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Causal association between physical activity and knee osteoarthritis – a systematic review and dose-response meta-analysis of cohort and mendelian randomization studies

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Authors' Contribution:

- A Study Design
- B Data Collection
- C Statistical Analysis
- D Manuscript Preparation
- E Funds Collection

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Abstract:

Background and Study Aim: Previous studies have reported an association between physical activity (PA) and the occurrence and progression of knee osteoarthritis (KOA). However, the existing evidence remains limited and of low-quality. This meta-analysis aims to synthesize existing knowledge on the dose-response relationship between PA and the risk of KOA, with the goal of informing precise PA recommendations for the primary prevention of KOA.

Material and Methods: This meta-analysis included 7 cohort studies and 7 Mendelian randomization (MR) studies comprising 2840 cases of KOA, selected from three databases: PubMed, Web of Science, and CNKI up to April 4, 2024. In the qualified studies, PA was primarily restricted and classified into exercise or sport, and the primary outcome indicators included the risk of KOA.

Results: The Categorical dose–relationship analysis from the MR study showed that moderate-to-vigorous physical activity (MVPA), and light physical activity (LPA) are the protective factors for developing KOA (OR = 0.83, 95%CI: 0.73-0.94; OR = 0.71, 95%CI:0.63,0.80). meeting WHO PA guidelines (≥10 Met/week) is not a significant factor for preventing KOA. The continuous dose–relationship analysis showed that there was a significant nonlinear positive dose-response relationship between PA and the risk of KOA. The linear model showed that the OR of KOA increased by 3% for every additional 4.5 met-h/week (OR = 1.03, 95% CI 1.00-1.07).

Conclusions: This meta-analysis showed that LPA and MVPA within a specific dose range were associated with a reduced risk of KOA, and high-dose PA was associated with an increased risk of KOA. There was a significant nonlinear positive dose-response relationship between PA and the risk of KOA.

Keywords: physical activity, Knee osteoarthritis, meta-analysis, Mendelian randomization, cohort

Dictionary

Knee Osteoarthritis – Knee osteoarthritis (KOA) is a chronic degenerative joint disease characterized by the progressive loss of articular cartilage, sclerosis of the subchondral bone, osteophyte formation, and joint space narrowing [69].

Physical Activity – Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure [70].

Mendelian Randomization – Mendelian randomization is an epidemiological method that uses genetic variants, which are strongly associated with a modifiable exposure (e.g., a lifestyle factor or biomarker), as instrumental variables to infer a causal relationship between the exposure and a disease outcome [71].

MET (Metabolic Equivalent of Task) – The MET (Metabolic Equivalent of Task) is a unit used to represent the intensity of physical activities [72].

1. Introduction

Osteoarthritis is a degenerative disease that is one of the main causes of joint pain [1]. Epidemiological surveys have found that more than 50 percent of knee pain patients aged 65 and over have osteoarthritis and that 80 percent are aged 75 and over [2,3]. Knee osteoarthritis (KOA) is a prominent factor in causing disability, which hampers both function and movement [4]. It significantly diminishes the quality of life and is the main reason for knee replacement surgery [5]. Additionally, it is linked to considerable medical expenses. Excessive mechanical stress is a significant contributing factor to the development of osteoarthritis (OA), especially in the load-bearing knee joint [6]. It can result in harm and permanent harm to the joint. However, engaging in regular physical exercise can effectively maintain or enhance joint health by strengthening the muscles around the joint, facilitating the passage of nutrients through synovial fluid, and reducing cartilage loss or abnormalities by maintaining optimal physiological processes [7,8].

