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The different influence of high levels of physical activity on the incidence of knee OA in overweight and obese men and women-a gender specific analysis

H. Soutakbar, S.E. Lamb, A.J. Silman*

University of Oxford, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences, Oxford, UK

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SUMMARY

Objective: To investigate the influence of physical activity on incidence of knee osteoarthritis (OA) in overweight and obese men and women.
Design: Data were extracted from the Osteoarthritis Initiative cohort on 1,667 participants without symptomatic knee OA at baseline. We used logistic regression and marginal effect models to estimate the effect of body mass index (BMI) and reported physical activity score, together with the interaction between them, on the development of radiographic knee OA, symptomatic knee OA and joint space narrowing (JSN) after 96-months.
Results: Men in the most active quartile had almost double the likelihood of knee OA, independent of OA definition [e.g., odds ratio (OR) 2.4 (95%CI: 1.2–4.5) for radiographic knee OA]. Interaction analyses showed statistically significant interactions between physical activity and BMI on developing knee OA (i) radiographic OA $_{\text{interaction}}$ ($P = 0.039$), (ii) symptomatic OA $_{\text{interaction}}$ ($P = 0.022$), (iii) JSN $_{\text{interaction}}$ $P = 0.012$). The margin plots in men also demonstrated that the effect of physical activity on different measures of knee OA were modified by high levels of BMI. These effects were not mirrored in women where at all BMI levels, the level of reported physical activity did not influence likelihood of knee OA independent of OA definition.
Conclusions: In overweight and obese men, there appears to be a threshold above which increasing levels of physical activity are associated with higher risk of knee OA. This is absent in women.

Introduction

There is an important clinical and public health concern regarding the association between physical activity and the development of knee OA[1]. Current evidence is limited and conflicting[2]. This may be due to inconsistencies in the definition of physical activity[3], including differences in the level of joint loading due to variations in the type and intensity of activities considered[3,4].

OA is in part a mechanically-driven disease[5], therefore imposing additional joint stress through excess body weight may cause greater damage during activity. However, there is no robust evidence on which to base advice for people who are overweight or obese about appropriate levels of physical activity. Some studies report no interaction between physical activity and BMI[6,7], while others show that high levels of physical activity in individuals with high body mass index (BMI) have a greater effect on developing knee OA[8]. There is a need for further studies of the risks and benefits of increasing physical activity in protecting against the development and, or progression of knee OA in overweight and obese people. Therefore, we aimed to investigate the influence of physical activity on incidence of knee OA in overweight and obese men and women.

Method

Assessment of knee osteoarthritis

We used publicly available data from the Osteoarthritis Initiative (OAI), a longitudinal study of incidence and progression of knee OA risk factors in men and women aged between 45 and 79 years.

* Address correspondence and reprint requests to: A. J Silman, University of Oxford, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences, Oxford, UK. Tel: 1865-737831.

E-mail addresses: Hessam.soutakbar@ndorms.ox.ac.uk (H. Soutakbar), Sarah.lamb@ndorms.ox.ac.uk (S.E. Lamb), alan.silman@ndorms.ox.ac.uk, alan.silman@ndorms.ox.ac.uk (A.J. Silman).

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Between 2004 and 2006, 4,796 participants from diverse ethnic backgrounds with or at high risk of knee OA were recruited from Columbus, Ohio; Baltimore, Maryland; Pittsburgh, Pennsylvania and Providence, Rhode Island in the US[9]. This was based on an age-specific inclusion criterion in which younger participants required to have more risk factors for eligibility. Risk factors were frequent knee symptoms, being overweight and obese, history of knee surgery, family history of total knee replacement, Heberden's nodes, frequent knee bending activity, and history of knee injury causing difficulties in walking ability for at least 1 week.

Clinical, radiological images and a range of other data were collected at baseline assessment. Measurements were repeated annually for 96 months.

