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Recreational Physical Activity and Risk of Incident Knee Osteoarthritis: An International Meta-Analysis of Individual Participant–Level Data

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Objective. The effect of physical activity on the risk of developing knee osteoarthritis (OA) is unclear. We undertook this study to examine the relationship between recreational physical activity and incident knee OA outcomes using comparable physical activity and OA definitions.

Methods. Data were acquired from 6 global, community-based cohorts of participants with and those without knee OA. Eligible participants had no evidence of knee OA or rheumatoid arthritis at baseline. Participants were followed up for 5–12 years for incident outcomes including the following: 1) radiographic knee OA (Kellgren-Lawrence [K/L] grade ≥2), 2) painful radiographic knee OA (radiographic OA with knee pain), and 3) OA-related knee pain. Self-reported recreational physical activity included sports and walking/cycling activities and was quantified at baseline as metabolic equivalents of task (METs) in days per week. Risk ratios (RRs) were calculated and pooled using individual participant data meta-analysis. Secondary analysis assessed the association between physical activity, defined as time (hours per week) spent in recreational physical activity and incident knee OA outcomes.

Results. Based on a total of 5,065 participants, pooled RR estimates for the association of MET days per week with painful radiographic OA (RR 1.02 [95% confidence interval (95% CI) 0.93–1.12]), radiographic OA (RR 1.00 [95% CI 0.94–1.07]), and OA-related knee pain (RR 1.00 [95% CI 0.96–1.04]) were not significant. Similarly, the analysis of hours per week spent in physical activity also showed no significant associations with all outcomes.

Conclusion. Our findings suggest that whole-body, physiologic energy expenditure during recreational activities and time spent in physical activity were not associated with incident knee OA outcomes.

INTRODUCTION

Osteoarthritis (OA) is a leading cause of global disability and a major cause of reduced function and pain (1). As life expectancy increases, along with rising levels of obesity, the number of people living for prolonged periods with severe OA is expected to grow (2). Currently, there is a lack of disease-modifying treatments for OA, and subsequently, attention has

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turned to identifying modifiable risk factors to help alleviate disease onset and burden.

Physical activity appears to have a positive, long-term influence on noncommunicable diseases such as coronary heart disease and type 2 diabetes mellitus (3), and it is clear that efforts are needed to encourage increases in physical activity for health (4). In contrast, while there are some well-established risk factors for knee OA, including joint injury (5), obesity (6), and female sex (7), the effect of physical activity on the risk of OA is unclear. A systematic review by Richmond et al (8) demonstrated that physical activity was deemed a risk factor for OA in 4 studies and seen as protective in another, with joint injury the potentially mediating factor. Further, in the same study, cumulative physical activity and physical activity in midlife were not shown to be risk factors for incident knee OA; however, a borderline association was observed for exercise in early adult life. In this systematic review, published in 2013, it was concluded that a meta-analysis exploring the relationship between physical activity and risk of OA was not possible using the current published literature due to heterogeneity in the definitions of physical activity and OA (8). Additionally, there is evidence to suggest that physical activity in the form of exercise improves clinical outcomes among those with OA (9). There is also evidence to suggest that some types of physical activity are a potential risk factor for the development of structural change at the knee (10–12). Despite this, "exercise" is recommended as a core treatment for the nonsurgical management of OA, with "low-impact aerobic exercise" recommended by most treatment guidelines (13).

Among the likely explanations for the lack of consensus are the variable definitions of physical activity, differences in assessment of the physical activity constructs (e.g., duration, severity, intensity), and differences in physical activity domains (e.g., leisure, recreation, occupation). Further research is required to examine the components of physical activity using the different metrics of physical activity. This may help advance our understanding of the biomechanical and pathophysiologic changes that occur with physical activity which may ultimately help identify and explain the threshold between risk and protection.

It is important to identify the role of physical activity in disabling diseases such as OA and to inform prevention strategies targeted to reduce the global burden of OA and encourage, where appropriate, participation in physical activity for the benefits of overall health. To overcome the difficulties in synthesizing aggregate data, which use a variety of definitions for both physical activity–related exposures and OA outcomes, individual patient–level meta-analysis provides a method to harmonize original raw data from cohorts and use standardized statistical methods to analyze and produce pooled estimates (14). This method also provides the opportunity to gain a better clinical understanding of the degree to which different components of knee OA (pain and/or structure) are affected by physical activity. Therefore, our aim was to investigate the association between recreational physical activity and risk of incident knee OA outcomes in 6 prospective cohort studies of adults at risk of developing knee OA.

PATIENTS AND METHODS

Study design. The wider study comprised 2 parts. First, due to the novel aspect of combining this type of data, 3 separate expert committees convened to do the following: 1) establish a common physical activity variable, 2) harmonize knee OA outcome variables, and 3) establish a statistical strategy. The results of these consensus studies have previously been published (15,16). The current study used those previous decisions on outcome and exposure definitions to examine the relationship between recreational physical activity and incident knee OA outcomes (radiographic, painful radiographic [radiographic OA plus symptoms], and OA-related knee pain).

