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People with short symptom duration of knee osteoarthritis benefit more from exercise therapy than people with longer symptom duration: An individual participant data meta-analysis from the OA trial bank

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SUMMARY

Objective: To investigate whether duration of knee symptoms influenced the magnitude of the effect of exercise therapy compared to non-exercise control interventions on pain and physical function in people with knee osteoarthritis (OA).

Method: We undertook an individual participant data (IPD) meta-analysis utilising IPD stored within the OA Trial Bank from randomised controlled trials (RCTs) comparing exercise to non-exercise control interventions among people with knee OA. IPD from RCTs were analysed to determine the treatment effect by considering both study-level and individual-level covariates in the multilevel regression model. To estimate the interaction effect (i.e., treatment x duration of symptoms (dichotomised)), on self-reported pain or physical function (standardised to 0–100 scale), a one-stage multilevel regression model was applied.

Results: We included IPD from 1767 participants with knee OA from 10 RCTs. Significant interaction effects between the study arm and symptom duration (≤1 year vs > 1 year, and ≤2 years vs > 2 years) were found for short- (~3 months) (Mean Difference (MD) −3.57, 95%CI −6.76 to −0.38 and −4.12, 95% CI-6.58 to −1.66, respectively) and long-term (~12 months) pain outcomes (MD −8.33, 95%CI −12.51 to −4.15 and −8.00, 95%CI −11.21 to −4.80, respectively), and long-term function outcomes (MD −5.46, 95%CI −9.22 to −1.70 and −4.56 95%CI −7.33 to-1.80, respectively).

Conclusions: This IPD meta-analysis demonstrated that people with a relatively short symptom duration benefit more from therapeutic exercise than those with a longer symptom duration. Therefore, there seems to be a window of opportunity to target therapeutic exercise in knee OA.

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Introduction

Knee osteoarthritis (OA) is a serious chronic condition characterised by pain and impaired function and strongly contributes to physical disability.[1] The disease process in OA represents a continuum from the presence of OA biomarkers (e.g. detected in blood or advanced imaging), to early-stage OA with first presentation of symptoms, to established OA and finally end-stage OA.[2] There is increasing emphasis in the literature on identifying and initiating treatment of OA in the early phases of the disease.[2,3] A recent scoping review on early-stage knee OA definitions found substantial variability in definitions applied.[4] Diagnosing OA at an earlier stage provides the opportunity to manage the disease sooner with currently recommended first-line programmes involving exercise, weight loss and education. Early interventions may prevent the progression of the disease, the development of chronic pain and more severe disability and thereby partly prevent the socioeconomic impact of OA. Therefore, early-stage knee OA could present a 'window of opportunity' in which to arrest the disease process.[2] However, the question remains whether existing treatments for OA are effective in these early OA populations in order to decrease the risk of disease progression.

Therapeutic exercise (subsequently referred to as exercise therapy) is one of the cornerstones of OA management.[5] It involves participation in physical activity that is planned, structured, repetitive and purposeful for the improvement or maintenance of a specific health condition such as OA. It encompasses general aerobic exercise, strengthening, flexibility, balance or body-region-specific exercises.[6] The effectiveness of exercise therapy for knee OA is well established ((Standardised Mean Difference) SMD 0.4–0.6) and is for now one of the most effective treatments in OA, but still with moderate effectiveness.[7] Systematic reviews and meta-analyses have reported small to moderate improvements in pain and physical function outcomes in favour of exercise therapy compared to non-exercise controls.[7,8] However, most randomised controlled trials (RCTs) of exercise for knee OA have so far been performed in mixed populations with well-established knee OA, with symptom durations mostly for several years. When chronic pain has already developed and structural joint changes and disability have become severe, an active lifestyle and initiating and maintaining exercise therapy can be difficult. The Subgrouping and TargetEd Exercise pRogrammes for knee and hip OsteoArthritis (STEER) OA project studied moderators of the effect of exercise on pain and physical function in people with knee and/or hip OA.[9] No interaction between symptom duration as a continuous measure, and treatment was found in this study.[9] Many RCTs included in STEER OA did not include patients with relatively short symptom duration (these are excluded in current analysis), and symptom duration was only continuously analysed. Within this study, we therefore investigated whether duration of knee symptoms (as a measure of stage of OA) influenced the magnitude of the effect of exercise therapy compared to non-exercise controls on pain and physical function at short- and long-term follow-up. Early-stage knee OA is variably defined in literature, and a wide range of cut-offs for symptom duration are used.[4] Though, as ongoing studies used criteria of symptom duration less than one and two years,[4] these cut-offs were applied to test whether the effect of exercise therapy is more effective in these populations with knee OA.

