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Physical exercise therapy for chronic non-specific neck pain: protocol for a meta-analysis of individual participant data

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Abstract

Background Every 7 out of 10 people will experience neck pain at some point during their lifetime. A large proportion of these cases will develop into recurrent or chronic conditions. Typically, physical exercise for neck pain seems to be modestly beneficial, but differential effects across participants of randomised trials have not yet been appropriately considered. This individual participant data meta-analysis (IPD MA) will provide a consolidated synthesis of randomised controlled trials (RCTs) that have been conducted to date. We aim to investigate the effectiveness of exercise therapy for chronic non-specific neck pain.

Methods/design This study will address the following research questions: (1) what are the effects of exercise therapy compared to no intervention or control interventions on neck pain intensity, pain-related disability, and quality of life? (2) What are the responder and non-responder rates for exercise therapy? (3) What participant characteristics are associated with a clinically meaningful response to exercise therapy? (4) What are the minimal clinically important difference (MCID) and/or minimal detectable change (MDC) values for neck pain intensity, pain-related disability, and quality of life?. This study will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The raw data will be requested from the primary authors of included RCTs. The received original data will be collated into a main datasheet with all the details on every single study, including study details, methodological details, participant demographics, details about intervention and comparison groups, treatment effect modifiers (e.g. workload, medicine usage), and the main outcome measures: pain intensity, pain-related disability, and quality of life. This IPD MA will be performed following a one-step approach, where data from all studies are analysed together while considering the grouping of participants within each study. Risk of bias of included RCTs will be evaluated using the ROB 2.0 tool, and the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach will be used to assess the certainty of evidence.

Discussion We will analyse IPD of available RCTs exploring the exercise effectiveness for chronic non-specific neck pain. The expected large sample size and consistent presentation of data will allow for further analyses to investigate patient-level heterogeneity in treatment outcomes and the prognosis of chronic non-specific neck pain.

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Keywords Neck pain, Chronic pain, Physical exercise, Exercise therapy, Individual participant data, Meta-analysis, Systematic review, Randomised controlled trial

Background

Neck pain is a prevalent condition associated with disability and psychosocial implications [1, 2]. Every 7 out of 10 people will experience neck pain at some point during their lifetime, which may develop into a recurrent or chronic condition [3, 4]. Healthcare costs associated with chronic neck pain are therefore high [5]. National and international clinical practice guidelines suggest physical exercises as the primary choice for managing neck pain [6].

Despite physical exercise therapy being the mainstay treatment for chronic neck pain, randomised controlled trials (RCTs) and systematic reviews demonstrate that physical exercise is often only modestly effective in improving neck pain intensity and pain-related disability [7–11]. There might be various reasons for these findings; however, it is likely that differential effects across participants contribute to this. In other words, while exercise therapy may be effective for some people, it might not be effective for others. Whilst RCTs do not commonly report responder/non-responder rates, the notion that only a subgroup of participants may improve through exercise therapy is supported by a trial identifying non-responder rates as high as 50% [12, 13]. With some people with chronic neck pain responding positively to exercise therapy and others not responding, it is possible that RCTs fail to reflect these differential responses to exercise therapy. As some people improve and some people do not respond or even get worse, improvements by responders may get 'washed out' by non-responders. These details are not commonly reported in RCTs, as traditionally they have not been classified as 'adverse events'.

A systematic review is a useful study design to summarise the available evidence of the effectiveness of a treatment based on previously published studies, with meta-analyses (MA) providing quantitative data that increase the ability to estimate a treatment effect [14]. However, traditional meta-analyses pool studies and collect published aggregate data to evaluate the overall effect, and therefore they have limitations. Specifically, as exercise therapy may be effective for neck pain in some people and might not be effective for others, analysis of aggregate data from RCTs loses important details of individual participants' improvements or deteriorations. Whilst overall a powerful tool, the clinical relevance of these meta-analyses is compromised due to the lack of generalisation of heterogeneous information [15].