For the purpose of this analysis, we included participants with data on knee X-ray at baseline and 96-month follow-up. X-rays were taken in posteroanterior view in full weight bearing with knees in 20–30° flexion and feet in 10 degrees of internal rotation. Radiographs were graded centrally using the Kellgren and Lawrence scoring system (KL) for knee OA (https://oai.epi-ucsf.org/datarelease/SASDocs/kXR_SQ_BU_descrip.pdf). Each participant's radiograph was also graded for joint space narrowing (JSN) according to the Osteoarthritis Research Society International atlas.[10]

Baseline data collection

We extracted the relevant questionnaire and clinical examination baseline data collected in the OAI on age, gender, BMI, history of knee injury, frequency of knee symptoms, and physical activity. BMI was calculated as weight in kilograms divided by the square of height in meters. History of previous injury for each knee was determined as binary based on the question "have you ever injured your knee badly enough to limit your ability to walk for at least 2 days?". Physical activity was assessed using the Physical Activity Scale for Elderly (PASE). PASE is a validated questionnaire for older adults[11], which is used in OAI to assess the leisure, household and occupational activity levels of participants over the past 7-days at baseline and follow-up visits (Supplementary file 1). Participants were also asked about the presentence of frequent knee symptom for each knee that was defined as any pain, aching, or stiffness in or around knee on most of the past 30 days.

Analysis

We only included participants without symptomatic knee OA in either knee at baseline and analyses were restricted to knees of those participants with KL < 2. Eligible knees were then followed for three outcome measures at 96-month follow-up: (i) incident radiographic knee OA, (ii) incident symptomatic knee OA, and (iii) the progression of JSN. Incident radiographic knee OA was defined as a knee with KL $\geq$ 2, the incident symptomatic knee OA was defined as the co-occurrence of frequent knee symptoms as defined above and radiographic knee OA, and the progression of JSN was defined as a minimum of one grade worsening in tibiofemoral joint space at 96-month follow-up.

All outcome measures were binary and all analyses were performed at knee level, i.e., a participant could have both knees included separately in the analysis. Logistic regression models with generalized estimating equation (GEE) and exchange correlation were used to calculate the crude and adjusted odds ratios for the effects of BMI and physical activity on outcomes. Both BMI and physical activity score in these participants remained stable during the 96-months of follow up. The mean individual change scores (SE) 0–96 months were 0.29 (0.04) for BMI and 18.67 (1.5) for PASE. Thus, the analysis was based only on the baseline BMI and physical activity data. BMI was used as a continuous variable in our statistical model. However, the PASE score was categorised into gender specific quartiles for men and women with the lowest quartile used as the reference (Supplementary file 1). This enabled us to report the trend of changes of ORs at each quartile level, which is more clinically meaningful than reporting the effect of one-unit change in PASE score on outcomes. In a sub-analysis we also examined the different constituent elements to the PASE score. All analyses were adjusted for the potential confounding effects of age (as a continuous variable) and the history of previous knee injury at baseline assessment.

We investigated interactions between physical activity and BMI on outcomes by adding the interaction term into the model. Our sensitivity analysis showed no differences between ORs for the first three quartiles of physical activity. Further, there is no agreed PASE score classification. Therefore, we categorised the PASE data, in this interaction analysis, into two categories of "high" and "moderately/low" active individuals to minimize the chance of type II errors or false negative finding of no statistically significant interaction. Cut-off points were selected based on previous research suggesting that a PASE score $\geq$200 was associated with higher cartilage/meniscal abnormalities than a PASE score <200[12]. Thus, participants were considered as "high active" if they had PASE score $\geq$200, and "moderately/low active" if they had PASE score <200. Clearly there are many different patterns of work, home and leisure activity, that would yield a PASE score of over 200 but as an indication for those not familiar with the measure: a combination of activities involving walking, light or heavy house work, a job with mainly standing or walking and lawn work or yard care would yield PASE score above that level.[1]

We then estimated the margin effect of physical activity in "high" and "low-moderate" active groups on the predicted probability of OA across a broad range of BMI, with the results expressed as increased risk of knee OA per unit increase in BMI (kg/m^2). Finally, we addressed the null hypothesis that there was no difference in these estimated interactions with BMI between the active and inactive groups and report the p value for this comparison. All analyses were performed using Stata version 14 for Windows.