Physical activity has always been regarded as an important component of overall health and can reduce the risk of metabolic and cardiovascular diseases [9]. Previous studies have revealed that exercise is closely associated with osteoarthritis, which is an important treatment for osteoarthritis patients. Scientific muscle training, physical and mental exercise, and aerobic exercise [10] can effectively improve the joint function and symptoms of osteoarthritis patients, improve the quality of life, and reduce the financial burden of patients [11]. In addition, traditional exercises such as tai chi, Ease of Practice, and Eight-Packing have low intensity, low impact, and full-body characteristics, and play a key role in enhancing flexibility, coordination, and mental health [12]. Lack of exercise exacerbates joint pain and functional decline, which in severe cases can lead to disability [13]. Although there is substantial evidence that there is a link between movement and arthritis since most studies are observational, there is an inevitable mixture of factors and reverse causation, and there is potential bias, the role of exercise in arthrosis pathology remains to be further confirmed.

In observational studies, the methods that can prove a causal relationship between variables are mainly Cohort studies and Mendelian randomization studies. Cohort studies are longitudinal observational designs that follow groups over time to examine exposure effects on outcomes. While they suggest associations, establishing causality requires ruling out biases and confounding [14]. Mendelian randomization (MR) is a method of using genetic variations to determine whether there is a causal relationship between the exposure factor and the outcome [15]. Genetic variations are randomly allocated during conception, and MR analysis can eliminate potential non-measurable mixed factors and reverse causal relationships, which is a major flaw in the evidence of observational studies [16]. The widespread availability of MR makes it a time-saving, cost-effective approach that overcomes the constraints of randomized controlled trials, prompting the increasing popularity of MR in the assessment and screening of potential causal relationships [17].

Meta-analyses of the association between physical activity and the risk of OA are also slowly emerging. However, meta-analyses focusing on the dose-response relationship between the risk of OA and physical activity have not been performed. Therefore, this study attempted to conduct a Categorical dose–relationship meta-analysis from MR study and a continuous dose-response meta-analysis from cohort study, to quantify the association between different doses of physical activity and the risk of OA, and this study only covers healthy populations.

2. Materials and Methods

Search method

Following the PRISMA guidelines, the researchers systematically searched electronic databases (from 1980 to date), including PubMed, CNKI, and Web of Science for literature on the association between physical activity and KOA [18,19]. We searched for literature using the keywords (knee or osteoarthritis or arthritis) and (physical activity or exercise or physical training) and (cohort or Mendelian), with a series of articles and relevant review articles. In addition, we searched the reference lists of all included studies to identify other eligible articles. No search language restrictions were applied.

Inclusion and exclusion criteria

The following four inclusion criteria were used in the current meta-analysis: (1) published observational cohort studies, case-control studies, or Mendelian randomization studies; (2) studies in which the participants were middle-aged and older adults over 45 years of age; (3) studies that reported the odds ratios, relative risks (RRs or HRs), and 95% confidence intervals (95% CIs) of physical activity levels related to the risk of KOA (or provided raw data to calculate these indicators). If multiple articles were published in the same group, those with longer tracking times or larger sample sizes were selected.

Study selection

The researchers (J.Z. and C.C.) searched the literature according to the above criteria separately, identified the studies that met the requirements, and then discussed the studies together to determine whether they should be included. In cases of disagreement, a third arbitrator (E.V.) was consulted to reach a consensus.

Quality assessment and risk of bias

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the cohort study. The higher the overall score, the higher the quality of the study, with a maximum score of 9. Studies with NOS scores of 0-3, 4-6, and 7-9 were considered low, moderate, and high quality, respectively [20]. If there was an inconsistent evaluation of the quality of the literature, the group focused on this issue and determined a final score based on quality [21,22]. As for MR Studies, we evaluated the research quality in accordance with the Guidelines for Strengthening the Reporting of MR Studies and its supplementary statement, also consulting the MR Reading Guide for further insights [23-25].

Data analysis

Meta-analysis was performed using STATA software (version 16.0; P values <0.05), and all tests were double-sided [26-28]. We performed separate meta-analyses for categorical and continuous variables to assess the association between physical activity and the risk of KOA [29, 30]. Pooled results were expressed as risk ratios (ORs) with 95% confidence intervals (CIs). Pooled analyses were categorized into cohort and cross-sectional studies based on study type, and pooled ORs were estimated using a random-effects model [31, 32]. Heterogeneity was assessed and described using the I2 statistic as the percentage of variation in the study, with I2 values of 25%, 50%, and 75% indicating low, medium, and high levels of heterogeneity, respectively [33]. A cut of 0.1 is for the p-value to assessing heterogeneity. Egger and Begg's tests were used to determine whether publication bias existed [34]. For the sensitivity analysis, each study was removed individually to check whether the combined effect of the remaining studies had changed [34, 35].