Cohort selection and participant inclusion criteria. We identified the appropriate cohorts by searching published literature for established longitudinal OA cohorts and by liaising with principal investigators and experts with knowledge of available data. Cohorts were included according to the availability of detailed data on physical activity, knee pain, and knee radiographic results. Specifically, cohorts were selected based on the following inclusion criteria: 1) presence of self-reported physical activity sufficient to allow for the calculation of hours per week spent in recreational physical activity and metabolic equivalent of task (MET) days per week at baseline, 2) OA-related knee pain and/or radiographic data at baseline and at follow-up, and 3) recruitment from the community (i.e., not identified through clinics, hospitals, or health care professionals). Cohorts were not excluded based on whether data on them regarding the relationship between physical activity and OA had previously been published.

Six cohorts were identified with appropriate data available for analysis: 2 US community-based cohorts (Framingham Osteoarthritis Study and Johnston County Osteoarthritis Project [JoCo OA]) (17–19) and 1 US enhanced risk factor cohort (Multicenter Osteoarthritis Study [MOST]) (20); 2 UK community-based cohorts (Chingford Women's Study and Hertfordshire Cohort Study [HCS]) (21,22); and 1 Australian community-based cohort (The Tasmanian Older Adult Cohort [TASOAC]) (23). Details on cohort selection are shown in Figure 1.

Cohorts without radiographic follow-up data were only included in the OA-related knee pain analysis (TASOAC). Cohorts without side-specific knee pain at follow-up (HCS) were only included in the OA-related knee pain and radiographic OA–only analyses. Across all analyses, participants were included if they were OA-free at baseline and did not have evidence of rheumatoid arthritis at baseline.

Physical activity as a primary risk factor. A number of questions were used to assess physical activity in each of the

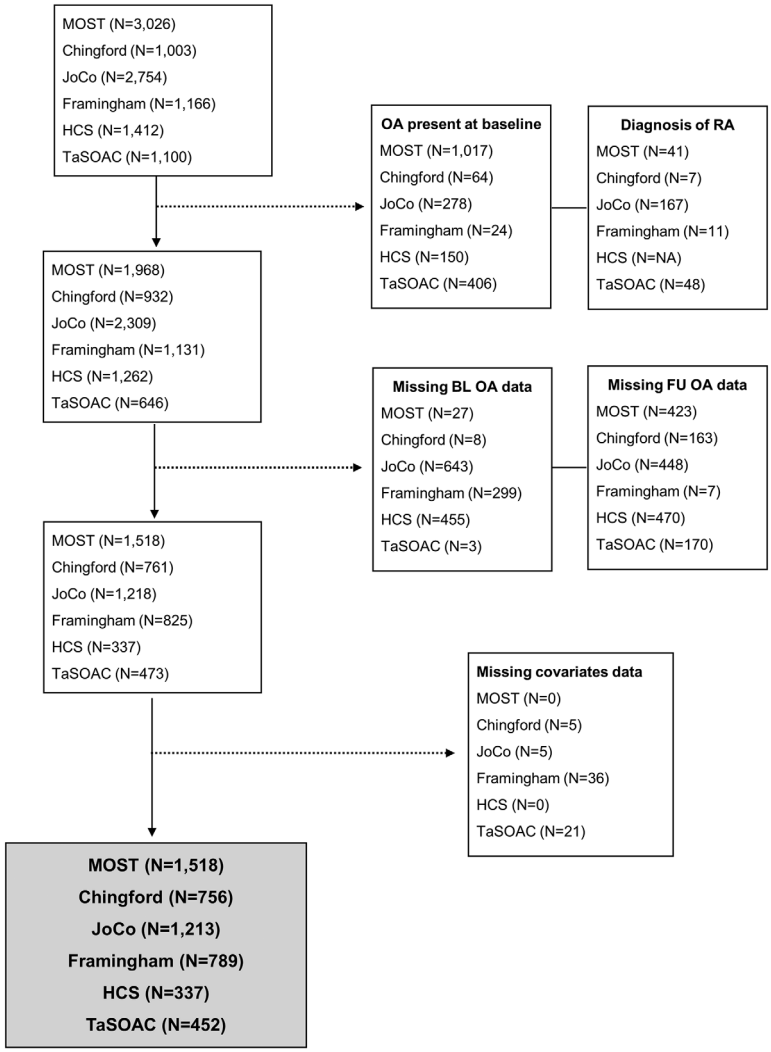

Figure 1. Flow chart of the cohort selection process. MOST = Multicenter Osteoarthritis Study; Chingford = Chingford Women's Study; JoCo = Johnston County Osteoarthritis Project; Framingham = Framingham Osteoarthritis Study; HCS = Hertfordshire Cohort Study; TASOAC = Tasmanian Older Adult Cohort; OA = osteoarthritis; RA = rheumatoid arthritis; BL = baseline; FU = follow-up.

