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Moderators of treatment effect of non-steroidal anti-inflammatory drugs for patients with (sub) acute low back pain: Protocol for a systematic review with individual participant data meta-analysis

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ABSTRACT

A Cochrane review found that non-steroidal anti-inflammatory drugs (NSAIDs) are slightly more effective than placebo on acute and subacute low back pain (LBP) outcomes (pain intensity, disability, and global improvement). Our objectives are: (1) to assess the overall treatment effect of NSAIDs in adults with acute and subacute LBP; (2) to identify the moderation of baseline patients' characteristics on treatment effect. We will conduct a systematic search of RCTs on effectiveness of NSAIDs compared with placebo in adults with non-chronic LBP in Medline ALL, Embase, Cochrane Central Register of Controlled Trials*. We will screen the records after January 2020, and include eligible RCTs before January 2020 screened by the Cochrane review mentioned above. Our primary outcomes are pain intensity, disability, and health-related quality of life, secondary outcomes are adverse events. Our IPD dataset will consist of the information on each eligible trial characteristics and included variables according to a predefined coding scheme. We will assess risk-of-bias of included RCTs with the Cochrane Risk Of Bias (RoB)-2 assessment tool. We will perform power calculations with closed-form solutions and prioritize a one-stage approach for IPD-MA. For reporting the results, we will adhere to the PRISMA-IPD statement.

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Reagents/tools:	*Not applicable*
Experimental design:	*IPD meta-analysis research*
Trial registration:	*We have submitted the record on PROSPERO with the ID: 503235.*
Ethics:	*This is an IPD meta-analysis conducted using existing data without involving recruitment or direct identification of participants. The IPD will be securely stored, with access restricted to members of the research team. The IPD-MA project will be governed by a data-sharing agreement or contract. Ethics approval is not mandatory for IPD-MA.*
Value of the Protocol:	*Our objective is to assess the overall treatment effect and the moderators of NSAID for improving pain, disability, and health-related quality of life in adults with acute and subacute non-specific LBP.*

Description of the protocol

Introduction

Low back pain (LBP) is a prevalent and costly symptom experienced worldwide [1], with a global mean point prevalence of LBP of 11.9 ± 2%, and a mean 1-month prevalence of 23.2 ± 2.9% [2]. Approximately 80% to 90% of LBP cases are categorized as non-specific LBP [3,4]. Acute LBP refers to new episodes lasting less than 6 weeks, while sub-acute LBP includes cases lasting between 6 weeks and 12 weeks [5]. Although acute low back pain (LBP) is mostly self-limiting, approximately 50% to 80% of individuals experiencing acute LBP will encounter a recurrence within one year [6,7]. Therefore, it is crucial to administer treatments to patients with acute LBP that will improve their outcomes and prevent the progression towards chronic LBP [6].

Reassurance, advice, and self-management are recommended as first-line care within the first two weeks of LBP symptom onset, with pharmacological treatments being suggested as second-line care [8–10]. Several types of pain medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and opioids, can be prescribed for pain relief in cases of acute LBP [5,6,11,12]. In an updated overview of clinical practice guidelines [11], most recommendations prioritize NSAIDs as the first-choice pharmacological treatment for acute LBP. In cases where pain medication is considered for a person with acute LBP, NSAIDs may offer a better harm-benefit balance compared to other pain medications [13]. Although the overall short-term effects of NSAIDs against placebo in patients with acute LBP are relatively small (reduction of pain intensity of 7.29 points on a 0–100 scale of Numeric Rating Scale (NRS), reduction of disability of 2.02 points on a 0–24 scale of Roland Morris Disability Questionnaire (RMDQ)) [14], we are interested to explore the existence of 'subgroups' of patients with acute and/or subacute LBP who may respond more (or less) positively to this intervention, in other words, find the treatment-covariate interactions to identify which patients benefit most from NSAIDs treatments.