In the continuous variable analysis, the MET values were included to reflect different levels of physical activity. We converted the duration of a given PA intensity (h/week) to MET-h/week by combining it with the weekly frequency. We classified as LPA (3 METs, e.g., walking exercise), MVPA (4.5 METs), and VPA (8 METs) [36]. The dose metabolic equivalent (MET) used in this study was a physiological index describing the metabolic equivalent of PA energy in humans, defined as the energy consumed per kilogram of body weight per hour: 1 MET = 1 kcal/kg*h.

A robust error meta-regression method described by Xu et al. (2018) [37] was used to calculate continuous dose-response relationship slopes (non-linear trends) and 95% CIs from the natural logs of the reported ORs and CIs across categories of LTPA measures. This method is based on a one-stage approach that considers each study as a cluster of the whole sample and treats the within-study correlations using clustered robust errors. Based on the goodness of fit test of the model, the Stata software XBLC command was used to draw a dose-response curve [38].

To evaluate the causal association between physical activity and KOA, A pooled OR model from cohort studies and Mendelian randomization studies was used to assess the effect of PA on KOA. To evaluate the association between the different doses of PA and KOA, A pooled OR model from cohort studies and Mendelian randomization studies was used to assess the effect of PA on KOA.

Literature screening results and process

Based on the PRISMA flow diagram provided, the literature screening process and results for this systematic review are summarized as follows. The initial search of databases yielded 767 records, with an additional 7 records identified from other sources, bringing the total to 774. After removing 249 duplicates, 525 records remained for the title and abstract screening phase. Following this initial screening, 360 records were excluded, leaving 165 studies for further evaluation. Subsequently, the full text of these 165 articles was assessed for eligibility against predefined inclusion criteria. This rigorous full-text assessment led to the exclusion of 143 articles. The primary reasons for exclusion were: 1) the study was not observational in design, 2) the reported effect values were not Odds Ratios or Risk Ratios, 3) there was no clear contrast between an exposure and a non-exposure group, or 4) the physical activity dose was not reported. Ultimately, 14 articles met all the eligibility criteria and were included in the final qualitative and/or quantitative analysis. This multi-stage screening process ensured a focused and relevant evidence base for the review.