respective cohorts, resulting in variation in the type of responses. A more detailed description of the individual variables captured in each cohort can be found in Supplementary Table 1 (available on the on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42001). To address these methodologic differences, an international consensus study involving experts in physical activity and clinical epidemiology was conducted to develop an approach to harmonize physical activity; key results from this have previously been described (15). Briefly, agreement was reached for the use of METs (24) as a method for harmonizing physical activity variables among cohorts. It was agreed that occupation is a less modifiable domain of physical activity, which may have a greater weighting over our findings compared to household and sport and leisure domains. Therefore, occupational physical activity was not included in the calculation of physical activity (15). Household activity data were missing in a number of cohorts, and therefore, this domain was also excluded. The exposure for all cohorts consisted of recreational physical activity except for Framingham and TASOAC, for which we could not determine the type of activity as the questions asked were "hours spent in sedentary/slight/moderate and heavy activity per day" and "days per week and minutes per day doing vigorous/moderate activities," respectively.

Primary and secondary exposures. *Primary exposure.* MET days per week were calculated based on time spent in a given activity (sports and walking/cycling activities) multiplied by the MET value for that activity (24). Once MET days per week were calculated, the original components of this physiologic measure could not be distinguished.

Secondary exposure. We included a second exposure based on the amount of time spent in recreational physical

activity, which was based on hours per week spent in physical activity at baseline. A lengthy process was undertaken to first assign a MET value to every activity recorded within each cohort according to the compendium of physical activity (24). For exposure 1 (MET days per week), MET values were multiplied by duration spent in the given activity. For exposure 2, each recreational activity was assigned to 1 of 3 intensity levels (light, moderate, or vigorous) according to the classification of METs (25). In cohorts in which physical activity questions were already based on light/moderate/vigorous physical activity (e.g., Framingham, MOST, and TASOAC), the cohort thresholds were used.

Incident knee OA outcomes. Comparing and pooling results between prospective cohorts is relatively rare in the study of OA. Therefore, a second expert consensus meeting was convened to determine how best to harmonize this variable between cohorts. Key results from this consensus study have previously been described (16). Briefly, knee OA was defined using both self-reported pain and the presence of radiographic OA.

Incident radiographic OA. The presence of radiographic knee OA was defined using the Kellgren/Lawrence (K/L) scale (26) in each cohort. Incident radiographic OA was defined as the occurrence of radiographic OA (K/L grade ≥2) during follow-up in either/both knee(s) without radiographic OA (K/L grade 0–1) in both knees at baseline. Person-level OA was calculated by assessing the OA status for each knee joint and using the "highest" level of OA based on this system. For example, if a participant had no evidence of OA (or data were not available) in their right knee and radiographic OA in their left knee, their person-level knee OA status would be radiographic OA. Total knee replacements that occurred during follow-up were included as incident radiographic OA cases if confirmed by radiography.

Incident OA–related knee pain. Current knee pain status was determined using the National Health and Nutrition Examination Survey (NHANES) (27), in which a positive response to "have you had pain on most days in the last month in your joint" would indicate the presence of pain. Alternatively, if a question like this NHANES question was absent, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (28) was used (for cohort-specific pain questions, see Supplementary Table 1, https://onlinelibrary.wiley.com/doi/10.1002/art.42001). Due to known variations in the wording of questions related to pain (29), an analysis was previously undertaken to determine the most comparable wording of the variety of NHANES-type questions and to establish an equivalent threshold to use in the WOMAC pain subscale to create a binary pain variable (30).

In participants with and those without radiographic OA at baseline, incident OA–related knee pain was defined as the occurrence of knee pain during follow-up in participants with no evidence of knee pain at baseline.

Incident painful radiographic OA. In participants with no evidence of radiographic OA with knee pain in the same knee at baseline (participant-level), incident painful radiographic OA was defined as the occurrence of both knee symptoms and radiographic OA in the same knee during follow-up. Side-specific radiographs and knee pain responses were available at baseline and follow-up in the Framingham, JoCo OA, MOST, and Chingford cohorts and, therefore, painful radiographic OA was calculated for these cohorts. In HCS, only person-level pain data were available at follow-up. In TASOAC, only person-level pain data were available, with no radiographs, at follow-up. Therefore, 2 cohorts were not included in the painful radiographic OA analysis.

Confounders. Age, sex, race, and body mass index (BMI) were considered as potential confounders. In all cohorts, age was defined as age at the time of the clinic visit, as was BMI (kg/m^2), which was based on objective height and weight measurements. The Chingford, HCS, and Framingham cohorts comprised predominantly White participants; the JoCo OA and MOST cohorts comprised both White and African American participants; and the TASOAC cohort comprised a small percentage of Asian and Indigenous Australian participants.