Method

We undertook an individual participant data (IPD) meta-analysis utilising IPD stored within the OA Trial Bank from RCTs comparing exercise to non-exercise controls among people with knee and/or hip OA.[10] The OA Trial Bank initiates meta-analyses of effect of treatment on predefined subgroups of patients with OA from existing studies using IPD.[11] This IPD was originally collected as part of the STEER OA project within the OA Trial Bank,[9,10] an IPD meta-analysis that aimed to identify individual-level moderators of the effect of exercise for reducing pain and improving physical function in people with knee and/or hip OA. For the current study purpose, IPD from patients with knee OA was selected. The research question and study protocol were approved by the steering committee of the OA Trial Bank. Ethical approval was not required as no new data were collected.[12] The study protocol for the presented analyses was not publicly registered.

Study selection

RCTs fulfilling the following criteria were selected from the OA Trial Bank for inclusion in this IPD meta-analysis:

- Study population: Study participants had to be aged 45 years or older with a diagnosis of knee OA, diagnosed by X-ray, clinical criteria, health care professionals or self-reported
- Intervention: Any land-based or water-based therapeutic exercise intervention regardless of content, duration, frequency or intensity
- Control: No exercise control group (including usual care, waiting list, attention control or no treatment) or sham treatment
- Outcome measure: Any self-reported pain and/or physical function at short- (closest to 3-months) or longer-term (closest to 12-months) follow-up
- Symptom duration: Measurement of symptom duration (continuous or categorical) and minimally including a sample ($n > 1$) of participants with a symptom duration ≤1 year

Identification of eligible studies, data collection and transfer

For the STEER OA project, a previous systematic review search strategy to identify RCTs comparing exercise to non-exercise or other exercise controls on pain and physical function outcomes among people with knee and/or hip OA was updated.[13] The electronic search was re-run in multiple databases from the date of the previous search (1st March 2012) up to February 25th 2019. Details on the search strategy are previously published.[10] Eligibility criteria of the present study were checked by two independent authors (MvM, DS) in the 31 eligible RCTs that compared exercise to non-exercise controls that shared IPD with the OA Trial Bank for the STEER OA project. Disagreements were resolved by discussion. Authors from eligible RCTs were approached following the standard procedures of the OA Trial Bank and permission was asked to re-use their data for the current study purpose. An amendment on the originally signed data transfer agreement to the use of their data had to be signed by both parties.

In addition, the search was updated to 2021 by the STEER OA project team and was used to identify new RCTs eligible for the current study purpose. Two review authors (MvM, DS) independently selected citations based on titles and abstracts. The two review authors assessed full articles that met the eligibility criteria independently before consensus was reached. Corresponding authors of these eligible trials were approached via email and requested to share their data. A data transfer agreement was signed before de-identified data were transferred to the OA Trial Bank. If approached authors had additional data available of which the authors were not aware of or results were published after 2020, these datasets were also included. All received data were checked for consistency with the published papers.

Risk of bias

We extracted the risk of bias scores, assessed with the Cochrane Collaboration's tool (version 1.0), from the previously published IPD from those studies included in the present study. For newly included studies, the same tool was used and two investigators (MvM, DS) independently graded the risk of bias based on the published papers.

Data extraction

From the original RCT publications and IPD, we extracted the following information on study level: sample size, country in which the study was performed, OA diagnostic inclusion criteria, total number of participants, age, sex, body mass index (BMI) (kg/m^2), symptom duration (≤1 year; > 1 year & ≤2 years; > 2 years) and interventions studied.