Compared with traditional pairwise meta-analysis, collecting aggregate data and then estimating overall effects, an individual participant data meta-analysis (IPD-MA) can collect raw participant-level data from different RCTs, including unpublished or unreported data, or even data on participants excluded from original trial analyses, which means that data analysis no longer relies only on what the original authors reported [15]. For example, researchers can correct the overall effect of interventions by adjusting for the baseline value. In addition, IPD-MA can derive standardized outcome definitions and apply a consistent method of analysis for each trial [15]. All the advantages mentioned above can result in a more precise and potentially more valid estimate of the effect. Another key benefit of IPD-MA is analyzing the interaction between intervention effect and moderators so that researchers can estimate how the participant's characteristics or other possible predictors influence the treatment effects [16]. Single RCTs are often insufficiently powered to detect nuanced differences in treatment effects among subgroups due to their focus on overall treatment effects across the entire participant population. Detecting genuine treatment-covariate interactions requires a significantly larger sample size, usually at least four times that needed for assessing overall treatment effects [17]. This makes such trials costly and often impractical [17]. Therefore, the IPD-MA is more suitable for exploring treatment-covariate interactions than the aggregate data meta-analysis. An IPD-meta-analysis (IPD-MA) increases the power to explore the genuine treatment-covariate interactions [17].

Our objectives are: (1) to assess the overall treatment effect of NSAID for improving pain, disability, and health-related quality of life in adults with acute and subacute LBP; (2) to identify the potential moderation of baseline patients' characteristics on treatment effects. Based on the precious studies [18,19], we hypothesize that the following subgroups: patients who are female; having high levels of physical activity-related fear avoidance; aged under 65 years; body mass index ≤ 30 kg/m2; experiencing slighter pain; without pain at rest; without pain at night; without spinal stiffness, may demonstrate a more favorable response to NSAIDs. Our primary outcomes of interest are pain intensity, disability, and health-related quality of life, secondary outcomes are adverse events. This will be achieved through an individual patient data meta-analysis (IPD-MA) of randomized controlled trials (RCTs). By doing so, we aim to pinpoint subgroups among individuals with acute and subacute LBP that exhibit a more effective response to NSAIDs.

Materials and methods

Data source and search strategies

Considering the overlap of our topic with a Cochrane systematic review conducted by van der Gaag et al. [20], we will ensure that the eligible studies identified in that review will be included in our search. Additionally, we will extend our literature search to

cover acute and subacute LBP up to the last date searched (7th January 2020) in the Cochrane review. We have enlisted the expertise of a professional librarian to develop a formal search strategy for relevant studies in databases, including Medline ALL, Embase, and the Cochrane Central Register of Controlled Trials* ('*' means manually deleted abstracts from trial registries). The search has been run on the 10th of March 2023 and will be updated at the beginning of 2024. The details of the search strategy can be found in Appendix 1.

Study inclusion/exclusion criteria

We will include all relevant studies without language limitations, adhering to the following criteria:

(1) The study design is a RCT.
(2) The participants are adults (i.e., aged over 18 years old) experiencing acute or sub-acute *non-specific* LBP (i.e., the duration of LBP < 12 weeks) with or without leg pain. In case a study involved a mixed population, we will also include these trials, and extract IPD from people with acute and subacute LBP for analysis.
(3) The intervention in the included studies is NSAIDs, regardless of route of administration (e.g., oral, topical).
(4) The comparison in the included studies is placebo.
(5) The outcomes of interest include pain intensity, physical functioning, and health-related quality of life, which are core outcome domains in LBP RCTs [21]. We have no restriction on the follow-up period.
(6) We included all eligible studies without restrictions on study characteristics such as research year, amount of missing data, and the overall study risk of bias.

We will exclude studies focusing on chronic LBP, LBP caused by serious underlying conditions such as tumors, vertebral fractures, infections, or axial spondyloarthritis, which may require specific treatments [1], such as anti-tumor therapy, surgery, or antibiotics.