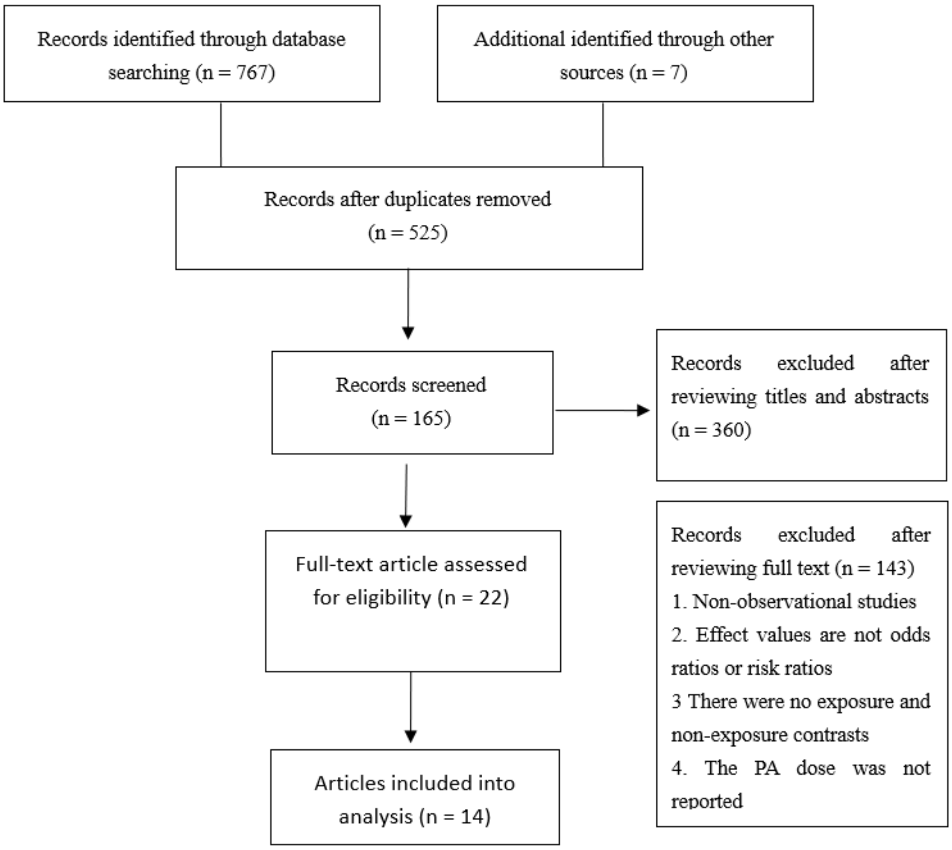

Figure 1. PRISMA flow diagram of study selection.

Literature search and study characteristics

A total of 767 potentially relevant citations were identified through the database and citation searches. We identified 258 articles in PubMed, 335 articles in Scopus, and 174 articles in Web of Science. According to the inclusion and exclusion criteria established in this study, seven cohort studies [23,39-44] and seven MR studies [45-51] were ultimately included. Table 1 and 2 summarizes the characteristics of each study. We conducted a quality assessment of all the included papers, and all MR studies received low scores on Power Calculations but were generally acceptable. Additionally, the quality of all cohort studies was relatively high, with scores ranging from 8 to 9. A flow chart of the literature search and study inclusion process is shown in Figure 1.

Table 1. Characteristics of the seven included cohort studies

Author (year）	Cohort or data resource	Age (years)	PA types	KOA Evaluation method	FU (years)	cases
1999 McAlindon et al. [39]	473 from Framingham	70.1（4.5）	LPA; MPA; VPA	X-ray and self-report	8	103
2000 Cheng et al. [40]	4073 from USA	n/r	MVPA	self-report	10.9	601
2003 Hootman et al. [41]	5284 from ACLS	n/r	LPA; MVPA; VPA	self-report	12.8	379

2013 Barbour et al. [23]	1528 from JoCo OA	59.8	LPA; MPA; VPA	X-ray and self-report	6.5	251
2016 Johnsen et al. [42]	66 964 from HUNT	46.8	LPA	self-report	14.3	1016
2020 Chang et al. [43]	1194 from USA	58.4 （8.9）	LPA; MVPA	X-ray and self-report	10	155
2024 Wu et al. [44]	5003 from Rotterdam	64.5 (7.9)	LPA; MVPA	X-ray and self-report	6.33	793

JoCo OA: Johnston County Osteoarthritis Project, Johnston County Osteoarthritis Project; ACLS: The Aerobics Center Longitudinal Study; n/r: no report.

Table 2. Characteristics of the seven included Mendelian randomization studies

Author (year）	Genetic variants	No of participants	PA types	KOA Evaluation method	cases	Study design
2023 He et al. [45]	12, 18 SNPs	455221(n/r)	LPA; MVPA	self-report	n/r	One-sample
2023 Li et al. [46]	15 SNPs	422,218(n/r)	LPA	X-ray and self-report	n/r	One-sample
2023 Wang (Bin) et al. [47]	108 SNPs	661399(n/r)	MVPA	self-report	403124	Two-sample
2023 Wang (Yanp) et al. [48]	17 SNPs	826690(n/r）	MVPA	self-report	177517	Two-sample
2024 Ma (Haoyu) et al. [49]	20, 6, 15 SNPs	440266(n/r)	LPA; MPA; VPA	X-ray and self-report	n/r	One-sample
2024 Ma (Xil) et al. [50]	15 SNPs	263615(n/r）	VPA	self-report	n/r	One-sample
2024 Xu et al. [51]	20 SNPs	460376(n/r)	LPA	self-report	24955	Two-sample

SNP: Single nucleotide polymorphism; **n/r**: no report.