Data analyses

Primary outcomes included self-reported pain and physical function (both standardised to 0–100 scale) at short-term (closest to 3 months) and longer-term (closest to 12 months). When more than one measure of pain was reported, we chose the highest in the hierarchy as proposed by Juhl et al., with the exception that VAS and NRS were considered similar in hierarchy: (1) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)/Knee Injury and Osteoarthritis Outcome Score (KOOS), (2) Visual Analogue Scale (VAS)/Numerical Rating Scale (NRS) during activity, (3) VAS/NRS during walking, (4) VAS/NRS while moving (5) VAS/NRS overall.[14] For physical function, the WOMAC disability subscale was selected. Both pain and function outcomes were standardised to a 0–100 scale (pain: 0 = no pain, 100 worst pain; function: 0 = best function, 100 worst function).

All participant-level data from RCTs were analysed in a one-stage IPD meta-analysis to determine the treatment effect by considering both study-level and individual-level covariates in the multilevel regression model. The specific treatment effect (i.e., the effect of the intervention versus control) was estimated using one-stage multilevel regression models with random effects, clustered at the trial level using a random trial intercept. Pain or physical function were considered as the dependent variable. All models were adjusted for baseline pain or physical function. To estimate the interaction effect, the interaction term pain or physical function x duration of symptoms (≤1 year compared to > 1 year, and ≤2 years compared to > 2 years) was added to the model. Analyses are based on complete data. The (interaction) effect estimates are expressed in mean differences (MD) and presented with accompanying 95% confidence intervals (CI).

Results

Of the 31 RCTs included in the STEER OA study, 23 were excluded from this study. This was due to: lack of reporting of symptom duration (n = 14); involving only participants with hip OA (n = 6); lack of consent for further use of the IPD (n = 2); lack of participants with symptom duration ≤1 year (n = 1). This left a total of eight RCTs included in this study. The search update identified another 15 RCTs, of which seven fulfilled our inclusion criteria. Of these, two signed the license agreement and provided IPD. Thus, this resulted in a total study sample of 1769 participants with knee OA from 10 individual RCTs [15–24] (Table I).

Study characteristics

The study sample size used for the analyses varied from 46 to 418 (Table I). Within the included RCTs, the percentage of women ranged from 48.3% to 71.7%, the mean age ranged from 61.6 to 68.5 years, and the mean BMI ranged from 27.9 to 34.3 kg/m^2. The percentage of participants within a single RCT with a symptom duration ≤1 year ranged from 4.0% to 47.3%. The diagnosis of knee OA was based on a combination of clinical and radiographic data in four RCTs.[15,16,20,22] Only one RCT based the diagnosis of knee OA on radiographic criteria only [24] while two RCTs relied on a self-reported diagnosis.[18,21] Most exercise interventions were land-based and included strengthening exercises, either individual or group based. All RCTs reported pain outcomes at short-term follow-up, and five reported on long-term outcomes. Physical function outcomes were available in eight of the ten included RCTs.

The risk of bias was generally low, with only two studies having a high risk of bias on the item 'incomplete outcome data' (Appendix 1).

Study population and overall treatment effects

The mean age of the 1769 participants was 65.1 (SD 9.0) years, with more women (66.0%) than men included. 12.8% had a symptom duration ≤1 year and 10.4% had a symptom duration of between 1 and 2 years (Table II).

One-stage IPD meta-analyses of the 10 included RCTs showed an overall effect in favour of exercise therapy compared to non-exercise controls on short- and long-term pain of MD −8.24 (95%CI −9.93 to −6.55) and MD −5.20 (95%CI −7.51 to −2.89), respectively and MD −6.98 (95%CI −8.43 to −5.53) and MD −4.88 (95%CI −6.90 to −2.87) for short- and long-term function on standardised 0–100 scales.

Symptom duration and treatment effects

Effect estimates of exercise therapy compared to non-exercise controls, for the different subgroups based on symptom duration are presented in Fig. 1 and Appendix 2. In participants with a symptom duration ≤1 year, exercise therapy resulted in a significant improvement in pain and function at both short- and long-term follow-up. Significant interaction effects between exercise therapy and symptom duration (≤1 year versus > 1 year) were found for short- (MD −3.57, 95%CI −6.76 to −0.38, and long-term pain (MD −8.33, 95%CI −12.51 to −4.15), and long-term function (MD −5.46, 95%CI −9.22 to −1.70, Table III). Similar results were found for ≤2 year symptom duration versus > 2 year, with significant interaction effects on short- and long-term pain outcomes (MD −4.12, 95%CI −6.58 to 1.66, and MD −8.00 95%CI −11.21 to −4.80, respectively) and long-term function (MD −4.56, 95%CI −7.33 to −1.80).