Results

Overall, 2,801 knees were included in the data analysis (Supplementary file 2). Baseline mean age and BMI was similar between men and women, but the mean PASE score and injury rate was higher in men (Table I). The pattern and volume of participation in various intensities of leisure activities, stratified by the overall level of activity, is described in Table II. The men in the high active group were more likely to undertake active sports than women with a similar PASE score (Table II).

Incident radiographic knee OA and progression of joint space narrowing

In all, 387 (13.6%) knees developed radiographic knee OA at 96-months follow-up, 300 (10.5%) developed JSN and 138 (4.8%) developed symptomatic knee OA.

The relationship between BMI and activity on the risks of incident radiographic OA is described in Table III. There was a greater increased odds of incident radiographic OA per unit increase in BMI in women than in men. Every unit increase in BMI was associated with a 15% increase in women compared to a 6% increase in men (Table III).

Active and inactive women had a similar odds of radiographic knee OA (aORs: 1.11, 95%CI: 0.80–1.54). This effect was not modified by changing BMI (P = 0.41) (Fig. 1). In contrast, high levels of

Table I
Participants' characteristics data at baseline

Baseline	Men	Women
Subject, **N (eligible knees)**	702 (1,173)	965 (1,628)
Age, **year, mean (SD)**	58.69 (8.97)	59.60 (8.49)
BMI, **kg/m^2, mean (SD)**	27.98 (3.96)	26.79 (4.70)
PASE, **mean (SD)**	186.18 (90.36)	161.79 (73.58)
History of knee injury, **N (%)**	305 (26.0)	293 (18.0)
KL 0 **N (%)**	856 (72.98)	1,157 (71.1)
KL 1 **N (%)**	317 (27.02)	471 (28.9)
Racial background N (%): Caucasian; African American	623 (89.2); 67 (9.4)	814 (84.8); 130 (13.04)
Martial Status N (%): Married; Never married	571 (81.3); 58 (8.3)	621 (64.4); 95 (9.8)

physical activity significantly increased the odds of radiographic knee OA in men (aOR-$_{\text{4th quartile/1st quartile-reference category}}$: 2.37, 95% CI: 1.23–4.54; aOR$_{\text{-active/inactive}}$: 1.91, 95%CI: 1.20–3.04). There was also some mild evidence of positive and statistically significant interaction between BMI and physical activity on further increasing the risk of incident radiographic knee OA *(P* = 0.039*)*. This indicated that, in men, BMI modified the effect of physical activity on the incidence of radiographic knee OA. This is also shown in Fig. 1, where the predicted probability of knee OA remained steady in low-moderate active individuals regardless of changes in BMI while the predicted probability of radiographic knee OA became greater in high active men once BMI increased to 27 or above.

Similar findings were observed for progression of JSN (Supplementary files 3 and 4).

Incident symptomatic knee OA

The analysis was repeated to consider the influence of BMI and activity on incident symptomatic OA. Again, increasing BMI was associated with an increased odds of incident symptomatic knee OA in women: adjusted OR per unit increase in BMI: 1.11 (95%CI: 1.06–1.16), and in men 1.07 (95%CI: 0.99–1.16). As for radiographic OA, no significant association was found between physical activity and the odds of incident symptomatic knee OA in women. This lack of effect was also seen in men (Table IV). However, in men, this effect was modified by changing BMI *(P* = 0.022*)*. The margin plot (Fig. 2) also showed that, as the BMI increased to 31 and above, the predicted probability of symptomatic knee OA became greater in high active, but not low-moderate active men.

Discussion

Our principal aim was to investigate the influence of physical activity on incidence of knee OA in overweight and obese men and women. We found that within the full range of BMI, physical activity had virtually no effect on the ~~risk of~~ odds of developing knee OA in women. By contrast, in men, our results suggest that high levels of physical activity had an effect on the developing knee OA, but only in men with BMI above the normal range.