3. Results

The association between the different intensities of PA and the Risk of KOA

Comparing the least active with the most active groups of participants resulted in pooled ORs of 0.83 (0.73; 0.94), 0.71 (0.63; 0.80), 0.78 (0.58; 1.04), 1.20 (1.07; 1.34), 0.89 (0.84; 0.96) for moderate-to-vigorous physical activity (MVPA), light physical activity (LPA), vigorous physical activity (VPA), total physical activity (TPA) and overall, respectively. In the sensitivity analysis, the overall pooled estimates of the respective results obtained in each analysis were very similar to those of the preliminary associations. In addition, we performed a funnel plot examination of the included studies, which showed no significant bias (Begg's test P value = 0.511> 0.05).

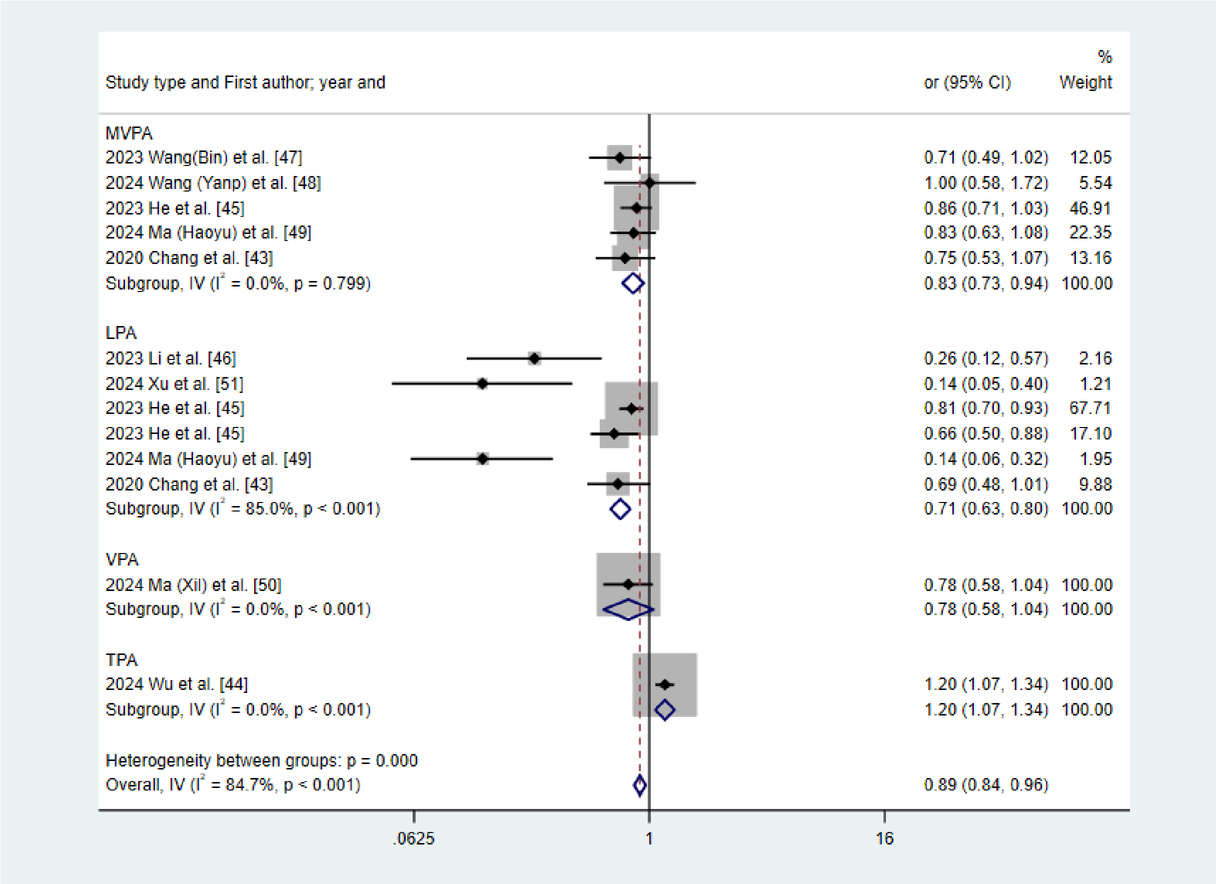

Figure 2. The association between the different intensities of PA and the risk of KOA

Comparing the least active with the most active groups of participants resulted in pooled ORs of 0.93 (0.65; 1.33), 1.00 (0.91; 1.10), 1.38 (1.13; 1.68) for <10 Met/week, ≥10 Met/week, ≥20 Met/week, respectively. In the sensitivity analysis, the overall pooled estimates of the respective results obtained in each analysis were very similar to those of the preliminary associations. In addition, we performed a funnel plot examination of the included studies, which showed a significant bias (Begg's test P value = 0.024 < 0.05).