Discussion

This study shows that there is an overall small but positive effect of exercise therapy on both short- and long-term pain and function in patients knee OA. Patients with a shorter symptom duration benefit significantly more from exercise therapy than those with a longer symptom duration, especially at longer-term outcomes. Results indicate that the benefit of exercise treatment compared to control improves in those with a short symptom duration with an estimated additional 8.3 points reduction in pain at long-term compared to those with a longer symptom duration.

To the best of our knowledge, no RCTs have previously investigated the effectiveness of non-invasive interventions in people with early symptoms of knee OA only. Although the effectiveness of exercise for knee OA has been well established within multiple RCTs and systematic reviews, none have specifically been undertaken among people with short-term symptom duration of knee OA population to compare our results with. In contrast to the literature, the beneficial effects of exercise therapy are maintained in the longer term, specifically for those with a relatively shorter symptom duration. The interaction effect for long-term pain outcome (MD 8.33) exceeds the minimal clinical important difference (MCID) of 4 to 17 on KOOS pain.[25] Though the 5.5 effect estimate for long-term physical function outcome does not exceed the MCID of 7.1 to 21 reported for WOMAC function.[25] Moreover, the effect estimates of −10.2 and −9.4 for short- and long-term pain effects in people with a symptom duration ≤1 year exceed or approach the minimal important change threshold of 10 reported for NRS pain and 4.3 to 20.1 for KOOS pain.[25] Therefore, exercise should be encouraged as early as

Study ID	Country	OA Diagnosis	Total participants in RCT / total included in IPD[a]	Sex (% women)	Age, yrs (SD)	BMI, kg/m^2 (SD)	Symptom duration (%)	Intervention (s) included in analyses	Pain outcome[b]	Function outcome	Follow-up data available Short- (S)/ long- (L) term[c]
Allen 2018[13]	USA	X-ray, clinical, or self-report	350/350	71.7%	65.3 (11.1)	31.4 (8.0)	≤1 yr: 4.0% 1–2 yr: 6.9% ≥2 yr: 89.1%	I1: Internet-based exercise training C: Control (waiting list)	WOMAC pain subscale	WOMAC disability subscale	S,L
Bennell 2010[14]	Australia	Clinical and X-ray	89/89	48.3%	64.6 (8.3)	27.9 (4.4)	≤1 yr: 15.7% 1–2 yr: 10.1% ≥2 yr: 74.2%	I1: Hip strengthening group C: Control (no intervention)	Pain overall (NRS)	WOMAC disability subscale	S
Bennell 2022[15]	Australia	Clinical	415/240	57.5%	65.3 (8.3)	33.3 (3.6)	≤1 yr: 13.3% 1–2 yr: 15.8% ≥2 yr: 70.8%	I1: Exercise programme comprised 6 physiotherapist consultations via videoconference for exercise, self-management advice, and behavioural counselling, plus exercise equipment and resources. C: Access to electronic OA information	Pain overall (NRS)	WOMAC disability subscale	S,L
Bossen 2013[16]	Netherlands	Self-report	199/158	65.8%	61.6 (5.5)	27.9 (4.6)	≤1 yr: 9.5% 1–2 yr: 12.7% ≥2 yr: 77.8%	I1: Automated web-based physical activity intervention C: Control (waiting list)	Pain overall (VAS)	Composite disability score other than WOMAC (KOOS/HOOS function)	S,L
Hinman 2007[18]	Australia	Clinical and X-ray	71/55	70.9%	62.5 (8.5)	34.1 (6.4)	≤1 yr: 34.5% 1–2 yr: 9.1% ≥2 yr: 56.4%	I1: Aquatic physical therapy C: Control (continue with usual daily activities and medication)	WOMAC pain subscale	WOMAC disability subscale	S
Hinman 2020[17]	Australia	Clinical	175/175	62.9%	62.4 (8.6)	31.1 (7.2)	≤1 yr: 8.0% 1–2 yr: 10.9 ≥2 yr: 81.1%	I1: Exercise advice and support (5–10 consultations with a physiotherapist trained in behaviour change for a personalised strengthening and physical activity programme) plus the existing service C: Existing telephone service (≥1 nurse consultation for self-management advice)	WOMAC pain subscale	WOMAC disability subscale	S,L
Hurley 2007[19]	UK	self-reported OA/pain	418/418	70.3%	66.6 (8.4)	30.2 (5.4)	≤1 yr: 9,1% 1–2 yr: 12.2% ≥2 yr: 75.8%	I1: Individual rehabilitation programme I2: Group rehabilitation programme C: Usual primary care	WOMAC pain subscale	WOMAC disability Subscale	S,L
Lim 2008[20]	Australia	Clinical and X-ray	107/107	55.1%	64.6 (8.5)	29.0 (4.8)	≤1 yr: 14.0% 1–2 yr: 4.7% ≥2 yr: 81.3%	I1: Quadriceps strengthening group C: Control (no intervention)	Pain on walking (VAS)	WOMAC disability subscale	S
Van Baar 2001[21]	Netherlands	Clinical	200/129	83.7%	68.5 (8.9)	NR	≤1 yr: 47.3% 1–2 yr: 6.2% ≥2 yr: 46.5%	I1: GP treatment + physical therapist-led exercise C: GP treatment	Pain overall (VAS)	Other algofunctional scale (IRGL)	S
Wallis 2017[22]	Australia	X-ray	46/46	43.5%	67.2 (7.5)	34.3 (6.3)	≤1 yr: 8.7% 1–2 yr: 8.7% ≥2 yr: 82.6%	I1: Walking programme C: UC (pharmacological and non-pharmacological treatment delivered at health service's hip and knee clinic. Advised not to include a prescription of physical activity in the 12-week study)	Pain overall (VAS)	WOMAC disability subscale	S

