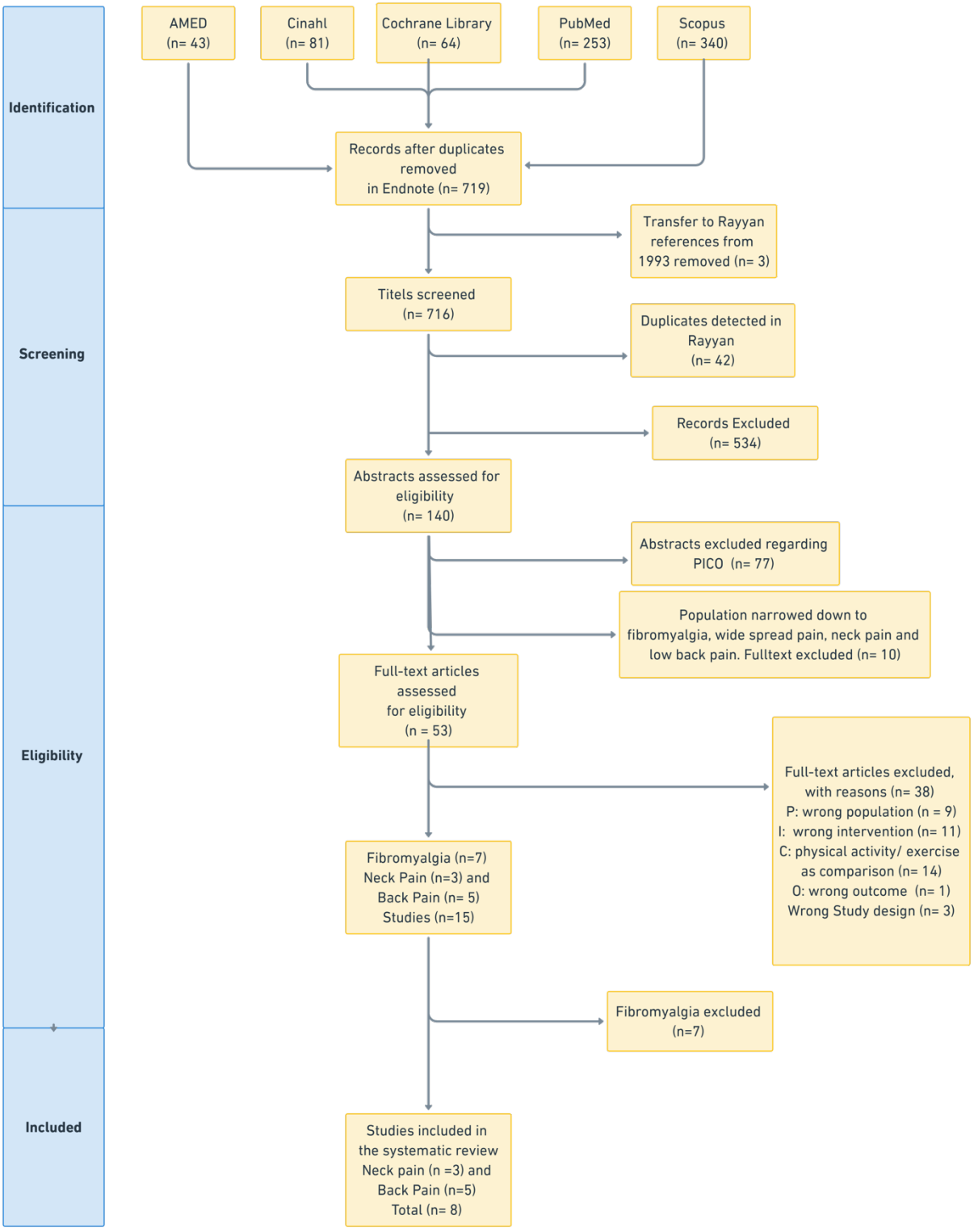

Figure 1 Flowchart of the literature search and study selection, n is the number of systematic reviews with or without meta-analysis. AMED, Cinahl, Cochrane Library, PubMed and Scopus =databases used to find material. Rayyan = online collaboration tool for making systematic reviews. PICO = systematic screening tool to select material in a systematic way.

7.2 QUALITY OF INCLUDED REVIEWS

The assessment of the quality of the included reviews is presented in Table 3.

Table 3. Assessment of Quality of Included Articles

Study	Design[1]	Selection[2]	Search[3]	Inclusion[4]	Number of Patients[5]	Bias[6]	Heterogenicity[7]	Score[8]	Quality[9]
Alzahrani et al., 2018 SR+ MA	1	1	1	0	1	1	1	6	High
Barros Dos Santos et al., 2020 SR+ MA	1	1	1	0	0	1	1	5	High
Owen et al., 2019 SR+ NMA	1	1	1	0	1	0	0	4	Moderate
Wieland et al., 2107 SR+ MA	1	1	1	1	1	0	1	6	High
Zou et al., 2019 SR+ MA	1	1	1	0	1	1	1	6	High
de Zoete et al., 2020 SR+ NMA	1	1	1	0	1	0	0	4	Moderate
de Zoete et al., 2019 SR.	1	1	1	0	1	0	0	4	Moderate
Griffin et al., 2017 SR+ MA	1	1	1	0	1	0	1	5	High

MA-Meta-analysis, NMA- Network Meta-analysis, SR-Systematic review

Quality assessment based on an interpretation of Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) tool by Pollock et al., 2016.

1. Design: Is there a straightforward design stated?
2. Selection: Was the selection and data extraction done by two independent researchers? Did they state how to solve conflicts?
3. Search: Was the database search extensive enough?
4. Inclusion: Was both published and unpublished data included?
5. Number of patients: Were over 200 participants included?
6. Bias: Did more than 75% of the articles have a low risk of bias?
7. Heterogenicity: For meta-analysis: Was the heterogenicity estimated as I^2 <75%?
8. Total score: 5 or more represent a good/high-quality SR/MA
9. Overall quality: Very low, low, moderate, or high quality.

7.3 RISK OF BIAS

Bias assessment: as the characteristics of physical activity interventions did not allow for appropriate blinding, many articles scored low on the quality assessment of included RCTs. Consequently, it lowered the quality of evidence for each outcome measure.

In total, five of the eight systematic reviews were qualified as high-quality systematic reviews/meta-analyses. To assess the quality of included reviews, the same quality measures as the evidence group at NRS, Gerdle et al., (2018) used in the last publicized evaluation of physical exercise. This quality assessment is based on a simplification of the GRADE taken from the article by Pollock et al. (2016).

7.4 DESCRIPTIONS OF INCLUDED REVIEWS

An overview of the included articles of the literature search is presented in Table 4 below.

Table 4. An overview of the included articles of the literature search

INCLUDED REVIEWS								
Number of articles (n)	Total: 8		Systematic Review: 8		Meta-analysis: 5		Network- meta-analysis: 2	
Quality (n)	High: 5		Moderate: 3					
Population (n)	CLBP: 5		CNP :3					
Intervention (n)	Yoga:5	Qigong:4	Aerobic exercise: 3	Core stabilization: 4	Tai Chi: 3	Pilates: 3	Resistance Training: 3	PPA:2
Outcome (n)	Pain: 8		Disability: 8		Mental health: 2		Quality of life :2	

n = number of articles CLBP= chronic low back pain CNP = chronic neck pain PPA- Prescribed physical activity

7.4.1 PARTICIPANTS.

The number of included RCTs in the different reviews included ranged from 3 to 89 RCTs. Thus, the included number of participants in the different reviews ranged from 169 to 5578, CLBP RCTs (n= 125, including 9,271 participants), CNP RCTs (n=52, including 4492 participants), making a total of 13,763 participants.