Individual participant data meta-analysis (IPD MA) is an alternative method for synthesising evidence, allowing the original participant-specific data from each individual trial to be analysed, as opposed to traditional MA, which provides an illustration of the mean values of included studies. Therefore, IPD can be considered as the original source material, while traditional MA is a derived form of it [16].

The utilisation of IPD presents a number of possible benefits over traditional MA. It allows the extraction of preferred information directly from the included studies in their original form, which might not necessarily be aligned with the findings presented in the primary article. It may also permit the evaluation of more participants, longer follow-ups, and more outcomes. Compared to IPD MA, traditional MA may lead to poor or incorrect reporting of results from individual trials [17], implying that IPD MA is potentially more reliable. Primarily, IPD MA has the capability to generate clinically meaningful outcomes that extend beyond the overall average results from traditional MA, possibly contributing to personalised treatment [17]. The IPD MA is able to assess subgroups of individuals with similar characteristics (e.g. selected by sex, age, or other participant characteristics); therefore, derived outcomes will be assessed more precisely for more specific subgroups, and the power of these analyses will be comparatively higher than the independent trials [18].

Though exercise therapy for neck pain has been found to be moderately effective [7–11], responder and non-responder rates have not been taken into account by systematic reviews of RCTs conducted to date. This highlights a significant gap in our understanding of the differential effects of exercise across individuals with neck pain. IPD MA offers a possible solution by allowing analysis of treatment effects at the individual level, rather than relying solely on aggregated data [19, 20], utilising within-trial information to estimate how patients' characteristics modify treatment benefits [21]. Addressing the variability in treatment response is essential for optimising clinical outcomes, as many patients do not experience significant relief from exercise therapy [7, 9, 11]. Additionally, recent studies indicate that individual characteristics, such as age, sex, and baseline pain intensity levels, play a role in treatment efficacy [19]. By conducting IPD MA, we will be able to identify specific patient profiles that are more

likely to respond positively to exercise therapy, thereby guiding more personalised treatment approaches.

The combination of the high prevalence of chronic neck pain, the variability in patient responses to exercise therapy, and the need for personalised treatment approach underscores the importance of conducting an IPD MA. This study will respond to an important knowledge gap and facilitate more effective and tailored interventions for individuals with chronic non-specific neck pain.

Study objectives

We will undertake an IPD MA, investigating the effects of exercise therapy for chronic non-specific neck pain. We aim to address the following research questions:

1. What are the effects of exercise therapy for chronic non-specific neck pain compared to no intervention or control interventions on neck pain intensity, pain-related disability, and quality of life?
2. What are the responder and non-responder rates for exercise therapy for chronic non-specific neck pain?
3. What participant characteristics are associated with a clinically meaningful response to exercise therapy for chronic non-specific neck pain?
4. What are the minimal clinically important difference (MCID) and/or minimal detectable change (MDC) values for neck pain intensity, neck disability, and quality of life, for chronic non-specific neck pain?

Methods/design

A protocol for this IPD MA was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42022323359).

Ethics

We contacted the Human Research Ethics Committee (HREC) of the University of Adelaide, Adelaide, SA 5005, Australia, and consulted regarding ethical permission for the proposed IPD MA. We were offered an exemption (ID 36188) for ethical clearance in accordance with the NHMRC's National Statement, section 5.1.22: Institutions may choose to exempt from ethical review research that (a) is negligible risk research (as defined in paragraph 2.1.7), and (b) involves the use of existing collections of data or records that contain only non-identifiable data about human beings.

Identification of studies

Relevant RCTs will be identified using standard systematic review methods supported by the Cochrane Collaboration. Methods for IPD MA [16] and the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [22] will be followed to implement this study. The search strategy will be designed in consultation with a medical librarian. The search will be performed by the main reviewers using a computerised search of electronic databases, including AMED, CINAHL, Cochrane Central Register of Controlled Trials, Embase, MEDLINE, PEDro, PsycINFO, Scopus, and SPORTDiscus, along with reference chaining.