Statistical analysis. We conducted a complete case analysis and calculated the percentage, mean ± SD, and/or median and interquartile range for baseline characteristics in all cohorts. Modified Poisson regression analyses were conducted to assess the association between baseline recreational physical activity (hours per week spent in activity and MET days per week) and incident radiographic OA, painful radiographic OA, and OA-related knee pain, respectively, at 5–12 years of follow-up. Models were adjusted for potential confounders. Sex and race were included in the fully adjusted models only when relevant to the specific cohort. When the study outcome is considered common, odds ratios overestimate the relative risk (31). Therefore, we used a modified Poisson approach to estimate the relative risk and 95% confidence interval (95% CI) using robust variances, as suggested by Zou (32).

Individual participant data (IPD) meta-analysis. IPD meta-analysis involved estimating an appropriate summary statistic for each study and then calculating a weighted average of these statistics across studies (33). It allowed for cohorts to be compared using identical risk factors, outcomes, and confounders. An IPD meta-analysis consisted of 2 distinct stages. First, each cohort was analyzed individually using identical methodology. Risk ratios (RRs) and 95% CIs were calculated for each individual cohort. Second, the results of each individual analysis were pooled using standard meta-analysis statistical methods (34). Data were pooled using random-effects analysis. The Stata

Table 1. Cohort characteristics of the subjects, stratified by baseline knee OA status*

	MOST			Chingford			JoCo OA			Framingham			HCS			TASOAC		
	ROA	OA-related knee pain	PROA	ROA	OA-related knee pain	PROA	ROA	OA-related knee pain	PROA	ROA	OA-related knee pain	PROA	ROA	OA-related knee pain	PROA	ROA	OA-related knee pain	PROA
Total no.	1,078	1,102	1,518	681	556	756	997	795	1,213	759	629	789	337	243	–	–	452	–
Knee OA outcome at follow-up	262 (24.3)	322 (29.2)	308 (20.3)	190 (27.9)	65 (11.7)	48 (6.4)	255 (25.6)	131 (16.5)	132 (10.9)	70 (9.2)	116 (18.4)	48 (6.1)	114 (33.8)	21 (8.6)	–	–	60 (13.3)	–
MET days/week, median (IQR)	1.2 (0.6–1.9)	1.1 (0.6–1.9)	1.1 (0.6–1.9)	0 (0–0.5)	0 (0–0.5)	0 (0–0.5)	0.3 (0.0–0.8)	0.3 (0.1–0.8)	0.3 (0.0–0.8)	11.4 (8.7–14.4)	11.4 (8.7–14.4)	11.3 (8.4–14.3)	0.2 (0–0.5)	0.2 (0–0.5)	–	–	1.4 (0.3–2.8)	–
Age, mean ± SD years	60.5 ± 7.7	62.3 ± 7.9	61.6 ± 7.9	53.5 ± 5.8	53.8 ± 5.9	53.7 ± 5.9	60.7 ± 8.5	61.9 ± 9.3	61.7 ± 9.0	51.9 ± 8.7	51.9 ± 8.7	51.9 ± 8.7	64.7 ± 2.7	64.8 ± 2.8	–	–	62.0 ± 7.0	–
Female sex	638 (59.2)	608 (55.2)	890 (58.6)	681 (100)	556 (100)	756 (100)	673 (67.5)	507 (63.8)	802 (66.1)	427 (56.3)	348 (55.3)	442 (56.0)	170 (50.5)	117 (48.2)	–	–	219 (48.5)	–
Race															–	–		–
White	945 (87.7)	969 (87.9)	1,325 (87.3)	681 (100)	556 (100)	756 (100)	731 (73.3)	577 (72.6)	879 (72.5)	759 (100)	629 (100)	789 (100)	337 (100)	243 (100)	–	–	446 (98.7)	–
African American	117 (10.8)	118 (10.7)	169 (11.1)	–	–	–	266 (26.7)	218 (27.4)	334 (27.5)	–	–	–	–	–	–	–	-	–
Chinese	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Other	16 (1.5)	15 (1.4)	24 (1.6)	–	–	–	–	–	–	–	–	–	–	–	–	–	6 (1.3)	–
BMI, mean ± SD kg/m^2	29.1 ± 4.7	29.6 ± 4.8	29.5 ± 5.0	25.1 ± 3.9	25.0 ± 3.9	25.3 ± 4.0	29.4 ± 5.5	29.5 ± 5.8	29.6 ± 5.8	27.0 ± 4.8	26.8 ± 4.6	27.1 ± 4.8	26.5 ± 4.0	26.3 ± 4.0	–	–	27.2 ± 4.2	–