7.4.2 INTERVENTIONS.

A total of eleven different types of physical exercise interventions evaluated against a non – active control was assessed in the included studies, and intervention time varied from 1 week to 12 months. The five reviews including patients with **CLBP** investigated Walking (n=1), Water based (n=1), Multimodal (n=1), Yoga (n=3), Pilates (n=1), Tai Chi (n=1), Qigong (n=2),

Aerobic exercise (n=2) in different levels of heart rate reserve (60 – 85%), Resistance training (n=1) and Stabilization/ core stabilization (n=1).

The three reviews including patients with **CNP** investigated Prescribed physical activity with or without physiotherapist (n=2), Yoga (n=2), Pilates (n=2), Tai Chi (n=2), Qigong (n=2), Aerobic exercise (n=1) in different levels of heart rate reserve (60 – 85%), Resistance training (n=2), Stabilization/ core stabilization (n=1), Multimodal training consisting of aerobic training and Balance/ Motor- control (n=1).

7.4.3 COMPARISONS

Non- active control in **CLBP** consisted of: No treatment (n=4), Education (n=3), Usual care (n=2) and Advice to remain active (n=1).

Non- active control in **CNP** consisted of: No treatment (n=2), Advice to remain active (n=2) and Usual care including Education (n=2).

7.4.4 OUTCOMES

All included reviews studied differences in pain intensity and disability or physical function. To simplify, in this thesis the result regarding physical function will be reported under disability. Other occurring outcomes were mental health or pain-avoidance behavior.

7.4.4.1 Measure instruments

Since pain is an individual state and varies depending on biological, psychological, and social factors. The results in the included reviews regarding pain intensity and disability were evaluated through self-report questionnaires. Measure instruments used for measuring **pain intensity** were either evaluated on a ten-point scale, i.e., Visual Analog Scale (VAS) or Numeric Rating Scale (NRS). Some RCTs in included reviews used Aberdeen Back Pain Scale (ABPS) or Low Back Pain Rating Scale (LBPRS), both 100-point scale, with a higher score equivalent to a worse health condition. **Disability/ physical function** was evaluated through: **For CLBP**: Roland–Morris Disability Questionnaire (RMDQ) A 24- points scale, where 0 indicates no disability, and 24 is the maximum score. LBP Rating Scale and Oswestry Disability Index (ODI) are both 100- point scales. A higher score is equivalent to a worse health condition. An 11-point reduction on a 100- point scale was considered clinically significant (38). **For CNP**; Neck Disability Index (NDI), Neck Pain and Disability scale (NPAD), and North- wick Park Neck Pain Questionnaire (NPNPQ) were used in the included reviews.

7.4.4.2 Follow-up time points

Time points for measured outcomes were for all included articles: at the starting point of the first time for enrolling in the intervention (baseline score) and at the end of the intervention time. For studies including longer interventions, pain and disability were usually measured at a pre-set interlude when encountering the participant. Regarding the effect of follow-up time, the time points for short-term, medium-term, and long-term were similar. Short term was usually defined as <3 months, medium-term = 6 months, and long-term >12 months. All eight reviews included short-term follow-up; four reviews included long-term follow-up.

7.5 ADVERSE EVENTS

In half of the included reviews, it was reported adverse events. The most common harm reported in the reviews was increased back or neck pain. The adverse events were equally minor in both the intervention and control groups. Physical exercise was not associated with a risk of serious adverse events, and physical activity is recommended as a remedy for pain and to help with improving disability.

Table 5. **Characteristics of the included reviews.**

Chronic pain condition	**Review Year Design Score**	**Participants (n) Number of RCTs (n)**	**Intervention**	**Control group**	**Outcomes**	**Time for Follow-up**	**Main results**	**Authors evaluation of evidence**	**Our conclusion**
Chronic Low Back Pain	Alzahrani et al. 2019 SR+ MA 6/7	**422** **3 RCTs**	Walking program for 2-12 months	Advice to remain active ± Education Usual care.	**Pain** **Disability**	**Short term = < 3 months** **Medium = 6 < 12 months** **Long-term = ≥12 months**	**Pain -**No difference in pain intensity between the intervention and control group. **Disability** -Incidental physical activity intervention provided improvements in medium- and long-term for people with chronic LBP, although this improvement was small and may not be clinically significant.	**GRADE – Moderate** **GRADE – Moderate**	A high-quality SR + MA. Including only low risk of bias RCTs. Moderate evidence that walking had no effect on pain intensity compared to non-active control. Moderate evidence that walking had effect on disability in medium and long-term follow-up, even if it may not be clinically significant.
	Barros Dos Santos et al. 2020 SR+ MA 5/7	**169** **4 RCTs**	Qigong (6 w) Core stabilization exercise (8 w) Aerobic exercise (6 w) at 60% HRR and 85% HRR	No treatment	**Pain** **Cortisol levels in blood sample**	**Pain: Pre- and post 6 weeks interventions.** **Core stabilization did not measure pain.**	**Pain -**the practice of Qigong or aerobic exercise for 6 weeks or more reduced pain intensity levels.	**GRADE – Moderate**	A high-quality SR + MA. Including only low risk of bias RCTs. Moderate evidence that Qigong and aerobic exercise for 6 weeks or more reduced pain intensity significantly for CLBP- patients.
	Owen et al. 2020 SR+ NMA 4/7	**5578** **89 RCTs**	Pilates Yoga Multimodal Water-based Core stabilization Resistance training Aerobic exercise Intervention time ≥4 weeks, 3 times a week	No treatment Therapist hands-on treatment: (i.e., Manual therapy, Massage.) Therapist hands-off treatment, i.e., Education Psychological interventions	**Pain** **Disability** **Mental health** **Core-strength**	**Pre- and post-intervention for ≥4 w.**	**Pain-** Pilates, core stabilization and aerobic exercise training are most likely to be the most effective training in improving pain intensity. **Disability** – Resistance and core stabilization training are most likely to be the most effective training in improving physical function. Pilates, Yoga and Water-based training also had a significant effect on disability.	**GRADE – Low** **GRADE – Low**	A moderate-quality SR + NMA Including RCTs with a high risk of bias. Low evidence that Pilates, core- or aerobic exercise for 6 weeks or more had significant effect on pain intensity. Low evidence in that resistance training and core training is the most effective in improving disability. Pilates, Yoga and Water-based training also had a significant effect.