Study selection

To manage duplicates, organize the bibliography, and facilitate the selection process, we will utilize EndNote. Two independent reviewers (YF and SM) will screen titles and abstracts. Subsequently, we will review the full texts of the included titles and abstracts. In cases where the two reviewers cannot reach a consensus on eligibility, a third reviewer (AC) will be consulted for a final decision. The reasons for excluding full-text articles will be recorded in an Excel file. The study selection process will be summarized using the PRISMA flowchart.

Power calculation

When we will confirm the trials willing to provide their IPD and the potential moderators included in those trials, we will conduct a power calculation. Power calculation before collecting IPD can reveal the value and viability of an IPD project [22]. Considering our outcomes, e.g., pain intensity measured by Numeric Rating Scale (NRS), disability measured by Roland Morris Disability Questionnaire (RMDQ), are commonly accepted as continuous variables in analysis, we plan to employ closed-form solutions to calculate the power of the IPD–MA [22]. We will perform the calculation on the online calculator provided by Ensor et al. on a website (https://seed-ipd.shinyapps.io/IPD_power_calculator/) [22] with the assumed minimally important interaction sizes suggested by clinical experts, and some published information e.g., total patients in study, number of patients in treatment group and mean of outcome values in treatment group. A planned IPD-MA project may be considered as worth investing in when the power is over 80% [22].

Data collection and quality assessment

We will collect all available data from identified trials. We will firstly extract aggregate data about eligible trials, e.g., method of randomization, allocation, interventions and the intervention characteristics (e.g., dose, type and administration method), comparisons, outcome measures and timing. We will use Microsoft Excel forms to collect the information above. We will extract outcome data for all follow-up periods and define the follow-up categories based on the Cochrane review [14]. Given the pain intensity decreases significantly in the first week of taking oral analgesics [23], we will define the follow-up categories as one week (very short term), 3 weeks (short term), and 12 weeks (moderate term). The outcomes will be categorized according to the time closest to these intervals.

After that, each included RCT will undergo an assessment for risk of bias conducted by two independent reviewers (YF and SM). We will adapt the assessment tools for IPD-MA based on those used for traditional meta-analysis. As the understanding of bias has evolved and research has progressed, Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2) has replaced the initial version. In our project, we will utilize the adapted Cochrane Risk Of Bias (RoB)-2 assessment tool by excluding the inapplicable domain 5 (section of the reported results) [15], as new analyses are carried out in the IPD context. We will assess the quality of eligible trials involving four domains (randomization process, deviations from the intended interventions (effect of assignment to intervention), missing outcome data, and measurement of the outcome) including 15 signaling questions [15]. By answering each signaling question (yes/probably yes/no/probably no/no information) in a designed Excel tool for (RoB)-2, we will get a judgment for each domain. We can make an overall judgment of risk-of-bias of each trial based on the criteria as follows (more details in Appendix 2): 1) Low risk of bias: the study is judged to be at low risk of bias for all domains for this result; 2) Some concerns: the study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain; 3) High risk of

Table 1
Potential moderators.

Possible moderators	Study	Type of study
Sex Level of fear avoidance	Hancock et al. [18]	Exploratory study
Age Body Mass Index Pain severity Occurrence of pain at rest Occurrence of pain at night Spinal stiffness	Karateev et al. [19]	Exploratory study

bias: the study is judged to be at high risk of bias in at least one domain for this result, or, the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the. We will present the RoB of each domain and the overall RoB in a 'traffic light' table. We will contact original authors for additional information when necessary.

For IPD, we will contact the corresponding authors of eligible trials following the procedure of the Spine Trial Bank, an initiative aimed at facilitating IPD-MA in the field of spine-related disorders. In the event of no response from the corresponding author within two weeks, we will send two follow-up emails at distance of two weeks among each other. If the corresponding authors cannot be reached, we will contact co-authors or the institutes where the trials were conducted. If all attempts to obtain data through various contact information fail, we will categorize this trial as 'unavailable'. All data deliverers (i.e., the research institutes who own the data) willing to participate will be requested to sign a data delivery license agreement. From authors of published RCTs, we will request the IPD of the RCTs including participants characteristics at baseline (e.g. age, sex), pain characteristics (e.g., duration, pain intensity at baseline, pain in other site), other pre-specified potential moderators in Table 1, and other clinical characteristics.