Data shown in the table are derived from IPD. Some slight discrepancies may therefore exist between data in the table and published report.
Abbreviations: BMI = body mass index; Comb. = Combined; IPD = Individual Participant Data; GP = General Practice; NR = Not Reported; NRS = Numeric Rating Scale; UC = Usual Care; UK = United Kingdom; USA = United States of America; VAS = Visual Analogue Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Relates to exclusion of intervention arms not eligible for current study purpose or study population, i.e. hip OA patients.

[b] Pain outcome chosen in accordance with the hierarchy as suggested by Juhl et al.[14]

[c] Follow-up time period categorised as: short-term (S) = nearest time-point to 12 weeks and long-term (L) = nearest time-point to 12 months.

Table I

Summary of RCTs that shared IPD.

Age, years	65.1 (9.0)[a]
Sex, women, n(%)	1166 (66.0%)[b]
BMI (kg/m^2)	30.8 (6.3)[c]
Symptom duration, n(%)	
≤1 year	226 (12.8%)
> 1 & ≤2 year	183 (10.4%)
> 2 year	1346 (76.7%)
Unknown	12 (0.7%)
Intervention randomised to, n(%)	
Exercise intervention	1112 (62.9%)
Control intervention	655 (37.1%)
Standardised pain score (0–100 (worst pain))	41.6 (21.0)[d]
Standardised physical function score (0–100 (worst physical function))	37.2 (19.0)[e]

[a] n = 1766.
[b] n = 1766.
[c] n = 1622.
[d] n = 1761.
[e] n = 1474.

Table II Osteoarthritis and Cartilage

Baseline characteristics of 1767 participants (means (SD) unless otherwise stated).