Chronic Low Back Pain	Wieland et al. 2017 SR+ MA 6/7	**1080** **12 RCTs**	Yoga (Iyengar, Hatha, Viniyoga forms of yoga.	No treatment Education Usual care	**Pain** **Disability** **Mental health** **Physical Quality of Life**	**Follow-up** **3-4 months** **6 months** **12 months**	**Pain-** Yoga compared to non-exercise control slightly more effective for pain at three and six months. However not clinically significant. **Disability-** Yoga gave small to moderate improvements at three and six months. Small improvements at twelve months.	**GRADE – Low to Moderate** **GRADE – Low to Moderate**	A high-quality SR + MA. Including some RCTs with a high risk of bias. Low to moderate evidence that Yoga, compared to no exercise, had a small improvement in pain intensity at 3 and 6 months. However not clinically significant. Low to moderate evidence that Yoga, compared to no exercise, had small to moderate improvements in disability at 3, 6 and 12 months.
	Zou et al. 2019 SR+ MA 6/7	**2022,** **17 RCTs**	Mindful exercises (Yoga, Tai Chi and Qigong) From once a week to once a day. During 1- 24 weeks.	No treatment Education: Self-care book	**Pain** **Disability**	**1 week to 6 months**	**Pain-** Mindful exercises compared to non-active control showed significantly reduced pain intensity. In sub- grouped analysis. Qigong had not a significant result but Yoga and Tai Chi had. Tai Chi had a better effect on pain intensity compared to Yoga and Qigong **Disability-** Yoga, Tai Chi and Qigong compared to control had significant effects in improving disability. With similar effect in subgroup analysis.	**NA** **Evidence not evaluated as GRADE** **NA** **Evidence not evaluated as GRADE**	A high-quality SR + MA. Including only low risk of bias RCTs. Compared to no treatment, self-care book and stretching, Yoga, Qigong and especially Tai Chi showed significant effects on pain intensity for CLBP patients in short-term follow-up. Yoga, Tai Chi and Qigong had all equally significant effects on improving disability for CLBP patients in short-term follow-up.

Chronic Neck Pain	de Zoete et al. 2020 SR+ NMA 4/7	**3151** **40 RCTs** 38 RCTs in Pain MA 29 RCTs in Disability Network MA	Yoga, Pilates,Tai Chi and Qigong (YPTCQ). Balance Stretching exercises Combined- ≥3 interventions Strength ±Stretch Strength ±Motor Motor- control ROM PPA Proprioceptive exercise	No treatment Comparing exercise interventions	**Pain** **Disability**	**3 weeks- 12 months** **Follow-up time:** **<3 months** **6 months** **12 months**	**Pain-** Motor- control, YPTCQ and Strengthening exercises had significant effect compared to no treatment. **Disability-** Motor- control**,** YPTCQ and Strengthening exercises had significant effect compared to no treatment	**GRADE- Very Low** **GRADE- Very Low**	A moderate-quality SR + NMA Including RCTs with high risk of bias. Very Low evidence that YPTCQ, core- and strengthening exercises had significant effect on pain intensity for CNP patients. Follow-up time not specified. Very Low evidence, That YPTCQ, core- and strengthening exercises had significant effect on disability for CNP- patients. Follow-up time not specified.
	de Zoete et al. 2019 SR 4/7	**955** **9 RCTs**	Individualized physical exercise (6, 12 weeks) Pilates (12 w) Pilates and Yoga (6w) Yoga (9w) Tai Chi (12 w) Qigong (12 w)	No treatment Advice only Paracetamol every 6 h Neck specific exercises – supervised or self-manual Usual care (Education +TENS+ Isometric neck exercises).	**Pain** **Disability** **Quality of life**	**Pre- and post-intervention** **(0- 6- 9- 12 w).**	**Pain-** Individualized physical exercise, neck-specific exercises, Pilates, Qigong, Yoga and Combined (TENS + Education + isometric neck exercises) reduced pain intensity. Supervised neck-specific exercises reduced pain intensity superior to individualized physical exercise. Tai chi had a superior effect to neck – specific exercises. **Disability-** Individualized physical exercise, Pilates, Yoga, Pilates and Yoga, Combined (TENS + Education + isometric neck exercises) significantly reduced disability.	**NA** **Evidence not evaluated as GRADE** **NA** **Evidence not evaluated as GRADE**	A moderate-quality SR Including RCTs with high risk of bias. Limited evidence that Individualized physical exercise, Yoga, Qigong, Pilates, Pilates + Yoga and Tai Chi significantly reduced pain intensity levels among CNP-patients at short-term follow-up. Limited evidence that Individualized physical exercise, Yoga, Pilates, Pilates + Yoga, significantly reduced disability levels among CNP-patients at short-term follow-up.

Chronic Neck Pain	Griffin et al. 2017 SR+ MA 5/7	**386** **3 RTCs**	Aerobic exercise Balance Core stabilization Manual therapy Multimodal training PPA ± supervision Whole-body functional activities	No treatment Advice to remain active Education booklet Reassurance Phone-contact twice: 2 and 4w later.	**Pain** **Disability**	**Follow-up after baseline measurement** **Medium-term: 12 w.** **Long-term: 1 y**	**Pain-** Physical intervention compared to non-active control gave a small significant improvement in pain intensity at medium-term follow-up. However probably not clinically significant. No significant improvement in pain intensity for physical intervention compared to non-active control at long-term follow-up. **Disability-** Physical intervention compared to non-active control gave a small significant improvement in disability at medium-term follow-up. However prob not clinically significant. No significant improvement in disability for physical intervention compared to non-active control could be seen at long-term follow-up.	**GRADE- High (Level 1a)** **GRADE- High (Level 1a)**	A high-quality SR+ MA Including only RCTs with low risk of bias. High evidence that physical intervention versus non-active control gave a small but probably not clinically significant improvement in pain intensity at 3 months follow-up. After 1 year, no significant improvement in pain intensity between physical intervention and active control could be seen. High evidence that, physical intervention versus non-active control gave a small but probably not clinically significant improvement in disability at 3 months follow-up. After 1 year, no significant improvement in disability showed between physical intervention and non-active control.

(C) LBP= (Chronic) Low Back Pain. CNP- Chronic Neck pain. GRADE = Grading of Recommendations, Assessment, Development and Evaluations. GP- General Practitioner. HRR- Heart reserve rate. MA= meta-analysis. Multimodal training = several (three or more) physical exercise interventions combined. NA = not available. NMA= Network meta-analysis. PPA = prescribed physical activity. RCT = randomized controlled trial. ROM = range of motion. SR= systematic review TENS = transcutaneous electric nerve stimulator. YPTCQ= Yoga/Pilates/ Tai Chi / Qigo

7.6 EVALUATION OF THE EVIDENCE OF A REVIEWS RESULT.

The evidence for a review result depended on the quality of its included RCTs.

For patients with **CLBP**, the five included reviews were divided into quality: Moderate evidence (2) Low to Moderate evidence (1), and Low evidence (1). Not using GRADE to evaluate evidence (1). For patients with **CNP,** the three included reviews were divided into quality: High evidence (1) Very Low evidence (1). Not using GRADE to evaluate evidence (1).

8 RESULTS DIVIDED INTO POPULATION

Data from each included systematic review and meta-analysis is presented in Table 5.

8.1 RESULTS CHRONIC LOW BACK PAIN

8.1.1 PAIN INTENSITY AND DISABILITY:

Comparing interventions at a moderate quality SR+ NMA including 89 RCTs showed with Low evidence that *Pilates, core stabilization and aerobic exercise for more than 6 weeks* had significant effect on pain intensity. Core- and resistance training three times a week for at least four weeks was the most effective in improving disability for CLBP patients. Pilates, Yoga and Water-based training also gave a significant improvement in disability in the same follow-up time and performance frequency.

It was demonstrated in a high-quality review that that non-structured physical activity (supervised Nordic walking twice a week for two months or measured by pedometer for two or 12 months) including 422 participants with short-, medium-, and long-term follow-up with moderate evidence there was no difference in pain intensity between intervention group and control group at any measured time point. However, with moderate evidence, non-structured physical activity improved disability at six months and at 12 months follow-up. But the difference between groups was not clinically important.