* Except where indicated otherwise, values are the number (%) of subjects. Subjects included in this analysis did not have a knee osteoarthritis (OA) outcome or rheumatoid arthritis at baseline, and did not have data missing on knee OA (at baseline or follow-up) or on physical activity, age, sex, race, or body mass index (BMI). The Multicenter Osteoarthritis Study (MOST) had a follow-up of 5 years and included 3,026 participants, the Chingford Women's Study had a follow-up of 9 years and included 1,003 participants, the Johnston County Osteoarthritis Project (JoCo OA) had a follow-up of 7 years and included 2,754 participants, the Framingham Osteoarthritis Study had a follow-up of 7 years and included 1,166 participants, the Hertfordshire Cohort Study (HCS) had a follow-up of 12 years and included 1,412 participants, and the Tasmanian Older Adult Cohort (TASOAC) had a follow-up of 5 years and included 1,100 participants. ROA = radiographic OA; PROA = painful radiographic OA; MET = metabolic equivalent of task; IQR = interquartile range.

admetan command was used to produce the pooled estimates, in addition to forest plots which graphically demonstrate the results (35). All analyses were conducted using Stata version 16.1 statistical software.

Sensitivity analysis. Occupational physical activity has been shown to be an important risk factor in the development of knee OA (36,37). Within the Framingham and TASOAC cohorts, it was not possible to isolate the contributions of occupational activity from recreational activity. Therefore, results are reported both with and without the inclusion of Framingham and TASOAC data.

Data availability. Requests for access to individual cohort–level data used within this report should be submitted to the cohort principal investigators.

RESULTS

The IPD meta-analysis included 5,065 participants. Incidence of painful radiographic OA at follow-up ranged from 6.1% to 20.3%, radiographic OA from 9.2% to 33.8%, and OA-related knee pain from 8.6% to 29.2%. The median physical activity in participants ranged from 0 MET days per week in the Chingford cohort to 11.4 MET days per week in the Framingham cohort (Table 1).