There are a number of methodological issues that need to be considered. Clearly as the outcome was the new development of OA we had to exclude those knees with pre-existing radiographic OA based on KL grade. It is possible that in those individuals with pre-existing radiographic OA in the contralateral knee, whether

Table II
Participants' pattern of participation in physical activity-stratified by gender and overall level of activity

Activity Profile		Men	Women
Pattern of participation in various intensities of leisure activities frequency*hours/week, mean			
High active group	Walking	9.1	8.2
	Moderate sport/recreation	9.1	5.8
	Muscle strength/endurance	5.8	6.0
	Light sport/recreation	5.9	4.2
	Strenuous sport/recreation	3.6	3.1
	Total average	**4.1**	**3.9**
Low-moderate active group	Walking	4.9	5.1
	Moderate sport/recreation	4.4	4.5
	Muscle strength/endurance	4.8	4.6
	Light sport/recreation	4.1	3.3
	Strenuous sport/recreation	2.3	2.3
	Total average	**6.7**	**5.4**
Heavy lifting and knee bending activity, **day per week, mean**			
High active group		1.14	1.04
Low-moderate active group		0.69	0.64

Table III
The effect of physical activity, BMI and their interactions on incident radiographic knee OA

Gender	Incident radiographic knee OA Adjusted odds ratio (95% confidence interval)					
	Activity (quartiles*)		Active vs Inactive†	BMI‡ (odds ratio per kg/m^2)	Effect of BMI by Physical Activity group§ (odds ratio per kg/m^2)	
Men	2nd	0.94 (0.48–1.86) *P = 0.88*	1.91 (1.20–3.04) *P* = 0.006	1.06 (1.00–1.11) *P = 0.031*	BMI in active group	1.07 (1.01–1.13) *P* = 0.01
	3rd	1.32 (0.68–2.53) *P = 0.40*			BMI in inactive group	1.04 (0.99–1.10) *P* = 0.09
	4th	2.37 (1.23–4.54) *P = 0.009*			*P interaction = 0.039*	
Women	2nd	1.17 (0.78–1.77) *P = 0.42*	1.11 (0.80–1.54) *P* = 0.504	1.15 (1.11–1.18) *P < 0.001*	BMI in active group	1.15 (1.11–1.18) *P < 0.001*
	3rd	1.40 (0.94–2.09) *P = 0.09*			BMI in inactive group	1.14 (1.11–1.17) *P < 0.001*
	4th	1.42 (0.93–2.17) *P = 0.10*			*P interaction = 0.41*	

* 4th Quartile includes individuals with the highest PASE scores. Odds ratios in the main effect model were adjusted for age, gender, BMI and injury.
† Active: PASE ≥200; Inactive: PASE <200, Odds ratios in the main effect model were adjusted for age, gender, BMI and injury.
‡ BMI (Kg/m^2): body mass index was used as continuous variable, Odds ratios in the main effect model were adjusted for age, gender, physical activity and injury.
§ Odds ratios in the interaction model were adjusted for age, gender and injury.