A high-quality SR+ MA included 3 RCTs and 153 participants for pain meta-analysis showed Moderate evidence that *Qigong and aerobic exercise for 6 weeks or more* reduced pain intensity significantly. *Yoga, Qigong* and especially *Tai Chi* compared to non-active control showed to have significant effect on pain in a high-quality SR + MA, including 17 RCTs with only low risk of bias. However, the evidence level was not evaluated according to GRADE. There was a

large variation in intervention time (30- 90 min) and frequency, from once a week (Qigong) to daily practice (Yoga). Tai Chi was performed 40-60 min twice to three times a week for 10-12 weeks.

A high-quality SR + MA including 17 RCTs with only low risk of bias showed that Yoga, Tai Chi, and Qigong had all equally significant effects on improving disability for CLBP patients, follow-up time ranging from 1 week (Qigong) to 6 months (Yoga). Another high-quality SR + MA (including 12 RCTs, some of high risk of bias, and 1080 participants) only investigating Yoga as intervention showed with Low to Moderate evidence that Yoga gave small to moderate improvements in disability in 3 and 6 months. Small improvements at 12 months. In pain intensity, no significant clinical improvements were seen even if it was a small improvement at 3-, 6- and 12-months follow-up for yoga versus non-active control.

In summary, the evidence for physical exercise in patients with CLBP is evaluated low to moderate for pain and disability. Low-intensity activity as walking had no effect on either pain or disability. Higher intensity aerobics gave pain relief in short-term follow-up. Mindful exercises seem promising in treatment for both pain and disability.

8.2 RESULTS CHRONIC NECK PAIN

8.2.1 PAIN INTENSITY AND DISABILITY

A high-quality SR+ MA with a low risk of bias, including 3 RCTs and 386 participants, reported high evidence that physical intervention compared to non-active control gave a small but probably not clinically significant improvement in pain intensity and disability at three months follow-up. After 1 year, no significant improvement in pain intensity or disability between physical intervention and non-active control could be seen.

Two moderate-quality reviews (one including NMA), with a total of 4106 participants from 47 RCTs reporting on pain intensity, stated limited and Very Low GRADE-evidence for that YPTCQ, compared to no treatment had significant effect on pain intensity for CNP-patients. Tai chi had superior effect to neck-specific exercises on pain. **Pilates,** compared to pharmacologic treatment, yoga or isometric exercise, seems to be more favorable in improving pain intensity and neck disability.

In comparing many physical interventions against each other and with no treatment, it was found with Very Low Evidence that no type of exercise was superior to the others in treating people with chronic non-specific neck pain. Core stabilization, Yoga/Pilates/Tai Chi/Qigong

and strengthening exercises had all, compared to no treatment, significant effects on pain intensity and pain-related disability. Proprioception exercises and prescribed physical activity showed less consistent effect. Balance, range of motion and multimodal exercises were found to be not effective.

In summary, the evidence for physical exercise in patients with CNP was limited to low for both pain relief and improvement in disability. Motor-control**,** YPTCQ and Strengthening exercises had significant effect on both pain intensity and disability compared to no treatment.

9 DISCUSSION

In this review, we found low to moderate evidence for physical activity in improvement on pain intensity and disability at short-term follow-up in CLBP and limited to low evidence for physical activity for pain and disability in CNP at short-term follow-up.

9.1 COMPARISON TO PREVIOUS FINDINGS.

Our findings in this thesis regarding pain intensity and disability among CNP patients, confirm but degrade the previous findings by Gerdle et al., 2018 (13), **from strong evidence to limited to low evidence**. Physical activity is helping on short and mid-term follow-up. Two of three studies included long-term follow-up, and we couldn't find any significant clinical effects in the long term.

Regarding **CLBP** and the use of exercise as a treatment to reduce pain and increase physical function, we found **low to moderate** evidence that physical exercise for more than six weeks is effective for pain relief at short- term follow-up and improving disability at short-, medium- and long-term follow-up. This is in line with previous studies by Hayden et al. and Haag et al. (10, 12). But is degraded from **strong evidence** if you compare to Gerdle et al., 2018 (13).

We found with **very low evidence** that **core stabilization** exercises for at least four weeks had a **significant effect on pain and disability in CNP** (39) and with **low evidence in CLBP** (38). This is the same as previous findings (12, 13).

We found **moderate evidence** that **aerobic exercise and Qigong** significantly **reduced pain** intensity in **CLBP** (40). This is in line with Haag et al., (12) previous findings: low to moderate evidence that aerobic exercise and strengthening exercises prevents reoccurring of back pain compared to no exercise.

In this review CNP- patients found a combination of three or more methods of training (i.e., Yoga, Pilates, Stretching and Strengthening exercises) to have an uncertain or insignificant effect regarding pain and disability (39, 41). This indicates that the treatment of CNP differs from CLBP, since it is described in previous reviews that a combination of several methods of training was preferred compared to a single method in treatment of CLBP (12).

As to previous findings, few clinical trials evaluated the effect of physical activity in long-term follow-up (≥ 12 months) (12, 24). This creates a gap for long-term follow-up that future studies could fill.

We found, with low evidence value, that he most common adverse event was increased soreness or muscle pain, which subsided after a couple of weeks. This is previously reported on adverse events in Geneen et al. (24). The benefits from physical exercise thus overdue the side effects (31, 38, 41, 42). One of the reviews recommended performing mindful exercises like Tai Chi Yoga and Qigong only with an instructor to prevent injuries (31).

9.2 Study Strength And Limitations

Strengths: The results are a synthesis of systematic reviews of high- and moderate quality. The heterogenicity in meta-analysis was <75% for over 60% of included reviews including meta-analyses, indicating that the result can be trusted. A methodology strength to this study is that the study selection was blinded by using *Rayyan* separately before final conclusion together of which articles to be included and why in this review.

Limitations. A methodology limitation is that it was only the main author reading all the reviews in the Full-text screening step. However, all were read by at least one of the co-authors. Publication bias: This review is based on systematic reviews; hence the latest published randomized controlled trials are not included. Selected reviews could include the same RCTs making an overlap of results. There was a language limit made to include English, Danish, Swedish or Norwegian. However, most systematic reviews and meta-analyses in the field were in English. One article written in French were excluded in abstract screening. We limited the patient group to CLBP and CNP; hence these are common subpopulations for patients suffering from chronic pain (7) and the data from musculoskeletal pain as diagnosis were too profound for this thesis. As this thesis was planned as an update. The comparison was limited to no treatment or non-active interventions and the search period was limited to the year 2017- January 2021. Although, the thesis is based on results from SRs and included RCTs, hence the time period of included data of the publications were from 1998 to 2019 altogether.

In this review, we have not looked into or divided the different groups (CLBP/CNP) from the cause of pain or co-morbidity. Our aim was neither to compare different types of physical exercise interventions even if two included reviews had network analyses. In the systematic reviews presented, several knowledge gaps are discussed, i.e., outcomes for pain on long-term follow-up and data on adverse effects.

There was a large variation in number of included participants, and not all reviews reported adverse events. The larger studies showed some inconsistency in results. Although high-quality systematic reviews were found, over 50 % of them were based on RCTs with a high risk of bias. The high risk of bias was in many included reviews due to RCTs that had problems with allocation and especially blinding of patients and staff. The blinding issue was expected since the intervention (physical exercise/activity) is difficult to blind for.