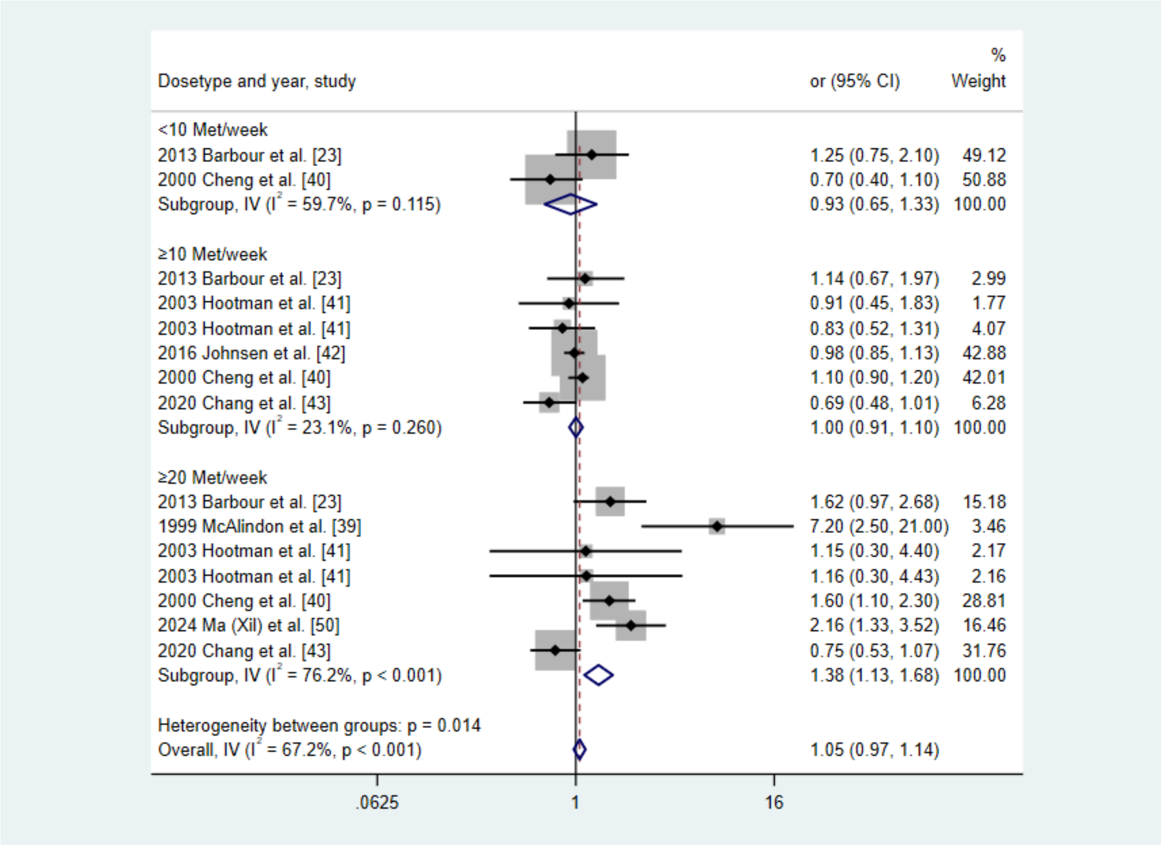

Figure 3. The association between the different doses of PA and KOA

The Continuous Dose-response Relationship Between PA and the Risk of KOA

Figure 4 shows the continuous dose-response relationship between PA and the risk of KOA. The results showed a nonlinear positive relationship between PA and KOA (Pnonlinear = 0.000< 0.05). The linear model showed that the OR of KOA increased by 3% for every additional 4.5 met-h/week (OR = 1.03, 95% CI 1.00-1.07). Therefore, physical activity cannot be excessive, and excessive physical activity is harmful to KOA.

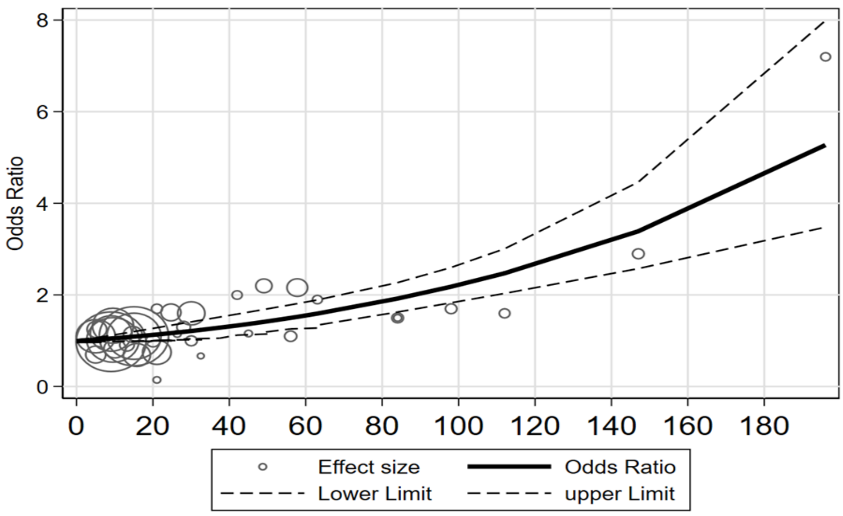

Figure 4. The continuous dose-response relationship between PA and the risk of KOA

4. Discussion

The results of this meta-analysis suggest that physical activity may be an important protective factor in reducing the risk of KOA. Specifically, point estimates of log-risk ratios for all included studies indicated that the most physically active group was less likely to develop KOA than the least physically active group from the meta-analysis results of the MR study. However, meta-analysis results from the cohort study do not show a significant association of low-dose PA and risk of KOA, specifical for <10 Met/week and ≥10 Met/week. Furthermore, Continuous Dose-response meta-analysis indicates that high-dose PA is a significant factor in the risk of KOA.

The existence of a causal relationship between PA and KOA has been the subject of a well-known controversy [52]. Nevertheless, the definition and extent of PA varied among the various investigations. Furthermore, there were variations in the methodologies employed to investigate knee osteoarthritis [53]. Furthermore, McAlindon et al. discovered a correlation between the risk of developing knee OA and high-intensity physical activity [39]. Although that association is feasible, it is imperative to acknowledge that the duration of PA was an integral component of the equation. Prolonged physical activity has been demonstrated to elevate the likelihood of knee osteoarthritis in certain investigations [54]. diverse occupations are also a significant factor in the prevalence of knee OA for diverse populations. Nonmanual laborers are at a lower risk of developing knee OA than manual workers [55].