Selection of studies

In the first stage of screening, two reviewers will independently screen and exclude irrelevant titles and abstracts based on pre-defined eligibility criteria. Full texts will be retrieved for all studies that are considered eligible or for which eligibility is unclear. Two independent reviewers will assess the suitability of full text on the basis of the same eligibility criteria. Disparities will be sorted out by two independent reviewers and if they are unable to reach an agreement, a third reviewer will be involved, and a decision will be made. The inter-rater agreement for both screening phases will be calculated and presented using the weighted Kappa score [23]. The entire screening process will be carried out in Covidence software (Covidence systematic review software, Veritus Health Innovation, Melbourne, Australia. Available at www.covidence.org) [24].

All studies (RCTs) examining the exercise therapy effects on adult patients (≥18 years old) with chronic non-specific neck pain (more than 12 weeks) will be considered. We will include any study that performed one or more exercise therapy types to treat neck pain, involving any purposive, planned, and structured activity designed to gain benefits in physical, physiological, psychological, and analgesic aspects through various mechanisms. Any comparator group with no exercise, placebo, or sham interventions will be included. Trials that include patients treated with exercises combined with any other intervention, for example, educational programs, mobilisation and manipulation, use of electrophysical agents, and physical activities, will be excluded. We will also exclude studies that involved individuals with acute or sub-acute, traumatic (e.g. whiplash-associated disorders [WAD]), or neuropathic neck pain, neck surgery, cancer pain, neck pain combined with cardiorespiratory problems, arthritic conditions, spinal diseases, and other associated disorders.

The main outcome measures of the current IPD MA are pain intensity, pain-related disability, and quality of life. If an eligible study assesses any of these outcomes, it will be included in this IPD MA. Study results at all time points will be extracted and analysed according to immediate post-intervention (the first time point after the intervention), short- to medium-term (up to 6 months),

and long-term follow-up (more than 6 months) measured post-intervention.

Risk of bias

We will evaluate the possible risk of bias (ROB) in every randomised controlled trial included in this IPD MA. The revised Cochrane 'Risk of Bias' tool for randomised trials (ROB 2.0) [25] will be used, which addresses five specific domains: (1) bias arising from the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in a selection of the reported results. Two reviewers will independently conduct an assessment of the ROB, and inter-rater agreement will be calculated. Any inconsistency in the ROB assessment will be settled by agreement; otherwise, another investigator will resolve the disagreements.

Certainty of evidence

We will use the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of evidence of implications for clinical practice [26].

Data collection

Collection of individual participant data

De-identifiied raw data will be requested from the primary authors of included RCTs. We will extract evidence from every suitable and included trial along with supplementary information, such as details of the sample of the relevant study, outcome measurements at the beginning and end of treatment, smaller group analyses, and factors modifying the therapeutic outcomes that were examined and reported in the primary studies. We will source the contact details of the corresponding author of the primary study, inform them about our IPD MA, and request that they share IPD if they are agreeable to participate. Datasets in any format will be accepted in order to reduce the amount of work, however, we will provide a preferred data extraction format with one individual participant per row, and parameters listed in columns, allowing authors to use this if they prefer. After receiving the de-identified raw data, it will be kept on a secure server. Original data will be compiled into a main datasheet, with all the details on each study in a consistent format.

If we do not receive a response from the corresponding author within 4 weeks, we will contact the first author and then a senior author of the study publication (if these are different from the corresponding author). We plan to make four efforts to communicate with the researchers: two requests directed to the corresponding author, one to the first author if needed, and another to the senior author if needed. If they do not reply or are reluctant to share their de-identified raw data, we will send a conclusive email advising that we will proceed without including their data and inquire about their reasons for not sharing the data.