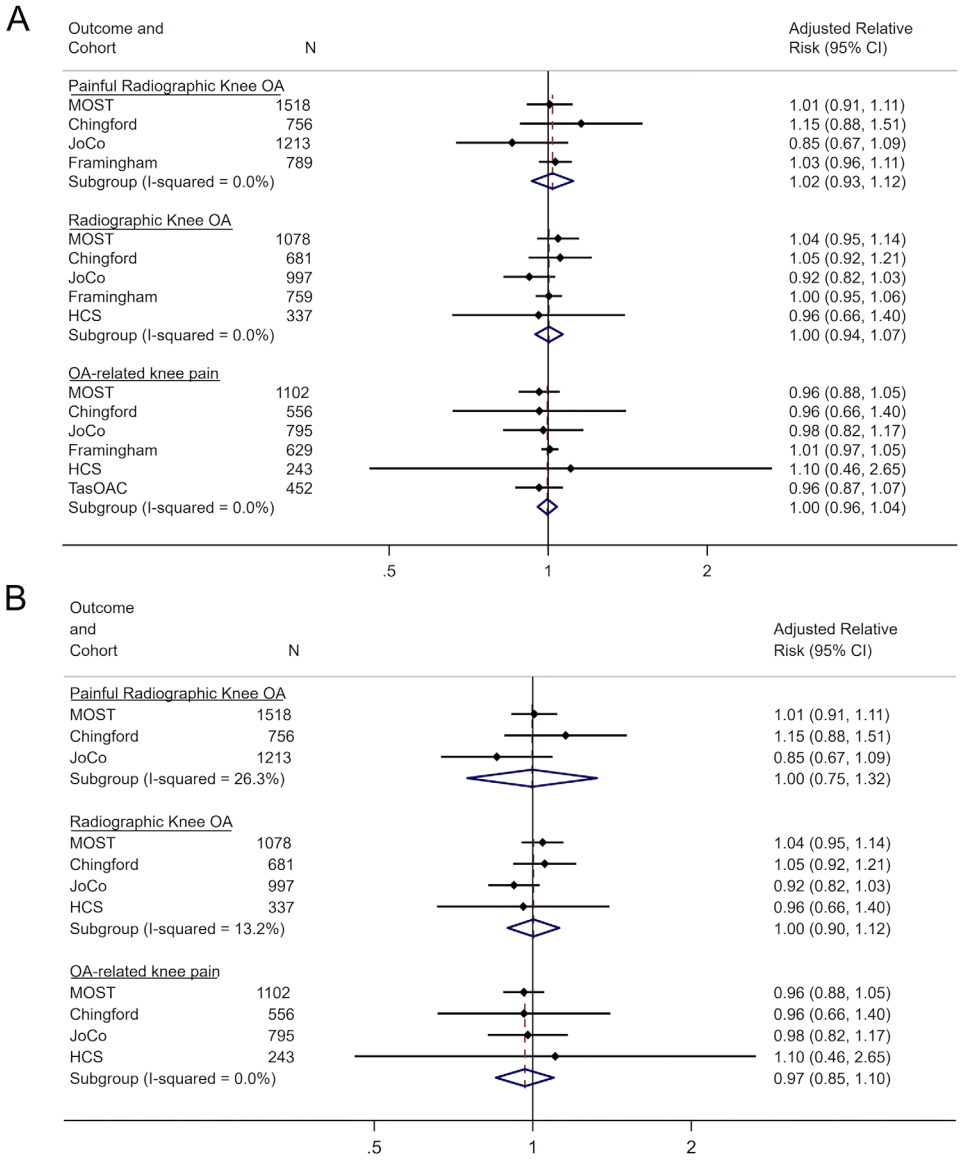

Figure 2. Forest plots for fully adjusted models showing the association of metabolic equivalents of task (days per week) with OA outcomes, stratified by cohort study. Results for all cohort studies (**A**) and all cohort studies excluding the Framingham and TASOAC cohorts (**B**) are shown. 95% CI = 95% confidence interval (see Figure 1 for other definitions). Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.42001/abstract.

IPD meta-analysis of painful radiographic OA, radiographic OA, and OA-related knee pain. *Analysis 1.* This analysis examined the association between physical activity (defined as MET days per week) and incident knee OA as painful radiographic OA, radiographic OA, and OA-related knee pain at follow-up, compared to participants who had no OA (pain and/or radiographic OA) at baseline. Multivariable meta-analyses adjusted for age, sex, BMI, and race showed a nonsignificant pooled RR of 1.02 (95% CI 0.93–1.12) for painful radiographic OA, 1.00 (95% CI 0.94–1.07) for radiographic OA, and 1.00 (95% CI 0.96–1.04) for OA-related knee pain (Figure 2A). Nonsignificant pooled RRs of 1.00 (95% CI 0.75–1.32) for painful radiographic OA, 1.00 (95% CI 0.90–1.12) for radiographic OA, and 0.97 (95% CI 0.85–1.10) for OA-related knee pain were calculated when the Framingham and TASOAC cohorts were excluded from the analysis (Figure 2B).

Analysis 2. This analysis examined the association of physical activity (defined as hours per week spent in physical activity) with incident painful radiographic OA, radiographic OA, and OA-related knee pain at follow-up, compared to participants who had no OA (pain and/or radiographic OA). In the models adjusted for age, sex, BMI, and race, meta-analyses of the effect of the duration of physical activity on painful radiographic OA, radiographic OA, and OA-related knee pain showed a nonsignificant pooled RR of 1.00 (95% CI 0.98–1.02) for painful radiographic OA, 1.00 (95% CI 0.98–1.01) for radiographic OA, and 1.00