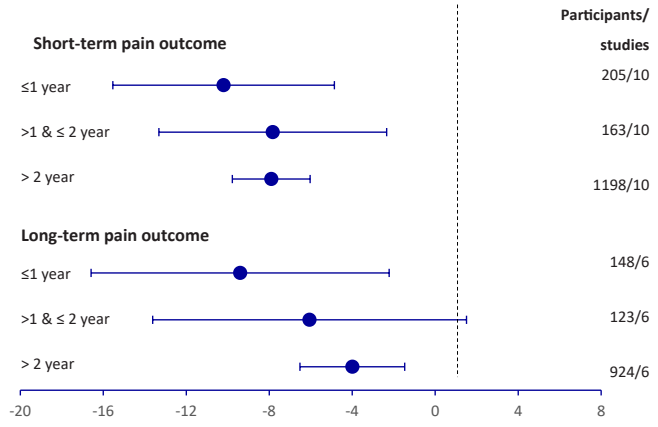

Fig. 1a Osteoarthritis and Cartilage

Effect estimates of exercise therapy on pain outcomes (adjusted for baseline values) for different symptom durations.

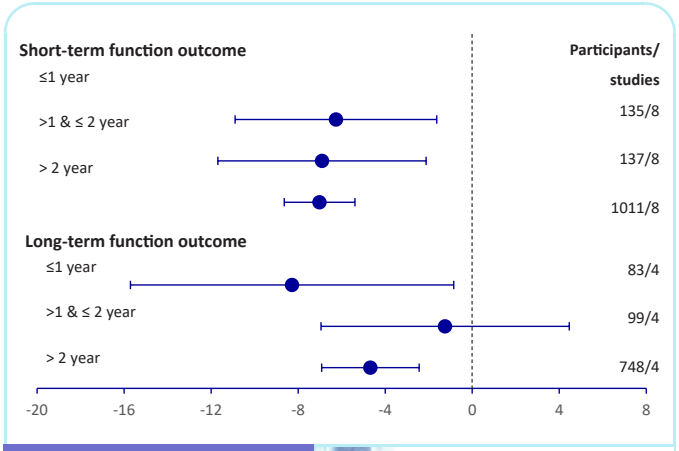

Fig. 1b Osteoarthritis and Cartilage

Effect estimates of exercise therapy on physical function outcomes (adjusted for baseline values) for different symptom durations.

possible once symptoms emerge in the disease process to take advantage of its effects in potentially slow disease progression within the suggested 'window of opportunity'.

Within this study, we defined early OA based on symptom duration. Whilst this seems the most simplified and obvious feature to include as a diagnostic criterion for symptomatic early-stage knee OA, symptom duration has not been incorporated as a criterion for symptomatic early-stage knee OA.[4] The currently proposed diagnosis of early-stage knee OA includes a chronic knee pain pattern developing over weeks to months, with periods of worse pain, stiffness and functional limitations for a week or more, interspersed with periods of little or no pain.[2] The diagnostic criteria for early OA and appropriate outcomes for this specific subpopulation of patients with OA are still under development and we therefore applied symptom duration as our criterion. Diagnostic criteria are thought to be of importance as a window of opportunity for treatment may exist in this early phase of the disease.[2] Different diagnostic criteria were used in the included RCTs in the current study. We included studies with a broad spectrum of knee OA definitions, based on radiography, clinical criteria, self-report and/or a diagnosis by a healthcare professional. Most included RCTs applied a combination of those features, with only one study applying Kellgren and Lawrence (KL) criteria using Xray.[24] The proposed diagnosis of symptomatic early-stage knee OA suggests little relevance of radiographic findings and it has been proposed that only patients with a KL grade of 0 or 1 fulfil the classification criteria for early-stage knee OA.[26] However, the use of KL grade does not seem to have any utility to classify early OA in clinical practice. We excluded 15 RCTs that did not measure symptom duration or included no study participants with a reported symptom duration ≤1 year. Of the included RCTs, the percentage of participants with a symptom duration ≤1 year ranged from 4.0% to 47.3%. This implies that even in studies examining the effectiveness of first treatment steps in OA care, i.e. exercise therapy, few seem to include the potential target population. As stated by Luyten et al. (2018), the identification of OA in its earliest stages in the primary care setting would allow the optimal multimodal management of the disease with patient education and exercise.[26] The findings of the current study support this and emphasise the need for early diagnostics, taking the duration of symptoms into account.