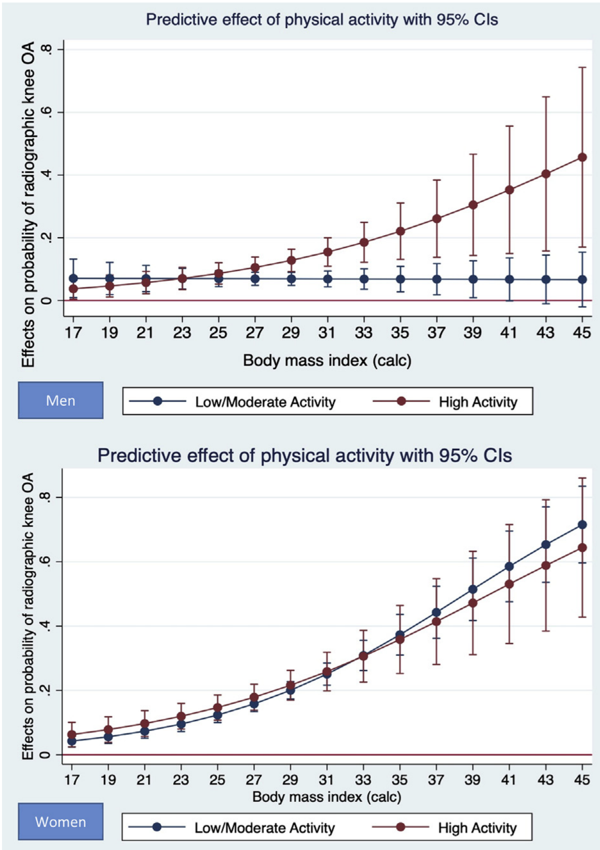

Fig. 1. The effect of physical activity on the predicted probability of radiographic knee OA at different level of BMI in men and women.

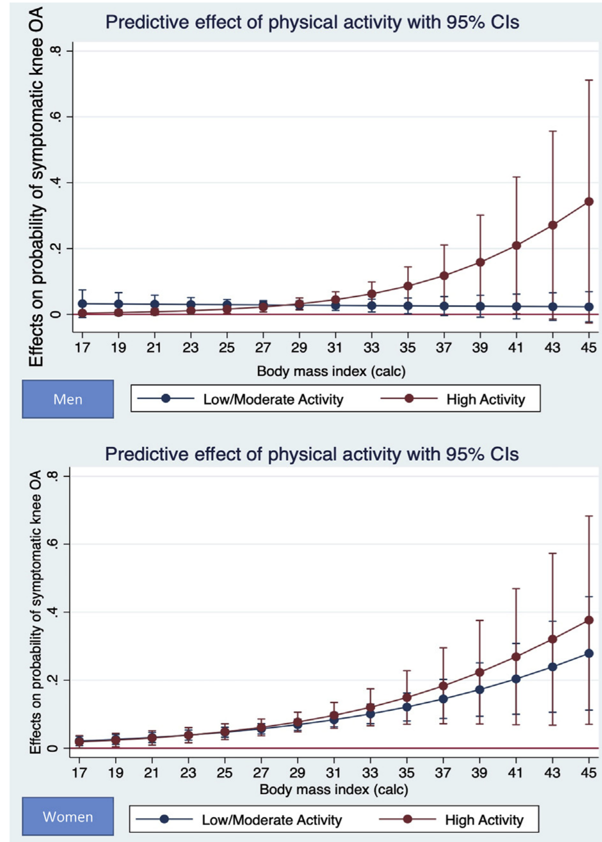

Fig. 2. The marginal effect of physical activity on the predicted probability of symptomatic knee OA at different level of BMI in women and men.

asymptomatic or not, there may be differences in their response to loading. Given the relatively large number of knees excluded this limit the external validity of our findings. We therefore undertook a subgroup analysis of those excluded knees. This analysis showed a similar trend although it did not reach a statistically significance but was underpowered to do so.

The data for this analysis were extracted from OAI which a cohort of middle-aged and older adults is-deemed to be at high risk of knee OA. Thus, our results are only generalizable to similar high-risk populations. However, the impetus for our analysis was to help inform clinicians and the public regarding the potential harm and benefit of physical activity on developing knee OA in overweight and obese individuals who are at increased risk of knee OA. Indeed, individuals at the highest risk might be the most appropriate group to target for disease prevention[13,14]. OAI was selected as an appropriate population for this analysis, as the latter required a cohort with a sufficiently large number cases of disease at follow-up to enable us to analyse interactions.