9.3 Clinical Implications

Earlier studies strongly propose that physical exercise is easily accessible, safe, cost beneficial and most potentially an effective intervention for individuals with chronic pain and other chronic health conditions. Physical activity decreases the risk of being affected by a large number of common diseases, as hypertension, type- 2 diabetes, cancer, and all-cause mortality (3, 25). Physical activity also has beneficial effects on mental health, sleep, and memory, and obtains work-capacity longer in life (3, 7, 25, 30, 42, 43). All these factors and co-morbidities may affect the patient's experience and prevalence of pain in a longer time perspective.

This thesis confirms positive effects as pain relief and improved disability in CLBP- and CNP-patients. For individuals with CNP and CLBP Aerobics and YPTCQ seem promising as exercise interventions. For CLBP patients it was seen a significant reduction in pain from aerobic exercise with an intensity of 60%-85% of HRR (38, 40). For disability in CLBP; Yoga, Tai Chi, Qigong, Resistance training and Core training had effect with low to limited evidence. For CNP it was limited to very low evidence that YPTCQ, core, and strengthening exercises had pain relief (39) in <3-6 months follow-up (30).

With a high prevalence of patients with chronic pain and only 2% of them treated by specialists, these patients are to be found in the primary care (7). Physical exercise is said to be the best medication (3, 25) without side effects. If physical activity and exercise interventions effectively and safely reduce pain intensity and disability, they may be used as an alternative to pharmacological and/ or surgical treatments. By reducing the use of painkillers and surgery,

you both reduce the cost and side-effects for patients as increasing their quality of life (7, 25). Reducing the cost of treatment is beneficial for the individual, but also for the society.

9.4 FUTURE RESEARCH

In the systematic reviews presented, several knowledge gaps are discussed, i.e., outcomes for pain on long-term follow-up and data on adverse effects.

Five of eight included reviews investigated the effect of some form of mindful exercise (Yoga, Pilates, Tai Chi or Qigong). One of the reviews (31) reported that Tai Chi had a significantly superior effect on pain. In previous studies, it is stated that mindful exercises (Tai Chi and Qigong) can alternate brain mechanisms (44). Since central sensitization is due to alternations in the nervous system, it would be interesting to study if these brain alternations could be connected to the experience of pain.

For future studies, it would be interesting to investigate the reasons for not participating in regular physical activity and reasons for non-compliance to prescribed physical exercises in patients with chronic pain. Non- compliance is frequently a problem in the treatment of patients in general, and previous studies have shown that by creating a sense of control and being in charge of the treatment you receive, you also get a better result from the treatment (43).

10 CONCLUSION

Physical exercise is shown effective for pain relief and improvement of disability in the rehabilitation of patients with CLBP (low to moderate evidence) and CNP (limited to low evidence) in the short-term follow-up (<3 - 6 months).

At six months and at 12 months, there was no clinically significant evidence for improvement in pain or disability for neither CLBP nor CNP. Small effects were although seen but probably not clinically important. Even if there is no evidence for the effectiveness of physical exercise for pain and disability after 12 months of follow-up, physical exercise is not associated with any serious adverse events and is recommended for general health benefits. Exercise prevents a variety of diseases and health conditions including decreasing mental health.

11 ACKNOWLEDGEMENT

I have the greatest respect for all those men and women doing research all over the world. It's thanks to their hard work and all hours they have put in, that the rest of the world's clinicians can perform evidence-based labor, helping patients in the best way. Thanks to my supervisors for helping me in this thesis, all excellent researchers. Thanks for the support from my sister, Carola, my boyfriend, Daniel and my friends. A special thanks to Therese Nöjd for cheering me on all the way at the same time as she's making an invaluable effort standing strong, working 12 hours night shifts in the ICU care at Gefle Hospital treating patients with Covid-19. The same acknowledgement to my dear friend Emelie Keinström, working as a midwife, and her family here in Gothenburg, always supporting me and making me smile even in the darkest sorrow.

THANK YOU

/Charlotte Ankarborg

12 REFERENCES

1. IASP. Terminology International Association for the Study of Pain; Washington, D.C 2018 [2021-01-18]. Available from: https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698#Pain.
2. Treede RD, 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.
3. WHO. Guidelines on physical activity and sedentary behaviour. : WHO; 2020 [2021-04-03]. Available from: https://www.who.int/publications/i/item/9789240015128.
4. Kosek E, Cohen M, Baron R, Gebhart GF, Mico J-A, Rice ASC, et al. Do we need a third mechanistic descriptor for chronic pain states? PAIN. 2016;157(7):1382-6.
5. Löfgren M, Mannerkorpi, K., Bergman, S., Knardahl, S. Fysisk aktivitet vid långvariga utbredda smärttillstånd. Kapitel Långvariga Smärttillstånd. 2016
6. Björnsdóttir SV, Jónsson SH, Valdimarsdóttir UA. Functional limitations and physical symptoms of individuals with chronic pain. Scandinavian Journal of Rheumatology. 2013;42(1):59-70.
7. Breivik, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. 2006;10(4):287-333.
8. Fredheim OM, Kaasa S, Fayers P, Saltnes T, Jordhøy M, Borchgrevink PC. Chronic non-malignant pain patients report as poor health-related quality of life as palliative cancer patients. Acta Anaesthesiol Scand. 2008;52(1):143-8.
9. Hoy D, March L, Brooks P, Blyth F, Woolf A, Bain C, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis. 2014;73(6):968-74.
10. Hayden JA, Wilson MN, Stewart S, Cartwright JL, Smith AO, Riley RD, et al. Exercise treatment effect modifiers in persistent low back pain: an individual participant data meta-analysis of 3514 participants from 27 randomised controlled trials. British Journal of Sports Medicine. 2020;54(21):1277-8.
11. Kolber MR, Ton J, Thomas B, Kirkwood J, Moe S, Dugré N, et al. PEER systematic review of randomized controlled trials: Management of chronic low back pain in primary care. Can Fam Physician. 2021;67(1):e20-e30.
12. Haag T, Beck H, Korthals I, el M, Schneider C. The evidence of physical activity and training for the therapy of chronic non-specific back pain. Deutsche Zeitschrift fur Sportmedizin. 2018;69(7):255-61.
13. Gerdle et al. AK, Olle Skogberg, Frida Svanholm, Martin Södermark, Tobias Wiklund, Christine Wennersten, Ulrika Wentzel-Olausson, Lovisa Amkéus, Elena Dragioti, Linn Karlsson & Britt Larsson. Evidens för icke-farmakologiska interventioner inklusive multimodal rehabilitering vid kroniska smärtor –ett kontinuerligt evidensarbete: NRS; 2018 [Available from: https://www.ucr.uu.se/nrs/forskning/evidensdokument-multimodal-rehabilitering/viewdocument/1123.
14. Misailidou V, Malliou P, Beneka A, Karagiannidis A, Godolias G. Assessment of patients with neck pain: a review of definitions, selection criteria, and measurement tools. Journal of Chiropractic Medicine. 2010;9(2):49-59.
15. Haldeman S, Carroll L, Cassidy JD, Schubert J, Nygren Å. The Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. European Spine Journal. 2008;17(S1):5-7.