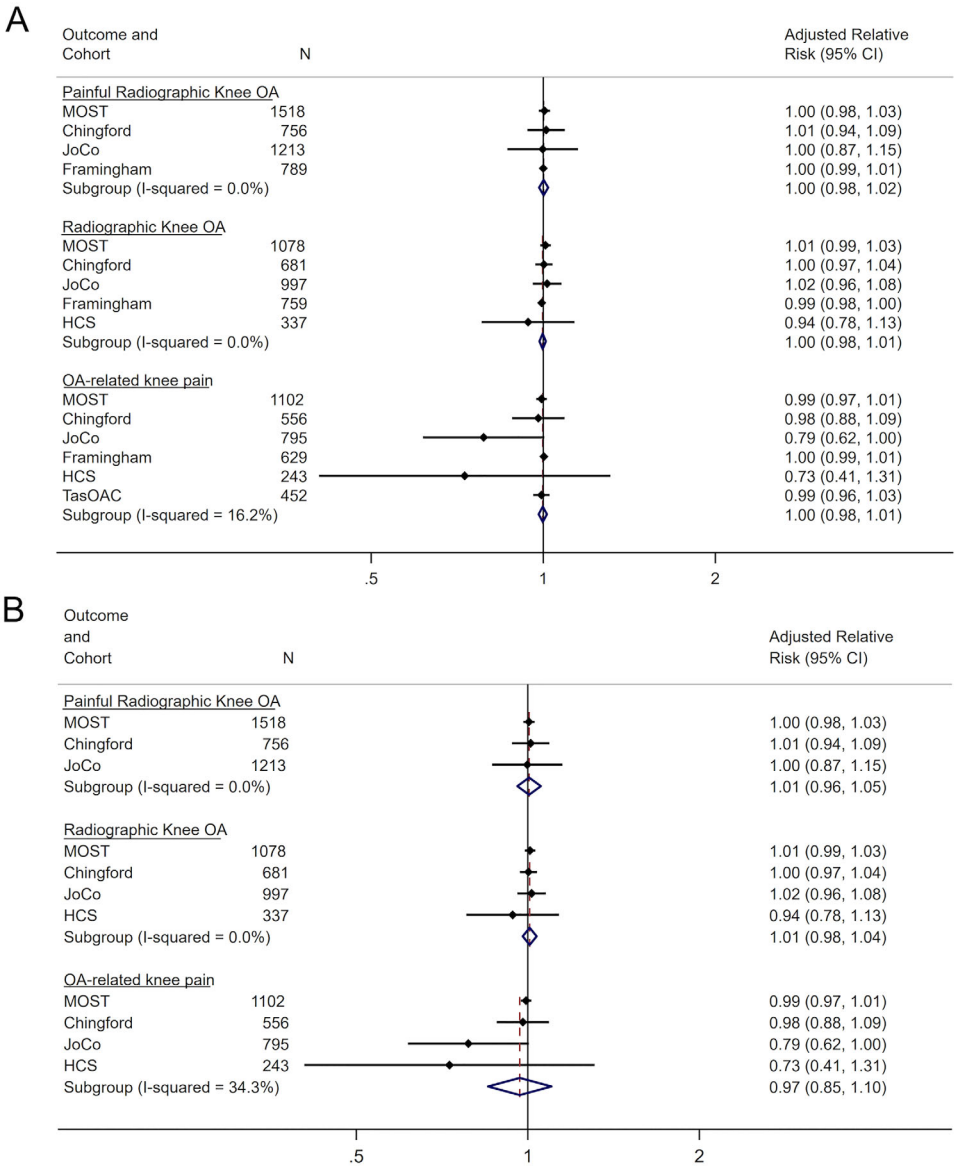

Figure 3. Forest plots for fully adjusted models showing the association of duration (hours per week) of physical activity with OA outcomes, stratified by cohort study. Results for all cohort studies (**A**) and all cohort studies excluding the Framingham and TASOAC cohorts (**B**) are shown. 95% CI = 95% confidence interval (see Figure 1 for other definitions). Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.42001/abstract.

(95% CI 0.98–1.01) for OA-related knee pain (Figure 3A). Nonsignificant pooled RRs of 1.01 (95% CI 0.96–1.05) for painful radiographic OA, RR 1.01 (95% CI 0.98–1.04) for radiographic OA, and RR 0.97 (95% CI 0.85–1.10) for OA-related knee pain were calculated when the Framingham and TASOAC cohorts were excluded from the analysis (Figure 3B).

DISCUSSION

This multicohort study, utilizing data from 6 national and international OA cohorts, examined the relationship between recreational physical activity and incident knee OA outcomes. Exposure to recreational physical activity, a composite of leisure sports and walking/cycling activity, was assessed using MET days per week to estimate whole-body energy expenditure. While this overall physiologic measure of recreational physical activity is useful for the interpretation of the effect of recreational physical activity on incident knee OA, further information is required to provide a clearer public health message. Therefore, to consider the role that duration of physical activity may play, we also investigated the effect of time spent in physical activity.

No association was observed between physical activity defined as total energy expenditure (MET days per week) and incident painful radiographic knee OA, radiographic knee OA, or OA-related knee pain. There was also no association observed between time spent in physical activity (hours per week) and incident painful radiographic knee OA, radiographic knee OA, or OA-related knee pain.

The role of physical activity in knee OA remains questionable, as demonstrated in the findings of a comprehensive literature review (8). As the first study to harmonize and analyze original individual-level OA and physical activity data from multiple cohorts, our findings suggest that recreational physical activity, as defined by physiologic energy expenditure and time spent in physical activity, was not associated with incident knee OA outcomes.

The variation in physical activity and OA definitions and follow-up times makes the true comparison between the previous and current findings difficult. For instance, Felson et al found that physical activity increased the risk of OA using data from the Framingham study (38). Physical activity was not limited to recreational activity but was defined as activity over a period of 24 hours, and OA was based on a radiographic definition. McAlindon et al also found an association in the Framingham study, with vigorous activity only (10). In the current study, physical activity levels within the Framingham and TASOAC cohorts were markedly higher than all other cohorts. This is likely due to the inability to differentiate between particular activities (question based on time spent in slight, moderate, and/or heavy activities), which meant, unlike all other cohorts, we were unable to exclude household activities, gardening, or occupation-related activities. Also, participants self-reporting vigorous activities are perhaps more likely to consider hours spent in heavy occupations as part of vigorous activity. Previous evidence suggests that occupations, particularly manual jobs, are associated with radiographic and symptomatic knee OA (36,37,39,40).

