

Title page

Title:

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

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

Corresponding author:

Professor Alan J Silman, University of Oxford, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences, Oxford, UK. alan.silman@ndorms.ox.ac.uk , Telephone: 01865 737831

Co-authors:

Dr Hessam Soutakbar, University of Oxford, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences, Oxford, UK. Email: Hessam.soutakbar@ndorms.ox.ac.uk , Telephone: 01865 737446

Professor Sarah E Lamb, University of Oxford, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences, Oxford, UK. Sarah.lamb@ndorms.ox.ac.uk , Telephone: 01865 223427

Professor Alan J Silman, University of Oxford, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences, Oxford, UK. alan.silman@ndorms.ox.ac.uk , Telephone: 01865 737831

ABSTRACT

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 1667 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 risk 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_{interaction} OR 1.2, (95%CI: 1.0- 1.2), (ii) symptomatic OA_{interaction}: OR: 1.2 (95%CI: 1.0-1.4), (iii) JSN_{interaction}: OR 1.2, (95%CI: 1.0- 1.3). 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 risk 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.

Keywords: Knee, osteoarthritis, physical activity, obesity

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 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 45-79 years. Between 2004 and 2006, 4796 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 one 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 degrees 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 two 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 presence 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 ≥ 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 ≥ 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 ≥ 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, 2801 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 1). The pattern and volume of participation in various intensities of leisure activities, stratified by the overall level of activity, is described in Table 2. The men in the high active group were more likely to undertake active sports than women with a similar PASE score (Table 2).

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 3. There was a greater increased risk 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 3).

Active and inactive women had a similar risk of radiographic knee OA (aORs: 1.11, 95%CI: 0.80-1.54). This effect was not modified by changing BMI ($p=0.41$) (Figure 1). In contrast, high levels of physical activity significantly increased the risk of radiographic knee OA in men (aOR^{4th quartile/1st quartile-reference category}: 2.37, 95%CI: 1.23-4.54; aOR^{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 Figure 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 risk 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 risk of incident symptomatic knee OA in women. This lack of effect was also seen in men (Table 4). However, in men, this effect was modified by changing BMI ($p=0.022$). The margin plot (Figure 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 developing knee OA in women. By contrast, in men, our results suggest that high levels of physical activity had an effect on the risk of 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 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 pattern of

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

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

212 Allowing for these caveats, it is relevant to consider how the current findings fit in with existing
213 knowledge. Our findings of a much greater influence of increasing BMI on OA risk in women confirm
214 the results of several other studies.¹⁶⁻²¹ It is interesting to consider if the differential gender association
215 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 four hours 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 risk 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 risk of knee OA to understand whether the effect of physical activity on the risk of 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 OA³⁵. 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.

ACKNOWLEDGMENTS

Professor Sallie Lamb receives funding from the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care Oxford at Oxford Health NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. Professor Alan Silman receives supports from the National Institute for Health Research (NIHR) Biomedical Research Centre at Oxford Health NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. We also express our gratitude to Professor Brigitte Scammell, Dr Kimberley Edwards, and Dr Lisa Hodgson from the University of Nottingham for sharing their invaluable experience with us. This work was previously presented at the 2018 OARSI World Congress.³⁶

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.

288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308

REFERENCES

1. Felson DT, Niu J, Yang T, Torner J, Lewis CE, Aliabadi P, et al. Physical activity, alignment and knee osteoarthritis: data from MOST and the OAI. *Osteoarthritis and cartilage* 2013;21(6):789-95. doi: 10.1016/j.joca.2013.03.001 [published Online First: 2013/03/26]
2. Richmond SA, Fukuchi RK, Ezzat A, Schneider K, Schneider G, Emery CA. Are joint injury, sport activity, physical activity, obesity, or occupational activities predictors for osteoarthritis? A systematic review. *The Journal of orthopaedic and sports physical therapy* 2013;43(8):515-b19. doi: 10.2519/jospt.2013.4796 [published Online First: 2013/06/13]
3. Gates LS, Leyland KM, Sheard S, Jackson K, Kelly P, Callahan LF, et al. Physical Activity and Osteoarthritis. A consensus study to harmonise self-reporting methods of physical activity across international cohorts. *Rheumatology international* 2017;37(4):469-78. doi: 10.1007/s00296-017-3672-y
4. Litwic A, Edwards M, Dennison E, Cooper C. Epidemiology and Burden of Osteoarthritis. *British medical bulletin* 2013;105:185-99. doi: 10.1093/bmb/lds038

- 309 5. Felson DT. Osteoarthritis as a disease of mechanics. *Osteoarthritis and cartilage / OARS,*
310 *Osteoarthritis Research Society* 2013;21(1):10-15. doi: 10.1016/j.joca.2012.09.012
- 311 6. Lo GH, Driban JB, Kriska AM, McAlindon TE, Souza RB, Petersen NJ, et al. Is There an
312 Association Between a History of Running and Symptomatic Knee Osteoarthritis? A
313 Cross-Sectional Study From the Osteoarthritis Initiative. *Arthritis care & research*
314 2017;69(2):183-91. doi: 10.1002/acr.22939 [published Online First: 2016/06/23]
- 315 7. Mork PJ, Holtermann A, Nilsen TI. Effect of body mass index and physical exercise on risk
316 of knee and hip osteoarthritis: longitudinal data from the Norwegian HUNT Study.
317 *Journal of epidemiology and community health* 2012;66(8):678-83. doi: 10.1136/jech-
318 2011-200834 [published Online First: 2012/04/19]
- 319 8. Martin KR, Kuh D, Harris TB, Guralnik JM, Coggon D, Wills AK. Body mass index, occupational
320 activity, and leisure-time physical activity: an exploration of risk factors and modifiers
321 for knee osteoarthritis in the 1946 British birth cohort. *BMC Musculoskeletal Disorders*
322 2013;14:219-19. doi: 10.1186/1471-2474-14-219
- 323 9. Nevitt MC, Felson DT, Lester G. OAI Protocol, Osteoarthritis Initiative: a Knee Health Study
324 2006 [updated 0.6/21/2006. version 1.1:[Available from: [https://oai.epi-](https://oai.epi-ucsf.org/datarelease/default.asp)
325 [ucsf.org/datarelease/default.asp](https://oai.epi-ucsf.org/datarelease/default.asp).
- 326 10. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised.
327 *Osteoarthritis and cartilage* 2007;15 Suppl A:A1-56. doi: 10.1016/j.joca.2006.11.009
328 [published Online First: 2007/02/27]