16. Fredenberg S, Vinge, E. & Karling, M. . Smärta och smärtbehandling Läkemedelsboken 2015 [updated 2015-08-27. Available from: https://lakemedelsboken.se/kapitel/smarta/smarta_och_smartbehandling.html#q1_6.
17. FASS. För vårdpersonal Lif – de forskande läkemedelsföretagen; [FASS-21.2.0-128:[Available from: https://www.fass.se/LIF/startpage?userType=0.
18. Staud R. The important role of CNS facilitation and inhibition for chronic pain: Int J Clin Rheumtol; 2013 [updated Dec 1PMC3904391]. 2014/02/04:[639-46]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3904391/pdf/nihms542027.pdf.
19. IASP. Wait-Times, SUMMARY AND RECOMMENDATIONS 2011 [Available from: https://s3.amazonaws.com/rdcms-iasp/files/production/public/Content/NavigationMenu/EducationalResources/IASP_Wait_Times.pdf.
20. SBU Sbfmu. Rehabilitering vid långvarig smärta. En systematisk litteraturöversikt. Stockholm2010 [Available from: https://www.sbu.se/sv/publikationer/SBU-utvarderar/rehabilitering-vid-langvarig-smarta/.
21. SBU. Metoder för behandling av långvarig smärta. En systematisk litteraturöversikt 2006 [Available from: https://www.sbu.se/sv/publikationer/SBU-utvarderar/metoder-for-behandling-av-langvarig-smarta/.
22. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-31.
23. Mattsson et al. Fysisk aktivitet – begrepp och definitioner: FYSS; 2016 [Available from: http://www.fyss.se/fyss-kapitel/fyss-kapitel-del-1-allman-del/.
24. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: An overview of Cochrane Reviews. Cochrane Database of Systematic Reviews. 2017;2017(1).
25. Hansen ASCJ. Hälsa på recept: träna smartare, må bättre, lev längre Fitnessförlaget; 2015.
26. Powell KE, Paluch AE, Blair S. Physical Activity for Health: What Kind? How Much? How Intense? On Top of What? Annual Review of Public Health. 2011;32(1):349-65.
27. Vanti C, Andreatta S, Borghi S, Guccione AA, Pillastrini P, Bertozzi L. The effectiveness of walking versus exercise on pain and function in chronic low back pain: a systematic review and meta-analysis of randomized trials. Disabil Rehabil. 2017;41(6):622-32.
28. WHO. Physical activity and health in Europe: evidence for action. WHO Regional Office for Europe, Copenhagen, Denmark.2006 [Available from: https://www.euro.who.int/__data/assets/pdf_file/0011/87545/E89490.pdf.
29. Vikranth GR, Lawrence, Mathias. & Ghori, M. M. . EFFECTIVENESS OF CORE STABILIZATION EXERCISES AND MOTOR CONTROL EXERCISES IN PATIENTS WITH LOW BACK ACHE. 2015 [544-51.]. Available from: https://www.ijphy.org/index.php/journal/article/download/89/85.
30. de Zoete RMJ, Brown L, Oliveira K, Penglaze L, Rex R, Sawtell B, et al. The effectiveness of general physical exercise for individuals with chronic neck pain: a systematic review of randomised controlled trials. European Journal of Physiotherapy. 2019;22(3):141-7.
31. Zou L, Zhang Y, Yang L, Loprinzi PD, Yeung AS, Kong J, et al. Are Mindful Exercises Safe and Beneficial for Treating Chronic Lower Back Pain? A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Med. 2019;8(5).
32. Zou L, Yeung A, Zeng N, Wang C, Sun L, Thomas GA, et al. Effects of Mind-Body Exercises for Mood and Functional Capabilities in Patients with Stroke: An Analytical Review of Randomized Controlled Trials 2018 [Available from:

https://res.mdpi.com/d_attachment/ijerph/ijerph-15-00721/article_deploy/ijerph-15-00721.pdf.
33. Qaseem A, Wilt TJ, McLean RM, Forciea MA. 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.
34. Association TWM. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 2018.
35. SBU. PICO modellen: SBU; 2009 [Available from: https://www.sbu.se/sv/publikationer/vetenskap-och-praxis/stall-tydligare-fragor-sa-far-du-battre-svar/.
36. Rayyan. Rayyan Intelligent Systematic Review 2021 [Available from: https://www.rayyan.ai/.
37. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology. 2011;64(4):401-6.
38. Owen PJ, Miller CT, Mundell NL, Verswijveren S, Tagliaferri SD, Brisby H, et al. Which specific modes of exercise training are most effective for treating low back pain? Network meta-analysis. Br J Sports Med. 2020;54(21):1279-87.
39. de Zoete RM, Armfield NR, McAuley JH, Chen K, Sterling M. Comparative effectiveness of physical exercise interventions for chronic non-specific neck pain: a systematic review with network meta-analysis of 40 randomised controlled trials. Br J Sports Med. 2020.
40. Barros Dos Santos AOPdC, J. B.; Lima, V. P.; da Silva, E. B.; de Souza Vale, R. G.;. Effects of physical exercise on low back pain and cortisol levels: a systematic review with meta-analysis of randomized controlled trials. Pain Manag - Volume 11, Issue 1, pp 49-57 - published. 2020.
41. Griffin A, Leaver A, Moloney N. General Exercise Does Not Improve Long-Term Pain and Disability in Individuals With Whiplash-Associated Disorders: A Systematic Review. J Orthop Sports Phys Ther. 2017;47(7):472-80.
42. Wieland LS, Skoetz N, Pilkington K, Vempati R, D'Adamo CR, Berman BM. Yoga treatment for chronic non-specific low back pain 2017 [updated Jan 12PMC5294833]. 2017/01/12:[CD010671]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28076926 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5294833/pdf/CD010671.pdf.
43. WHO. User empowerment in mental health – a statement by the WHO Regional Office for Europe 2010 [Available from: https://www.euro.who.int/en/health-topics/noncommunicable-diseases/mental-health/publications/2010/user-empowerment-in-mental-health-a-statement-by-the-who-regional-office-for-europe.
44. Liu J, Tao J, Liu W, Huang J, Xue X, Li M, et al. Different modulation effects of Tai Chi Chuan and Baduanjin on resting-state functional connectivity of the default mode network in older adults. Soc Cogn Affect Neurosci. 2019;14(2):217-24.