Hootman et al found that participation in physical activity as an adult does not increase the risk of knee OA (41). In their study, physical activity was based on calculation and quantification of physical activity–related joint stress, and knee OA was based on self-reported physician-diagnosed OA. The current study aimed to overcome these variations by harmonizing measures across cohorts prior to analysis. An early case–control study by Imeokparia et al combined the physical activity components of occupation, sport leisure/recreational, and home-based activities to derive 4 activity categories in METs (very hard, hard, moderate, and light activities) (42). They demonstrated gender differences in high levels of cumulative physical activity as a risk factor in the development of OA of the knee, with women (but not men) ages 55–64 at increased risk of knee OA. Manual occupation is a well-known risk factor for knee OA (36,37,39,40), and the combination of manual occupation with leisure and home-based activities in the case–control study by Imeokparias and colleagues means it is possible that these effects were being driven by occupation.

Physical activity is a complex behavior with numerous components to consider. For example, the ability to measure a specific type of activity (e.g., running, swimming, gardening) over a specific volume (e.g., duration per day over the prolonged period until incident disease occurs), while capturing all relevant covariates (e.g., injury, lifestyle factors), would be the ideal method, but this would be time-sensitive, costly, invasive, and unrealistic.

There are several potential limitations to this study. First, the 6 cohorts were all drawn from Western, and largely White, populations whose demographics, diet, anthropometry, and types of physical activity may not be applicable to all societies. The included cohorts were designed as independent studies and were not designed for direct comparison. Therefore, recreational physical activity and knee OA were assessed differently in each cohort. It is known that self-reported physical activity is susceptible to reporting bias, including recall and social desirability bias, which may lead to overestimation of physical activity (43). Moreover, and importantly for this study, there are indications that social desirability bias is larger in individuals with lower education levels (44). It is also known that even small variations in the way a question about pain is worded or the way radiographs are graded can result in differences in OA prevalence estimates (16,45). In order to minimize this variation, we made every effort to harmonize physical activity, pain, and radiographic OA variables between cohorts by conducting 2 international expert consensus studies (15,16).

Self-reported physical activity provides its own challenges in terms of potential recall bias. In this instance, while there was an arguably appropriate temporal proximity between the measure

of exposure and incident outcome, we cannot be certain that physical activity, which is mostly based on relatively current activity, and all other covariates for that matter, remained continuous throughout the study period. Also, the absence of data on particular variables, such as previous injury and knee surgery, across cohorts meant that these variables could not be adjusted for within the analysis. In addition, weight change may play a role in incident knee outcomes; unfortunately, capturing BMI data over multiple time points throughout the study period was not possible.

In an attempt to identify a global, whole-body physiologic risk factor for knee OA, we used physiologic energy expenditure (MET days per week) as our exposure. To our knowledge, this is the first time METs have been used to describe the relationship between recreational physical activity and incident knee OA. The use of METs could be considered a limitation as we could not extrapolate the individual contributions of type, frequency (or intensity), or duration of each respective activity on the risk of developing knee OA. All of these components are likely to contribute differently to knee OA development.

To overcome the potential limitations of using an exposure representative of whole-body energy expenditure, we undertook a secondary analysis in which we created an exposure based on time spent in physical activity (hours per week). This in itself was also limited, as it does not show duration of time spent in particular activities or activity intensities. We were unable to categorize duration according to intensity level (light, moderate, or vigorous), as a number of cohorts did not capture activities representative of light intensity.

In addition to variation in variable definitions (e.g., OA, physical activity), the key differences between cohorts were year of baseline visit, length of follow-up, age of participants at baseline, and lack of side-specific pain and radiographic follow-up data in 1 cohort. Differences in physical activity observed between cohorts were also likely due to differences in self-reported questions. It has been suggested that self-reported physical activity measures are likely to overestimate or underestimate activity levels compared to directly measured levels of physical activity (46). Also, for cohorts in which duration or frequency of the activity was not reported, a mean value was derived from a cohort where this information was present and was applied to the missing values, which may also contribute to over- or underestimation of activity levels.

Individual types of activities (e.g., hockey, swimming) would be a useful exposure to consider in order to provide a clearer public health message. We were unable to explore this further given the limitations in the self-reported physical activity measures available. However, it would be valuable to understand which specific activities are associated with knee OA, and ideally via prospective objective measures of physical activity.

In conclusion, this is the first study to assess the relationship between physical activity defined as MET days week and knee OA. It is a comprehensive analysis of 6 well-described observational studies of knee OA, pooling ~5,000 study participants who were >45 years of age. These findings suggest that physical activity as defined by whole-body, physiologic energy expenditure during sports or walking/cycling activities is not associated with knee OA. Likewise, time spent in recreational physical activity is not associated with incident knee OA. Further investigation with clear disaggregation of all components of physical activity (including type of activity, intensity, frequency, and duration) over a lifetime would be of most use, but it is incredibly difficult to obtain such robust data. Given what we also know about the effects of a manual occupation on knee OA, it would be useful to understand the association between activities according to loading, along with relative lifetime volume (intensity and duration), and knee OA, using prospective investigation.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Gates and Sanchez-Santos had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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