The optimal assessment of physical activity is always a challenge in large population studies. There are two major issues. First issue is what activities should be captured. PASE captures occupational, household and leisure activities but does not have the precision to distinguish between high impact and low impact knee activity[15]. High impact activities such as running or frequent squatting and kneeling may have a different effect on the knee joint compared to low impact activities such as swimming. Thus, the gender difference found in this study might be related to differences in the

Table IV
The effect of physical activity, BMI and their interactions on incident symptomatic knee OA

Gender	Incident symptomatic knee OA Adjusted odds ratio (95% confidence interval)					
	Activity* (quartiles)		Active vs Inactive†	BMI‡ (odds ratio per kg/m^2)	Effect of BMI by Physical Activity group§ (odds ratio per kg/m^2)	
Men	2nd	1.03 (0.41–2.58) *P* = *0.93*	1.18 (0.56–2.46) *P* = 0.65	1.07 (0.99–1.16) *P* = *0.06*	BMI in active group	1.09, (0.99–1.17) *P* = 0.053
	3rd	0.53 (0.17–1.65) *P* = *0.27*			BMI in inactive group	1.07, (0.99–1.16) *P* = 0.084
	4th	1.47 (0.55–3.92) *P* = *0.43*			*P interaction* = *0.022*	
Women	2nd	1.27 (0.66–2.45) *P* = *0.46*	1.12 (0.68–1.82) *P* = 0.64	1.11 (1.06–1.16) *P* < *0.001*	BMI in active group	1.12, (1.07–1.17) *P* < 0.001
	3rd	1.74 (0.94–3.22) *P* = *0.07*			BMI in inactive group	1.11, (1.06–1.16) *P* < 0.001
	4th	1.61 (0.83–3.11) *P* = *0.15*			*P interaction* = *0.65*	

* 4th Quartile includes individuals with the highest PASE scores. Odds ratios in the main effect model were adjusted for age, gender, BMI and injury.
† Active: PASE ≥200; Inactive: PASE <200, Odds ratios in the main effect model were adjusted for age, gender, BMI and injury.
‡ BMI (Kg/m^2): body mass index was used as continuous variable, Odds ratios in the main effect model were adjusted for age, gender, physical activity and injury.
§ Odds ratios in the interaction model were adjusted for age, gender and injury.

pattern of participation in physical activity, in which our data showed that men in high active group had greater participation in moderate sport and recreation than women. The second issue is the time period over which activities should be measured. We used a single estimate of PASE score based on the 7 days prior to the baseline assessment as the measure of the physical activity levels of participants. By implication our analysis firstly can only relate this single time estimate to outcome and thus excludes any consideration of individual changes in activity during follow up. Much changes may be a consequence of injury, or general behavioural change. Interestingly and reassuringly, the actual mean individual change in PASE score between the baseline and 96-month follow-up was small. This is perhaps not surprising as many individuals may have a relatively consistent lifestyle. There is also a complexity in including assessments of physical activity post baseline, as they may themselves be consequent on the development of knee symptoms or injury. It would nevertheless be appropriate using a more robust approach to exercise recording and control for other factor such as interim injuries and malalignment that might mediate the effect of activity on knee OA.

The decision as to how best to categorise PASE score also needs to be considered. We firstly looked for interaction by dividing the PASE scores into quartiles. The strongest suggestion of an interaction, which was not statistically significant, was in men in the upper quartile of physical activity. Interestingly, this corresponded to a PASE close to the previously suggested cut-off point of 200, above which there is evidence for higher cartilage and meniscal abnormalities[12]. Dichotomizing the PASE score into high active and less active groups based on this threshold gave sufficient statistical power and revealed a significant interaction. It would be necessary to validate this effect and the cut off in further populations with larger numbers of subjects, also allowing for a greater investigation of a dose–response effect.