Data collection for traditional meta-analysis

In addition to the IPD MA, we plan to conduct a traditional meta-analysis using aggregate data to assess the consistency and accuracy of published results. Trial details such as treatment types, control groups, study results, and participant characteristics will be extracted and summarised in a standardised format, consisting of: study details (author, year), methodological details, participant demographics (age, sex, neck pain duration), details about intervention and comparison groups (type of exercise, dosage including intensity, duration, frequency), factors modifying the therapeutic outcomes (sufficient rest, medicines used for chronic NSNP), and the self-reported clinical outcomes (neck pain intensity, neck disability, and quality of life). One investigator will summarise the trial details from each study, and the correctness of the data will be verified by a second investigator. If required, additional data will be requested from them as per the communication strategy outlined.

Data management

We will save each raw dataset in its original version and later convert it to a common layout. The common datasets will be used to rename and label the variables for each included study in a consistent manner. A pre-specified primary structure will be used for mapping and categorising sufficiently similar variables, as shown in Table 1. This structure is adapted from a similar study on chronic low back pain [27] and modified accordingly.

Data analysis process

Each dataset will be evaluated to identify the parameters and determine whether their values are reasonable, absent, or misplaced, compared with the primary study publication. An effort will be made by the research team to reproduce the results obtained in the original publication by re-conducting the statistical methods mentioned by the primary authors. If there are inconsistencies between our outcomes and the original study results, we will deliberate and elucidate those with the investigators of the primary trials.

If authors send data not originally presented in the primary article, we will use the data received for analyses. Missing baseline data will be controlled for using multiple imputation techniques where suitable, under a missing-at-random assumption, to avoid the exclusion of participants from the statistical analysis and to

Table 1 Preliminary list of potential baseline variables and constructs [27]

Baseline data	Example of the measurement
Primary outcome measures	
Pain intensity	Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), Northwick Park Neck Pain Questionnaire (NPQ)
Pain-related disability	Neck Disability Index (NDI), Neck Pain and Disability Scale (NPAD)
Quality of life	36-Item Short Form Health Survey (SF-36), 12-Item Short Form Health Survey (SF-12), World Health Organisation Quality-of-Life Scale (WHOQOL-BREF), self-reported health outcomes (physical performance, functional ability, life satisfaction, overall cognitive functioning, etc.)
Demographic data of participants	
Age	Present age
Sex	Male, female
Body mass index (BMI) or height and weight	Individual's BMI or height and weight
Occupation	For the past year
Day-to-day life	
Leisure activities	Sporting events, outdoor activities, and personal interests
Physical health	Physical fitness level
Physical activity level	Mild/moderate/vigorous
Cigarette smoking	Habits of smoking
Alcohol use	Drinking quantity/rate
Computer use	Hours per day
Socio-demographic features	
Economic and financial background	Academic achievements, income
Employability	Workplace, job title, current work status
Relationships	Relationships with partners, relations, peers, and neighbours
Healthiness	Feeling well/lethargy levels
Medication usage	Medications used for current condition (chronic non-specific neck pain)
Associated health problems	Presenting other health-related conditions (e.g. other types of muscular pain except chronic non-specific neck pain, breathing difficulties, gastrointestinal problems, severe headaches, pain in more than one site of the body)
Past trauma reported	Medical leave (except for chronic non-specific neck pain), or traumatic incidents
Settlement and legal compensation	
Employee's recompense; lost working hours, absence from regular work, paybacks, retirement fund	Evidence of employee's recompense, lost working hours/days, absence taken as a consequence of chronic non-specific neck pain, paybacks, applied or expect to apply for retirement fund
Attribute to chronic non-specific neck pain	Legal process, negligence for damage/harm, pain-inducing work, causes, and the rationale for chronic non-specific neck pain
Pre-existent chronic non-specific neck pain (affected prior to present incidence)	
Pain onset	Onset of chronic non-specific neck pain (e.g., quick or continuing)
Time length of the incidence	Time length of chronic non-specific neck pain, duration concerning the incidence, and putting assertions
Clinical features of chronic non-specific neck pain at baseline	
Gravity of the discomfort due to chronic non-specific neck pain	Pain rating scales, factors increasing or decreasing pain, tools, and questionnaires to assess pain severity, numeric rating scale
Restrictions in the day-to-day activities	Questionnaires and tools to assess the activity limitations, disability level, and participation restrictions
Alteration of clinical features	Recovering or deteriorating
Outcomes of the physical tests performed at baseline	
Joint movement ranges	Change in range of motion
Behaviour of the pain (central pain)	Behaviour of the pain (on and off)
Any different outcomes from other tests performed	Muscle strength, endurance, flexibility, palpations, and attitudes of the limbs related to the body