Previous observational studies have confirmed the association between exercise and osteoarthritis, and in knee and arthritis patients, regular exercise helps to maintain physical function and alleviate pain symptoms [56,57]. Specifically, a cohort study involving 12,796 participants showed that patients with knee arthritis were able to obtain long-term and sustained pain relief after receiving guidance exercise therapy [57]. Another study showed that moderate low-intensity exercise can reduce the risk of knee arthritis. In the context of different PA intensities and their relationship with KOA risk, our study found that LPA and MVPA are significant protective factors, while VPA and TPA are not significant protective factors. A recent longitudinal study in Chinese adolescents demonstrated that MVPA was positively associated with better motor skills (particularly object control skills) and negatively associated with sedentary time [58]. However, Jakiela et al. recommend to adults with knee arthritis: "Strengthen to walk at least 10 mins a day, whether indoors or outdoors," which takes into account the tolerable pain limits, the intensity equivalent and the dose-response benefits of exercise in patients with osteoarthritis [59]. While other intensity exercises show similar trends, such as regular moderate and high-intensity exercise that helps maintain physical function and relieves pain by enhancing the patient's local muscle strength [60], a significant causal relationship was observed in the meta-analysis study. Our meta-analysis is based on the results of Mendelian randomization studies, which more clearly confirm this causal relationship: the relationship between physical activity and KOA risk is significantly positive.

In the relationship between different PA doses and KOA risk, our study found that low doses are protective factors, but not significant, while high doses of PA are significant risk factors. The dose of PA involves complex factors, such as intensity, time, and frequency, so we analyze the dose-response relationship according to classification and continuous dose [61]. The two-classification dose-response relationship explains the difference between exercise and nonexercise, and the multi-classification dose-response relationship explains the dose effect of increasing PA relative to low-dose PA. Meeting WHO PA guidelines is not a significant protective factor can be attributed to several factors [62-64]. Firstly, relying on self-reported measures from cohort studies can introduce biases related to mood, memory accuracy, and social desirability [65]. Second, as this study shows, high-intensity physical activity is a risk factor for KOA. Meeting the WHO PA guidelines may include VPA, which could lead to the development of KOA. Lastly, the complexity of the relationship between physical activity and KOA, influenced by various moderating factors like metabolic disorders, age, socioeconomic status, and environmental exposures, necessitates a nuanced approach to interpreting results [66,67]. Overall, while recent evidence strongly supports a protective effect of physical activity against KOA, the lack of a reciprocal causal relationship underscores the need for further investigation into the mechanisms underlying these associations and the development of targeted interventions.

Finally, our study is the first meta-analysis of the dose-response relationship between PA and the risk of KOA. The results of this study, which are relatively stable, are based on large cohort and MR studies. However, this study had several limitations. First, the number of included studies may not have been sufficient. This study strictly followed the inclusion and age criteria, and few studies met all the criteria. Second, the PA assessment methods in the literature included in this study were subjective measures, which may lead to inaccurate doses and different methods of measuring and observing physical activity and may also have an impact on the results of the study. Third, some of the included cohort studies did not adjust for confounding factors such as BMI, age, and other comorbid conditions. In addition, while our meta-analysis focused on the overall dose of PA, the role of specific muscle groups around the knee is also crucial. Although one study on karate athletes found no significant imbalance between knee flexors and extensors [68], the assessment of muscle strength and balance using objective methods like isokinetic testing could be an important direction for future research in general populations to better understand the mechanisms linking PA and KOA risk.

5. Conclusions

This meta-analysis showed that low-to-moderate doses of LPA and MVPA were associated with a reduced risk of KOA compared to physical inactivity, while higher doses of PA were associated with an increased risk. The protective effect of LPA and MVPA may only apply within a specific dose range, and should not be extrapolated to high-dose exposures. There was a significant nonlinear positive dose-response relationship between PA and the risk of KOA. Ultimately, we underscore the necessity for future research endeavors to deeper into understanding how various types of physical activity affect KOA risk and to devise effective preventive strategies and interventions aimed at mitigating the occurrence of physical activity-associated KOA.

Data Availability Statement: The data supporting this study's findings are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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