The identification of OA in the early phase of the disease typically occurs in a primary care setting. However, many patients with knee pain that could be due to OA typically do not consult a clinician immediately and instead have had symptoms for quite a while before seeking care. In a prospective observational cohort study of participants with first complaints in knee and/or hip, 68% had these complaints already for more than a year and one-third of them for more than 2 years.[27] This implies that with current common practice, we may never be able to identify all these patients in a timely manner in a primary care setting. As such we need to get a better understanding as to why these patients do not consult with their knee pain in an early phase and what attributes would change their consulting behaviour. This would allow exercise to be implemented earlier in order to maximise its effects. Moreover, health care professionals in primary care should also be equipped to provide an early-stage OA diagnosis and handle as such. The urgent need for early diagnostic criteria for knee OA has been recognised in the literature.[2,3] Still, although exercise therapy is recommended as a first treatment for knee OA in many (inter)national guidelines, these recommendations are not always adhered to. A recent study showed that only 59% of the patients on a waiting list for knee arthroplasty received exercise therapy.[28] This implies that next to the development of diagnostic criteria for early-stage OA, more insights are needed into reasons for consultation and barriers and enablers of early diagnosis experienced

	≤1 year symptom duration * exercise therapy[a]	≤2 year symptom duration * exercise therapy[b]
Short-term pain	−3.57 (−6.76;−0.38), p = 0.028	−4.12 (−6.58;1.66), p = 0.001
Long-term pain	−8.33 (−12.51;−4.15), p < 0.001	−8.00 (−11.21;−4.80), p < 0.001
Short-term function	−1.44 (−4.29;1.40), p = 0.320	−1.03 (−3.14;1.09), p = 0.341
Long-term function	−5.46 (−9.22;−1.70), p = 0.005	−4.56 (−7.33;−1.80), p = 0.001

[a] Symptom duration > 1 year = reference group in analyses.
[b] Symptom duration > 2 year = reference group in analyses. Mixed models adjusted for baseline pain or physical function, including symptom duration and interaction term.

Table III

Osteoarthritis and Cartilage

Interaction effects (effect estimates with 95% CIs).

by health care professionals in primary care. Moreover, the implementation of exercise therapy for knee OA should be optimised.

In light of the identified association between the effectiveness of exercise therapy and OA symptom duration, it becomes pertinent to explore possible underlying mechanisms influencing this significant interaction. On one hand, it can be argued that people with a longer symptom duration may already have a longer trajectory of activity avoidance, challenging the possibility of changes in physical activity behaviour. On the other hand, symptom duration may be a proxy variable for an alternate variable, such as coping strategies. It is conceivable that patients with shorter symptom durations may exhibit a proactive inclination to address their condition independently, thereby potentially yielding more pronounced effects from an exercise intervention. It is therefore of interest to gain more knowledge on the behavioural aspects of patients with OA towards symptom duration, health seeking behaviour and interventions.

Our study has a number of strengths. The use of IPD data, with general low risk of bias, enabled us to be the first to study the effects of exercise therapy in people with short-term symptom duration. Though the process of obtaining IPD is challenging,[29] and we only used IPD data of 10 RCTs, which limits the generalisability of the outcomes. The IPD allowed us to standardise all outcomes to a 0 to 100 scale and to apply subgroup and interaction analyses, although, differences in exercise therapy intervention characteristics may hamper study interpretation. The IPD used in this study was part of the STEER OA project, which studied moderators of the effect of exercise on pain and physical function in people with knee and/or hip OA.[9] In this study, no interaction between symptom duration as a continuous measure, and treatment was found. This likely relates to the large percentage of study participants having long-term symptom duration, with a wide reported range of pain duration up to 65 years. This likely masked the effect of the smaller group of participants with a short symptom duration. As no clear criteria for early-stage knee OA are available yet, we applied an arbitrary cut-off to dichotomise symptom duration, based on applied cut-offs in literature. The study is further limited by the absence of information on radiographic OA severity, as most studies did not have this variable available in the dataset. The study is also limited by a relatively short follow-up time, impeding interpretation of the impact of exercise on long-term OA progression. Moreover, symptom duration strongly relies on patient recall and could lead to misclassification within our analyses. Our last literature search was performed in 2021, therefore our analyses do not include any eligible RCTs published since then. Finally, results only apply to patients with knee OA and are not generalisable to other OA populations, which could be the subject of future research.