Table 1 (continued)

Baseline data	Example of the measurement
Outcomes of the assessment of the nervous system at baseline	
Location; nerve root; radiculopathy	Pain located in the neck region, radiating pain
Participant's mental state	
Depression	Questionnaires and tools to assess the condition
Conditions that can affect the participant	E.g. post-traumatic stress disorder, mood disorders, schizophrenia
Chronic non-specific neck pain findings	
Type and cause	Detailed findings about type and causes (pain arising from muscles/ligaments/spinal joints, herniated disc, facet joint involvement)
Participant's ability to comprehend his/ her clinical features	Participant's ability to comprehend clinical features
Participant's predictions regarding the improvement of the condition	
Self-assessed job readiness	Self-assessed job readiness regarding chronic non-specific neck pain
Self-evaluated job proficiency	Self-assessment to continue the same work previously engaged, barriers, and capacity with chronic non-specific neck pain
Psychological capability of returning to work	Psychological capability to return to work, worker role interview
Opportunities for returning to previous job	Opportunities for returning to previous job
Participant's desire after treatments	Patient satisfaction Self-reported treatment success Minimal side effects

ensure the reliability of baseline data among treatment groups involved [28, 29]. Where imputation is not possible, participants' missing data may be removed from the final analyses. However, these exclusions will be assessed to confirm that there is no impact on the similarity of groups at baseline.

Synthesis strategy

Descriptive analysis

Included studies will be described with trial-related and individual-specific features. Details of the studies and aggregate data with traditional MA will be compared to the trials that are eligible but do not supply IPD. Furthermore, we will inspect whether the available IPD represents a sample of the full set of existing studies [30].

Analysis of overall treatment effect by study-level meta-analysis and meta-regression

We will conduct traditional meta-analyses and, as an extension of it, a meta-regression based on the data reported in the original studies. Study data about the effects of exercise therapy will be synthesised, and trial-level variables will be assessed. A one-step approach will be employed to simultaneously model IPD obtained from all the studies, taking into consideration the clustering of participants within each study [16]. The meta-analysis model applied to the IPD will be tailored to the specific outcome being synthesised. It will encompass a linear analysis of the covariance model, which accounts for the baseline value, for continuous outcomes. For time-to-event outcomes, such as survival data, a Cox regression or a related survival model will be incorporated. By conducting these analyses, we will be able to compare the findings obtained from IPD with those obtained from traditional MA. This comparison will enable us to assess the disparities between IPD MA and traditional MA, specifically in terms of the treatment effect of exercise therapy. Whenever feasible, we will examine and compare the impact of each exercise therapy with respect to the duration of the exercise program and follow-up outcomes. This can be subject to potential study-level confounding, as this will be recognised as a study-level comparison.

Analysis of treatment effect modification by IPD at patient-level

IPD will be utilised to examine patient-level treatment effect modification and to evaluate whether the changes in the treatment response are linked to individual patient characteristics. We will identify studies that provide additional information on baseline variables, which could serve as potential predictors of treatment response for one or more of the outcomes of interest. We will analyse and present the treatment effects within subgroups defined by each of these potential predictors of treatment response. Furthermore, we will examine whether there is an interaction between each predictor and the treatment effect on pain intensity, pain-related disability, and quality of life outcomes.

The above-mentioned one-step IPD MA framework will be further extended to add variables in addition to the primary outcome measures (neck pain intensity,

pain-related disability, and quality of life), and interaction terms between each variable and the treatment. This will lead to further clustering of participants at the patient level and study level, helping to avoid ecological bias [31, 32].