In the field of subgrouping effects for NSAIDs on patients with acute/subacute LBP, there are some preliminary exploratory findings. Hancock et al. [18] found that female patients and patients having high levels of physical activity-related fear avoidance may respond better to NSAIDs as compared to males and those with low levels of physical activity related fear avoidance. In 2018, an observational study on patients with osteoarthritis and non-specific LBP [19] reported that the effect of NSAIDs was smaller in patients aged 65 years and older, with body mass index >30 kg/m2, experiencing severe pain, pain at rest, pain at night, and the presence of spinal stiffness. Given the potential variation in the effectiveness of NSAIDs in patients with LBP, we hypothesize the presence of distinct 'subgroups' among those with acute and sub-acute LBP, exhibiting differential responses to NSAIDs. We present several potential moderators that may yield a differential response to NSAIDs in patients with acute or sub-acute LBP in Table 1 for confirmatory analysis. Nevertheless, if we encounter other possible moderators in eligible trials during data collection, we will also conduct exploratory analyses by including moderators not pre-specified in the table.

We will provide the trial investigators a 'Data Transfer Guidance' for preparing data before transferring. The de-identified data will be accepted in any kind of electronic format (e.g., SPSS, Stata, SAS, Excel), if variables and categories are adequately labeled within the dataset or with a separate codebook. All the data collection documents and IPD will be securely stored on a server at the Erasmus MC Medical University in Rotterdam, the Netherlands.

Data checking and harmonization

We will develop a data dictionary for re-coding the data that we will receive. The data dictionary list all the variables included in the IPD-MA, indicating the variables names, types, definitions, values, and notes. The data dictionary will be saved as an Excel file.

When we receive the original data, we will convert the dataset into the same format for harmonization, e.g. Excel, CSV. Then we will initially check if:

- the data can be opened and are well structured,
- all the randomized participants appear to have been included,
- there are obvious omissions or duplicates in the sequence of participant identifiers,
- all outcomes, baseline covariates, and other variables we are interested in are included in the IPD,
- there are missing variables (e.g., randomized group variable, ID variables) or missing data (e.g., lost to follow up),
- there are invalid, outlying, or implausible values,
- the name, definition and value of variables align with dictionary.

And then, we will also check the received IPD against each publication and keep a record of the verification process. Following the verification, we will promptly contact the original study authors to seek assistance with any discrepancies found in the checked data and set a deadline for their response.

For data harmonization, once data checks are complete, each dataset sent to us will be combined to form a new master IPD dataset. We will use R or SPSS to rename, label and integrate the variables for each included trial with the master data dictionary consistently.

When the proportion of missing data (any missing value of covariates and outcomes) is less than 5%, we will conduct a complete case analysis for our main analysis [24]. When the data missingness is larger than 5%, we will apply the multiple imputation to deal with missing data in the fully conditional specification (FCS) approach with R package 'micemd' under the assumption of missing at

random (MAR) [25,26]. Suppose there is a high percentage of missing data (e.g. 20%). In that case, we will consider a sensitivity analysis to explore the robustness of the IPD-MA results with the multiple imputation under the MAR assumption compared with the results of the complete case analysis.

We will maintain data for continuous measurement of variables whenever possible. It is important to note that multiple questionnaires or measurements may be used to assess the outcome of interest in the included trials. There might be different hierarchies of measures. For instance, the collected IPD may include measures of pain intensity at the present time and/or average pain over the past one week. In that case, we will choose the average pain intensity over past week prior to the pain intensity at present time.