With this IPD analysis, we showed that there may be a window of opportunity in early-stage knee OA as patients with a relatively short symptom duration benefit even more from exercise therapy than those with a longer symptom duration with clinically meaningful differences found. Important remaining challenges in the identification, diagnosis and implementation should be addressed in future research.

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Author contributions

All authors contributed to the conception and design of the article, as well as analysis and interpretation of data. MH and MM contacted the potential data-deliverers, coordinated the data collection and MM performed the data analysis. The article was written by MM. All other authors critically revised and edited the manuscript draft and approved the final manuscript.

Declaration of competing interest

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Appendix 1. Summary of risk of bias of RCTs included in the IPD meta-analyses

Study, author year	Random sequence generation	Allocation concealment	Blinding of outcome assessors[a]	Incomplete outcome data	Selective reporting	Other sources of bias
Allen 2018[13]	Low	Low	Low	Low	Low	Low
Bennell 2010[14]	Low	Low	Low	Low	Low	Low
Bennell 2022[15]	Low	Low	Low	Low	Low	Low
Bossen 2013[16]	Low	Low	Unclear	High	Low	Low
Hinman 2007[18]	Low	Low	Low	Low	Low	Unclear
Hinman 2020[17]	Low	Low	Low	Low	Low	Low
Hurley 2007[19]	Low	Low	Low	Low	Low	Unclear
Lim 2008[20]	Low	Low	Low	Low	Low	Low
Van Baar 2001[21]	Low	Low	Low	Low	Low	Low
Wallis 2017[22]	Low	Low	Low	High	Low	Low

Assessed via the Cochrane Collaboration's tool (version 1.0) for assessing risk of, graded as unclear, high, or low risk of bias. Studies were not assessed for risk of bias against the criteria "blinding of participants and personnel" due to being unable to blind either participants or intervention deliverers to either receiving or delivering exercise.

[a] Where outcome measurement was collected via self-reported postal or digital questionnaire, this was classed as low risk of bias.

Appendix 2. Effect estimates of exercise therapy on pain and function (adjusted for baseline values)

Outcome	Mean score (0-100) (SD) Intervention group	Mean score (0-100) (SD) Control group	Effect estimate with 95% CI	Number of participants /studies in analyses
Short term pain				
Symptom duration ≤1 year	24.08(19.2)	33.0 (25.6)	−10.20 (−15.54;−4.86)[a]	205/10
Symptom duration > 1 & ≤2 year	26.90 (19.9)	30.69 (19.0)	−7.83 (−13.32;−2.34)[a]	163/10
Symptom duration > 2 year	28.8 (19.4)	37.7 (21.0	−7.90 (−9.78;−6.03)[a]	1198/10
Longer term pain				
Symptom duration ≤1 year	21.4 (21.2)	30.9 (24.3)	−9.40 (−16.59;−2.22)[a]	148/6
Symptom duration > 1 & ≤2 year	26.29 (21.1)	27.01 (21.0)	−6.06 (−13.62;1.51)	123/6
Symptom duration > 2 year	30.69 (21.3)	35.8 (22.7)	−3.99 (−6.52;−1.47)[a]	924/6
Short term function				
Symptom duration ≤1 year	23.0 (17.7)	28.6 (19.2)	−6.26 (−10.90;−1.63)[a]	135/8
Symptom duration > 1 & ≤2 year	26.38 (21.3)	29.25 (16.7)	−6.90 (−11.69;−2.12)[a]	137/8
Symptom duration > 2 year	26.97 (18.3)	35.48 (18.9)	−7.02 (−8.64;−5.39)[a]	1011/8
Longer term function				
Symptom duration ≤1 year	18.5 (18.5)	27.3 (17.3)	−8.28 (−15.71;−0.85)[a]	83/4
Symptom duration > 1 & ≤2 year	24.78 (20.9)	23.68 (19.4)	−1.25 (−6.95;4.46)	99/4
Symptom duration > 2 year	27.67 (19.6)	33.02 (19.9)	−4.68 (−6.92;−2.44)[a]	748/4

Short term = closest to 3 months; long term = closest to 12 months.

[a] p-value < 0.05.

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