Investigation of small study effects

Any MA consisting of ten or more trials will be assessed for minor study effects related to the overall treatment effect investigation [33]. Smaller trials are more likely to report important and optimistic outcomes compared to larger trials. Contour-enhanced funnel plots [33] and tests for funnel plot asymmetry will be used to achieve this purpose [34].

Statistical software R [35] will be used to conduct the statistical analysis of both traditional MA and IPD MA [36]. Stata or SAS will be used to conduct single-step IPD MA models. If the sophistication of the model justifies it, we will also explore the possibility of employing a Bayesian Markov Chain Monte Carlo approach and fitting it with Bayesian software WinBUGS [37, 38].

Discussion

This study will be the first IPD MA to explore the effectiveness of exercise therapy for chronic non-specific neck pain. It is expected that a large number of participant data will be included. Primarily, this study aims to address: (1) what are the effects of exercise therapy for chronic non-specific neck pain compared to no intervention or control interventions on pain intensity, pain-related disability, and quality of life? (2) What are the responder and non-responder rates for exercise therapy in chronic non-specific neck pain? (3) What participant characteristics are associated with a clinically meaningful response to exercise in chronic non-specific neck pain? and (4) What are the MCID and/or MDC values for neck pain intensity, pain-related disability, and quality of life, for chronic non-specific neck pain?

We propose to use advanced methods for analysing the original information collected from included studies to recognise individual features and smaller groups on the basis of treatment responsiveness, which is unachievable with traditional MA. In primary studies, smaller group analyses are not the main focus, and they are susceptible to unfairness and non-representation of the original trials in traditional MA [27]. Additionally, traditional MA have limited ability to identify genuine effect modifiers and are susceptible to biases at trial level [12, 16]. IPD MA responds to these limitations of traditional MA, and we will utilise several advantages that arise from this methodology: (1) access to raw data of large participants; (2) consistency of raw data; (3) opportunity to analyse participant-level and trial-level inconsistencies.

IPD MA offers significant advantages, but it also comes with notable limitations. One important potential limitation of this study will be the non-response from authors of included RCTs. We aim to mitigate this limitation by sending several reminders and allowing data to be provided in any preferred format. Whilst unavailability of data or limited and inadequate access will result in studies being removed from the IPD MA, such studies will be included in the traditional MA undertaken. Another possible limitation is the availability and quality of individual participant data from studies, which can impact the reliability of results if the data is incomplete or inconsistently documented [20]. Furthermore, IPD MA is often more resource-intensive than traditional MA, requiring advanced statistical expertise and collaboration among multiple research teams [14]. The potential for heterogeneity across studies, including differences in participant characteristics and exercise protocols, can complicate data synthesis and interpretation [39]. Finally, IPD MA aims to address issues of publication bias by incorporating unpublished data, yet the reluctance of researchers to share individual-level data can limit the completeness of the analysis [40].

Abbreviations

RCTs	Randomised controlled trials
IPD	Individual participant data
MCID	Minimal clinically important difference
MDC	Minimal detectable change
PROSPERO	Prospective Register of Systematic Reviews
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
NSNP	Non-specific neck pain
ROB	Risk of bias
ROM	Range of motion

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Not applicable

Authors' contributions

RdZ and IW conceived the protocol. DS, RdZ, and IW developed and drafted the initial protocol with input from MH, KC, and SF. All authors read and approved the final protocol manuscript.

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Data availability

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable, described under methods/design. We received an exemption (ID 36188) for ethical clearance in accordance with the NHMRC's National Statement, Sect. 5.1.22.

Consent for publication
For the purpose of this IPD MA, we will conduct secondary analyses of primary, deidentified data, which will be collected from previously conducted RCTs. We will synthesise data from primary studies, for which consent was already obtained by the original investigators.

Competing interests
The authors declare that they have no competing interests.

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