Data analysis

Overall treatment effect

We will perform IPD meta-analysis to estimate the overall treatment effect of NSAIDs compared with placebo. Our primary outcomes of interest are pain intensity, disability, and health-related quality of life, secondary outcome are adverse events. For the different scale of outcome measures, we will transform the outcomes into a standardized scale or use the standardized mean difference (SMD) to lump together the outcome measures. For instance, if pain intensity is measured using diverse scales across different trials (such as VAS (ranging from 0 to 100 points), and NRS (ranging from 0 to 10 points)), we will convert all scores to a single scale (e.g., VAS 0–100) to ensure consistency. If the disability is measured by the Oswestry Disability Index (ODI) and Roland Morris Disability Questionnaire (RMDQ) in separate trials, we will standardize the results of the studies to a uniform scale with the SMDs.

Considering the fact that around half of the eligible trials have sample sizes that are very close to the small sample size criterion, i.e., ≤ 30 participants per group or ≤ 10 events per group [27], and the greater power than two-stage approach [28], we will conduct a one-stage IPD meta-analysis in the generalized linear mixed model (GLMM) framework [27,29], taking into account for clustering of participants within trials [30]. We will fit random effect models with restricted maximum likelihood (REML) estimation and derive the confidence intervals (CI) of treatment effect with the Kenward-Roger approach. Then, the equation for participant j in trial i including a covariate $x_{ij} = 1$ for treatment group or $x_{ij}=0$ for control group depends on the type of outcome variables, e.g., for continuous outcomes the basic equation is: $y_{ij} = \alpha_i + \theta_i x_{ij} + e_{ij}$, $\theta_i \sim N(\theta, {\tau_\theta}^2)$, $e_{ij} \sim N(0, {\sigma_i}^2)$; the parameter α_i represents the expected value of the outcome in trial i for a participant whose covariate values are all zero; the parameters θ_i, represent the treatment effect in trial i, and ${\tau_\theta}^2$, the between-trial variability in treatment effect suggesting the heterogeneity in treatment effect across trials; the model's residual errors (e_{ij}) are the differences between participants' true observed outcome values and their predicted outcome values based on the fitted regression equation; e_{ij} are assumed normally distributed with a mean of zero and a variance of ${\sigma_i}^2$ [30]. We will adjust the models with corresponding baseline outcomes (pain intensity or disability). We will consider the overall effect is clinically relevant if the magnitude of the effect is more than 10 points on a 100-point pain scale and more than 0.5 for Standardized Mean Difference (SMD) on disability. These clinical relevance thresholds were based on expert consensus among the authors of this review, and they are in line with those adopted by van der Gaag et al. in their Cochrane review on the efficacy of NSAIDs in patients with acute LBP [14]. Considering the heterogeneity across trials, we will report the ${\tau_\theta}^2$ and the intraclass correlation coefficient (ICC) (an estimate of the proportion of group-level variance in the population) [31,32]. The criteria of ICC for the level of between-trials heterogeneity refers to the guideline reported by Koo et.al. [33]: 1). Below 0.5: might not be important; 2). 0.5 to 0.75: may represent moderate heterogeneity; 3). 0.75 to 0.9: may represent substantial heterogeneity; 4). above 0.9: considerable heterogeneity.

To get a robust result of estimated overall treatment effect, we will conduct a two-stage analysis as sensitivity analysis. In the initial stage, we will establish models for separate analysis in each trial to derive a treatment effect estimate ($\hat{\theta}_i$) and its variance ($\text{var}(\hat{\theta}_i)$). The models are grounded in the types and distribution of outcome measures. For instance, we will apply linear regression models for continuous outcomes. Typically, the treatment effect estimate of interest will be a difference in means for continuous outcomes, an odds ratio or risk ratio for binary outcomes or a hazard ratio for time-to-event outcomes. In the second stage of a two-stage IPD meta-analysis, the treatment effect estimates for each trial and their variances will be pooled in a random effects model, then $\hat{\theta}_I \sim N(\theta_i, \text{var}(\hat{\theta}_i))$, $\theta_i \sim N(\theta, \tau^2)$. We will report τ^2 and I^2 as the measures for quantifying the between-trial heterogeneity of treatment effects. The criteria of I^2 for the level of between-trials heterogeneity refers to the Cochrane handbook for systematic review [34]: 1). Below 40%: might not be important; 2). 30% to 60%: may represent moderate heterogeneity; 3). 50% to 90%: may represent substantial heterogeneity; 4). 75% to 100%: considerable heterogeneity.