SUPPLEMENT
TABLE 6 FULL-TEXT ARTICLES EXCLUDED WITH REASON

#	AUTHOR, YEAR	TITLE	REASON FOR EXCLUSION
1.	Adamse et al., 2018.	The effectiveness of exercise-based telemedicine on pain, physical activity and quality of life in the treatment of chronic pain: A systematic review.	**Wrong population**
2.	Ahmed et al., 2018	Effect of aerobic exercise in the treatment of myofascial pain: A systematic review.	**Wrong population**
3.	Alanazi et al., 2018.	Effect of stabilization exercise on back pain, disability and quality of life in adults with scoliosis: a systematic review	**Wrong population**
4.	Amaral et al., 2020.	Efficacy of conservative therapy in older people with non-specific low back pain: A systematic review with meta-analysis and GRADE recommendations.	**Wrong intervention**
5.	Andrade et al., 2018.	A systematic review of the effects of strength training in patients with fibromyalgia: clinical outcomes and design considerations.	**Wrong comparison**
6.	Bernard et al., 2018.	Cognitive behavior therapy combined with exercise for adults with chronic diseases: Systematic review and meta-analysis.	**Wrong population**
7.	Blomgren et al., 2018.	Effects of deep cervical flexor training on impaired physiological functions associated with chronic neck pain: A systematic review 11 Medical and Health Sciences 1103 Clinical Sciences.	**Wrong comparison**
8.	Byrnes et al., 2017.	Is Pilates an effective rehabilitation tool? A systematic review.	**Wrong comparison**
9.	Casey et al., 2020.	Multidisciplinary-based Rehabilitation (MBR) Compared with Active Physical Interventions for Pain and Disability in Adults with Chronic Pain: A Systematic Review and Meta-analysis.	**Wrong intervention**
10.	Cheng et al., 2019.	Effectiveness of physical and cognitive-behavioral intervention programmes for chronic musculoskeletal pain in adults: A systematic review and meta-analysis of randomised controlled trials.	**Wrong intervention**
11.	Chou et al., 2017.	Nonpharmacologic therapies for low back pain: A systematic review for an American College of physicians' clinical practice guideline.	**Wrong comparison**
12.	Coulombe et al., 2017.	Core Stability Exercise Versus General Exercise for Chronic Low Back Pain	**Wrong comparison**
13.	Dario et al., 2017.	Effectiveness of telehealth-based interventions in the management of non-specific low back pain: a systematic review with meta-analysis.	**Wrong intervention**
14.	Dong et al., 2019.	Whole Body Vibration Exercise for Chronic Musculoskeletal Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials.	**Wrong population**
15.	Edwards & Loprinzi., 2017.	Comparative effects of meditation and exercise on physical and psychosocial health outcomes: a review of randomized controlled trials.	**Wrong population** Postgraduate thesis
16.	Fredin & Lorås., 2017.	Manual therapy, exercise therapy or combined treatment in the management of adult neck pain – A systematic review and meta-analysis.	**Wrong intervention**
17.	Geneen et al., 2017.	Physical activity and exercise for chronic pain in adults: An overview of Cochrane Reviews.	**Wrong study design**
18.	Haag et al., 2018.	The evidence of physical activity and training for the therapy of chronic non-specific back pain.	**Wrong study design**
19.	Hall et al., 2107.	Effectiveness of tai chi for chronic musculoskeletal pain conditions: Updated systematic review and meta-analysis.	**Wrong population**
20.	Hayden et al., 2020.	Exercise treatment effect modifiers in persistent low back pain: an individual participant data meta-analysis of 3514 participants from 27 randomized controlled trials.	**Wrong study design**

#	AUTHOR, YEAR	TITLE	REASON FOR EXCLUSION
21.	Jasmin & Syahrul., 2019.	Effectiveness of Yoga Intervention for Chronic Neck Pain: A Systematic Literature Review.	**Wrong comparison**
22.	Jones et al., 2020.	Pain Education with Therapeutic Exercise in Chronic Nonspecific Low Back Pain Rehabilitation: A Critically Appraised Topic.	**Wrong intervention**
23.	Kolber et al., 2021.	PEER systematic review of randomized controlled trials: Management of chronic low back pain in primary care.	**Wrong comparison**
24.	Li et al., 2019.	Effects of yoga on patients with chronic non-specific neck pain: A PRISMA systematic review and meta-analysis.	**Wrong comparison**
25.	Luomajoki et al., 2018.	Effectiveness of movement control exercise on patients with non-specific low back pain and movement control impairment:.' A systematic review and meta-analysis.	**Wrong comparison**
26.	Martin-Gomez et al., 2019.	Motor- control using cranio-cervical flexion exercises versus other treatments for non-specific chronic neck pain: A systematic review and meta-analysis.	**Wrong comparison**
27.	Martinez-Calderon et al., 2020.	Which interventions enhance pain self-efficacy in people with chronic musculoskeletal pain? A systematic review with meta-analysis of randomized controlled trials, including over 12 000 participants.	**Wrong intervention**
28.	Martinez-Calderon et al., 2020	Conservative Interventions Reduce Fear in Individuals With Chronic Low Back Pain: A Systematic Review.	**Wrong intervention**
29.	Nduwimana et al., 2020.	Effectiveness of walking versus mind-body therapies in chronic low back pain: A systematic review and meta-analysis of recent randomized controlled trials.	**Wrong comparison**
30.	Parreira et al., 2017.	Back Schools for chronic non-specific low back pain.	**Wrong intervention**
31.	Polaski et al., 2019.	Exercise-induced hypoalgesia: A meta-analysis of exercise dosing for the treatment of chronic pain.	**Wrong outcome**
32.	Saragiotto et al., 2020.	The effectiveness of strategies to promote walking in people with musculoskeletal disorders: A systematic review with meta-analysis.	**Wrong population**
33.	Sitthipornvorakul et al., 2018.	The effects of walking intervention in patients with chronic low back pain: A meta-analysis of randomized controlled trials.	**Wrong comparison**
34.	Skamagki et al., 2018.	A systematic review on workplace interventions to manage chronic musculoskeletal conditions.	**Wrong population**
35.	van Erp et al., 2108.	Effectiveness of Primary Care Interventions Using a Biopsychosocial Approach in Chronic Low Back Pain: A Systematic Review.	**Wrong intervention**
36.	Vanti et al., 2017.	The effectiveness of walking versus exercise on pain and function in chronic low back pain: a systematic review and meta-analysis of randomized trials.	**Wrong comparison**
37.	Wewege et al., 2018.	Aerobic vs. resistance exercise for chronic non-specific low back pain: A systematic review and meta-analysis.	**Wrong comparison**
38.	Zou et al., 2018.	A systematic review and meta-analysis of mindfulness based (Baduanjin) exercise for alleviating musculoskeletal pain and improving sleep quality in people with chronic diseases.	**Wrong intervention**

TABLE 7 FULL-TEXT ARTICLES EXCLUDED WITH SUBPOPULATION FIBROMYALGIA

#	AUTHOR, YEAR	TITLE
	Bidonde, J., Busch, A. J., Schachter, C. L., Overend, T. J., Kim, S. Y., Goes, S. M., Boden, C., & Foulds, H. J. (2017).	Aerobic exercise training for adults with fibromyalgia.
	Bidonde, J., Busch, A. J., Schachter, C. L., Webber, S. C., Musselman, K. E., Overend, T. J., Goes, S. M., Dal Bello-Haas, V., & Boden, C. (2019).	Mixed exercise training for adults with fibromyalgia.
	Bidonde, J., Busch, A. J., van der Spuy, I., Tupper, S., Kim, S. Y., & Boden, C. (2017).	Whole body vibration exercise training for fibromyalgia.
	Estevez-Lopez, F., Maestre-Cascales, C., Russell, D., Alvarez-Gallardo, I. C., Rodriguez-Ayllon, M., Hughes, C. M., Davison, G. W., Sanudo, B., & McVeigh, J. G. (2020).	Effectiveness of Exercise on Fatigue and Sleep Quality in Fibromyalgia: A Systematic Review and Meta-analysis of Randomized Trials.
	Kim, S. Y., Busch, A. J., Overend, T. J., Schachter, C. L., van der Spuy, I., Boden, C., Goes, S. M., Foulds, H. J., & Bidonde, J. (2019).	Flexibility exercise training for adults with fibromyalgia.
	Martinez-Calderon, J., Flores-Cortes, M., Morales-Asencio, J. M., & Luque-Suarez, A. (2021).	Intervention Therapies to Reduce Pain-Related Fear in Fibromyalgia Syndrome: A Systematic Review of Randomized Clinical Trials.
	Oliveira, C. B., Franco, M. R., Maher, C. G., Ferreira, P. H., Morelhão, P. K., Damato, T. M., Gobbi, C., & Pinto, R. Z. (2018).	Physical Activity-Based Interventions Using Electronic Feedback May Be Ineffective in Reducing Pain and Disability in Patients with Chronic Musculoskeletal Pain: A Systematic Review with Meta-Analysis.