Allowing for these caveats, it is relevant to consider how the current findings fit in with existing knowledge. Our findings of a much greater influence of increasing BMI on OA risk in women confirm the results of several other studies[16–21]. It is interesting to consider if the differential gender association with BMI might explain the current results of gender difference in interaction between BMI and activity. Two potential factors of relevance are gender difference in body composition and quadriceps strength. Amongst those with a high BMI, women have a higher percentage of body fat and this has ‘downstream’ effects on metabolic and inflammatory pathways that might increase OA risk[22–25]. our sub-analysis also confirmed that mean quadriceps strength (N) was lower in women (men: 195 vs women: 118). Somewhat surprisingly we found no gender difference in the type of activity profile at least in the low-moderate active group. Despite this, lower muscle strength for a similar profile of activities may lead to less joint protection and more biomechanical stress on the knee joint in women. Hence, this may explain the greater risk of low–moderate activity in obese women as compared to men. To put it another way, this might explain why obesity in women is less influenced by the level of physical activity than in men. Ideally, we would have liked to have included an analysis of quadriceps strength in our interaction analysis, but such data was missing in a large number of subjects, and thus the statistical power to have been able to identify a specific influence of quads strength was too small. This hypothesis remains to be tested in a separate more complete dataset.

Given the complexities in regard to considering physical activity as a single exposure, it is perhaps not surprising that there are conflicting data on the balance between risks and benefits from activity. The beneficial effects of regular exercise on general musculoskeletal health is widely recognised[26]. However, several studies suggest that excessive physical activity might be a risk factor for OA with increased levels of leisure time physical activity associated with an increased risk of severe knee OA over a 10 year period[27]. Similarly, jogging and walking more than 20 miles per week in young men increased the long term risk[28]. A study of older adults in the Framingham Study reported that heavy physical activity for more than 4 h per day increased the risk of radiographic and symptomatic knee OA[29]. Another large population-based cohort study of Swedish adults also found a small trend of higher risk of severe knee OA with increasing levels of leisure time physical activity in middle aged people over an 11 year follow-up[30].

By contrast, two other studies from Framingham, covering both older adults and the “Offspring cohorts” did not support that moderate recreational activities were associated with the incidence of radiographic or symptomatic knee OA[31,32]. Indeed our analysis, using similar approaches to defining OA, did not show that low and moderate levels of physical activity increased the likelihood of developing JSN, radiographic or symptomatic knee OA in either men or women.

Our main focus was on the interactive effect of obesity and physical activity on the developing of knee OA to understand whether the effect of physical activity on knee OA is modified by changing BMI. Evidence to address this question is fairly limited[33], with only small numbers of comparable studies. One was a cohort study of the risk of radiographic or symptomatic knee OA in middle aged and older adults in the Framingham Study[34]. The other was a 12 year longitudinal study on the risk of self-reported doctor-diagnosed knee OA[35]. BMI was not found to modify the effect of recreational activities on knee OA on any of these two studies. Similarly, results from a prospective cohort of 77,216 Norwegians did not find any evidence of positive interaction between obesity and various levels of recreational activity on the risk of self-reported doctor diagnosed knee OA.[7]

As discussed above the challenges and hence differences in the assessment of physical activity might explain the divergent results. Thus, in an analysis of heavy physical activity in older adults in the Framingham Study, there was an association with a higher risk of radiographic knee OA in people with high BMI[29]. Data from large cohort of the UK population also showed that manual occupational activity was associated with a greater increase in risk of symptomatic knee OA in people with high BMI than individuals with low BMI[8]. Our study is the first to suggest there may be a differential gender effect on the BMI and activity relationship. Our interaction analyses suggested the presence of positive and statistically significant interaction between high levels of physical activity and BMI on developing JSN, radiographic and symptomatic knee OA in men.

In summary, unravelling the complex relationship between BMI and physical activity on the risk of knee OA is not simple. Obese and overweight individuals are well recognised to be at substantially greater risk of OA. Our analysis shows, within the constraints of our approach to assessing physical activity, there is little evidence that the amount of physical activity alters the risk of knee OA in women. By contrast, high levels of activity in overweight obese men might carry additional risks for that group.

Author contributions

All authors contributed to the design, analysis, and interpretation of the data in this manuscript and will take the responsibility for the content.

Conflict of interest

All authors declare no conflict of interest.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2019.05.025.

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