When the IPD of trials cannot be retrieved our approach will involve two steps: Step 1) We will perform a two-stage approach analysis using the available IPD [35], and Step 2) We will conduct the same approach but combine IPD with aggregate data from non-IPD trials in the second step of the two-stage approach as a sensitivity analysis.

Treatment-covariate interactions

To identify the moderation of NSAIDs treatment effect, we will extend the one-stage model by including the potential moderators in Table 1. Simply including treatment-covariate interaction terms within a one-stage model is often flawed, as it potentially merges within-trial and across-trial information [17]. Therefore, before extending the one-stage model, we can center the covariate z_{ij} about its trial-specific mean $\bar{z}_i$ and add an additional term that allows the covariate means $\bar{z}_i$ to explain between-trial heterogeneity in the treatment effect [17]. Then the equation for continuous and binary outcomes becomes: $y_{ij} = \alpha_i + \beta_{1i} z_{ij} + \beta_{2i} x_{ij} + \beta_{3i} y_{0ij} + \gamma_{Wi} x_{ij} (z_{ij} - \bar{z}_i) + \varepsilon_{ij}$; $\beta_{2i} \sim N(\varphi + \gamma_A \bar{z}_i, {\tau_1}^2)$, $\gamma_{Wi} \sim N(\gamma_W, {\tau_2}^2)$; where y_{ij} represents the outcome, α_i represents the expected value of the outcome (on the transformed scale) in trial i for a participant j whose covariate values are all zero, z_{ij} represents a participant-level covariate, x_{ij} represents the treatment, y_{0ij} represents the baseline value of outcome, γ_{Wi} indicates the expected change in treatment effect for a one-unit increase in z_{ij} for trial i, $x_{ij} z_{ij}$ represents the treatment-covariate interaction, the parameters β_{1i}, β_{2i}, β_{3i} represent

the effect of a one-unit increase in the corresponding covariate z_{ij}, x_{ij}, y_{0ij} on the value of y_{ij} in trial i, ${\tau_1}^2$ is the residual between-trial variance in the treatment effect (i.e. that not explained by $\bar{z}_i$), and ${\tau_2}^2$ is the between-trial variance of the within-trial interaction [17]. For the heterogeneity measures, we will report the ${\tau_1}^2$, ${\tau_2}^2$ and the ICC.

If the p values of coefficients of interaction terms are less than 0.05, the interaction terms are considered statistically significant. We will report treatment effects for subgroups with the 95% confidence interval of size of the interaction terms. We will consider there to be a clinically relevant moderator effect if the magnitude of the effect is more than 5 points on a 100-point pain scale and more than 0.25 for SMD on disability [36]. Meanwhile, the directions of moderator effects across follow-up periods should be consistent [36].

We will conduct a sensitivity analysis by excluding the high-risk included studies during the data analysis. We will modify and apply the GRADE adaptation used by de Zoete et al. for rating the certainty of evidence for our study [36]. We will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Patient Data systematic reviews (PRISMA-IPD) statement when reporting the manuscript corresponding to this protocol [37].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yanyan Fu: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Simon Dyrløv Madsen:** Data curation, Methodology, Writing – review & editing. **Christina Abdel Shaheed:** Methodology, Writing – review & editing. **Annemarie de Zoete:** Conceptualization, Methodology, Writing – review & editing. **Alessandro Chiarotto:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Bart Koes:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Data availability

This article is a protocol of an IPD meta-analysis. Currently, we have not got the data from original authors. We are not sure how much data we will get and whether we can share it.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mex.2024.102713.

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