SEARCH STRATEGIES FOR ALL FIVE DATABASES: PUBMED, AMED, CINAHL, COCHRANE LIBRARY AND SCOPUS.

Databases: PubMed (253), Scopus (340), Cinahl, AMED (43) and Cochrane Library (64). Articles: Total n = 719 Limitation. Year 2017- 2021 Language: Danish, English, Norwegian, Swedish.

PUBMED: DATE 27/1: 2021

#48 : (Exercise OR" Exercise Therapy" OR" Physical Activity" AND (Pain AND (Chronic OR persistent) AND Adult AND (Meta-Analysis OR Review OR Systematic Review)
Filter Year 2017-01-01- 20121- 01-31 gave 261 results. **FILTER LANGUAGE** *Danish, English, Norwegian, Swedish*
RESULT 253 articles

#48	Search: **(Exercise OR" Exercise Therapy" OR" Physical Activity" AND (Pain AND (Chronic OR persistent) AND Adult AND (Meta-Analysis OR Review OR Systematic Review)** Filters: **Danish, English, Norwegian, Swedish, from 2017/1/1 - 2021/1/31** ("exercise"[MeSH Terms] OR "exercise"[All Fields] OR "exercises"[All Fields] OR "exercise therapy"[MeSH Terms] OR ("exercise"[All Fields] AND "therapy"[All Fields]) OR "exercise therapy"[All Fields] OR "exercise s"[All Fields] OR "exercised"[All Fields] OR "exerciser"[All Fields] OR "exercisers"[All Fields] OR "exercising"[All Fields] OR ("exercise therapy"[MeSH Terms] OR ("exercise"[All Fields] AND "therapy"[All Fields]) OR "exercise therapy"[All Fields]) OR ("exercise"[MeSH Terms] OR "exercise"[All Fields] OR ("physical"[All Fields] AND "activity"[All Fields]) OR "physical activity"[All Fields])) AND ("pain"[MeSH Terms] OR "pain"[All Fields]) AND ("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields] OR ("persist"[All Fields] OR "persistance"[All Fields] OR "persistant"[All Fields] OR "persisted"[All Fields] OR "persistence"[All Fields] OR "persistences"[All Fields] OR "persistencies"[All Fields] OR "persistency"[All Fields] OR "persistent"[All Fields] OR "persistently"[All Fields] OR "persistents"[All Fields] OR "persister"[All Fields] OR "persisters"[All Fields] OR "persisting"[All Fields] OR "persists"[All Fields])) AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields] OR "adult s"[All Fields]) AND ("meta analysis"[Publication Type] OR "meta analysis as topic"[MeSH Terms] OR "meta analysis"[All Fields] OR ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]) OR ("systematic review"[Publication Type] OR "systematic reviews as topic"[MeSH Terms] OR "systematic review"[All Fields]))**Translations Exercise:** "exercise"[MeSH Terms] OR "exercise"[All Fields] OR "exercises"[All Fields] OR "exercise therapy"[MeSH Terms] OR ("exercise"[All Fields] AND "therapy"[All Fields]) OR "exercise therapy"[All Fields] OR "exercise's"[All Fields] OR "exercised"[All Fields] OR "exerciser"[All Fields] OR "exercisers"[All Fields] OR "exercising"[All Fields]**"Exercise Therapy":** "exercise therapy"[MeSH Terms] OR ("exercise"[All Fields] AND "therapy"[All Fields]) OR "exercise therapy"[All Fields]**"Physical Activity":** "exercise"[MeSH Terms] OR "exercise"[All Fields] OR ("physical"[All Fields] AND "activity"[All Fields]) OR "physical activity"[All Fields]**Pain:** "pain"[MeSH Terms] OR "pain"[All Fields] **Chronic:** "chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields] **persistent:** "persist"[All Fields] OR "persistance"[All Fields] OR "persistant"[All Fields] OR "persisted"[All Fields] OR "persistence"[All Fields] OR "persistences"[All Fields] OR "persistencies"[All Fields] OR "persistency"[All Fields] OR "persistent"[All Fields] OR "persistently"[All Fields] OR "persistents"[All Fields] OR "persister"[All Fields] OR "persisters"[All Fields] OR "persisting"[All Fields] OR "persists"[All Fields] **Adult:** "adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields] OR "adult's"[All Fields] **Meta-Analysis:** "meta-analysis"[Publication Type]. or. "meta-analysis as topic"[MeSH Terms]. or. "meta-analysis"[All Fields] **Review:** "review"[Publication Type] .or. "review literature as topic"[MeSH Terms]. or. "review"[All Fields] **Systematic Review:** "systematic review"[Publication Type]. or. "systematic reviews as topic"[MeSH Terms] or. "systematic review"[All Fields]

MeSH = Medical subject headings

DATABASE AMED 27/1 -2021	
#1: (exercise or "physical activity" or rehabilitation or "Exercise therapy").mp. [mp=abstract, heading words, title]	Result: 88055
#2 ((chronic or long-term or persistent) and pain).mp. [mp=abstract, heading words, title].	Result 7416
#3 1 AND 2	Result 2828
#4 (meta-analysis or "systematic review" or review).mp. [mp=abstract, heading words, title]	Result: 20395
#5 3 AND 4	
#6: 5 and Filter by YEARS 2017- 2021	**RESULT 43 articles**

DATABASE Cinahl S19. 27/1 – 2021

Query	
(exercise therapy or physical therapy or physiotherapy or rehabilitation or training) AND (chronic pain or persistent pain or long-term pain or long-term pain) AND (meta-analysis or systematic review or literature review)	
Limiters - Published Date: 20170101-20211231	
Expanders - Apply equivalent subjects	
Narrow by Language: - English	
Search modes - Find all my search terms	
Interface -EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full-text	
	RESULT 81 articles

DATABASE Cochrane Library: Date 28/1 - 2021	Search manager /Advanced search:
#6 Titel abstract Keyword	:
("chronic pain'‘ OR "longterm pain") AND (Exercise OR "physical activity" OR "rehabilitation")	RESULT 8086
Search limits year Jan 2017 – Feb 2021	RESULT 4944
Cochrane reviews: 62and clinical answers:2, Clinical Trials: 4879	64 references of interest
	RESULT 64 articles

DATABASE Scopus 28/1-2021	
("chronic pain" OR "long-term pain") AND (Exercise OR "physical activity" OR "rehabilitation") date range 2017- present :	3377 documents
Limit to publication type: Conference review and Review n= 504 – Excluding Conference review (notes)	500 Review articles
Limit to English Danish Swedish Norwegian:	472
Exclude chemistry: n= 7	465
Exclude Animal by Keyword:	443
Exclude Physiologic n= 8	435
Exclude Agricultural and Biological Science: n= 5	430
Exclude: Arts and Humanity, Dentistry, Computer science: Chemical engineering, Energy:	425
Exclude : View Current Pain And Headache Reports' source details n= 8	417
Exclude Keyword Fatigue n= -37	380
Exclude Keyword Nonhuman n= 29	351
Exclude CHRONIC OBSTRUCTIVE LUNGDISEASE n= 11	RESULT 340 articles