- 329 11. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly
330 (PASE): development and evaluation. *Journal of clinical epidemiology* 1993;46(2):153-
331 62. [published Online First: 1993/02/01]
- 332 12. Stehling C, Liebl H, Krug R, Lane NE, Nevitt MC, Lynch J, et al. Patellar Cartilage: T2 Values
333 and Morphologic Abnormalities at 3.0-T MR Imaging in Relation to Physical Activity in
334 Asymptomatic Subjects from the Osteoarthritis Initiative. *Radiology* 2010;254(2):509-
335 20. doi: 10.1148/radiol.09090596
- 336 13. Felson DT, Hodgson R. Identifying and treating preclinical and early osteoarthritis.
337 *Rheumatic diseases clinics of North America* 2014;40(4):699-710. doi:
338 10.1016/j.rdc.2014.07.012 [published Online First: 2014/12/02]
- 339 14. Felson DT, Nevitt MC. Epidemiologic studies for osteoarthritis: new versus conventional
340 study design approaches. *Rheumatic diseases clinics of North America* 2004;30(4):783-
341 97, vii. doi: 10.1016/j.rdc.2004.07.005 [published Online First: 2004/10/19]
- 342 15. Lin W, Alizai H, Joseph GB, Srikkum W, Nevitt MC, Lynch JA, et al. Physical activity in
343 relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4
344 years: data from the Osteoarthritis Initiative. *Osteoarthritis and cartilage / OARS,*
345 *Osteoarthritis Research Society* 2013;21(10):10.1016/j.joca.2013.06.022. doi:
346 10.1016/j.joca.2013.06.022
- 347 16. Wills AK, Black S, Cooper R, Coppack RJ, Hardy R, Martin KR, et al. Life course body mass
348 index and risk of knee osteoarthritis at the age of 53 years: evidence from the 1946
349 British birth cohort study. *Annals of the Rheumatic Diseases* 2012;71(5):655.

- 350 17. Holliday KL, McWilliams DF, Maciewicz RA, Muir KR, Zhang W, Doherty M. Lifetime body
351 mass index, other anthropometric measures of obesity and risk of knee or hip
352 osteoarthritis in the GOAL case-control study. *Osteoarthritis and Cartilage*
353 2011;19(1):37-43. doi: <https://doi.org/10.1016/j.joca.2010.10.014>
- 354 18. Sandmark H, Hogstedt C, Lewold S, Vingård E. Osteoarthrosis of the knee in men and
355 women in association with overweight, smoking, and hormone therapy. *Annals of the*
356 *Rheumatic Diseases* 1999;58(3):151.
- 357 19. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, et al. Risk factors for
358 incident radiographic knee osteoarthritis in the elderly: the Framingham Study.
359 *Arthritis Rheum* 1997;40(4):728-33. doi: 10.1002/1529-
360 0131(199704)40:4<728::AID-ART19>3.0.CO;2-D [published Online First:
361 1997/04/01]
- 362 20. Tukker A, Visscher TL, Picavet HS. Overweight and health problems of the lower
363 extremities: osteoarthritis, pain and disability. *Public health nutrition* 2009;12(3):359-
364 68. doi: 10.1017/s1368980008002103 [published Online First: 2008/04/23]
- 365 21. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee
366 osteoarthritis. The Framingham Study. *Annals of internal medicine* 1988;109(1):18-24.
367 [published Online First: 1988/07/01]
- 368 22. Sowers MR, Karvonen-Gutierrez CA. The evolving role of obesity in knee osteoarthritis.
369 *Current Opinion in Rheumatology* 2010;22(5):533-37. doi:
370 10.1097/BOR.0b013e32833b4682

- 371 23. Teichtahl AJ, Wang Y, Wluka AE, Cicuttini FM. Obesity and knee osteoarthritis: new
372 insights provided by body composition studies. *Obesity (Silver Spring, Md)*
373 2008;16(2):232-40. doi: 10.1038/oby.2007.30 [published Online First: 2008/02/02]
- 374 24. Bliddal H, Leeds AR, Christensen R. Osteoarthritis, obesity and weight loss: evidence,
375 hypotheses and horizons – a scoping review. *Obesity Reviews* 2014;15(7):578-86. doi:
376 10.1111/obr.12173
- 377 25. Issa RI, Griffin TM. Pathobiology of obesity and osteoarthritis: integrating biomechanics
378 and inflammation. *Pathobiology of Aging & Age Related Diseases*
379 2012;2:10.3402/pba.v2i0.17470. doi: 10.3402/pba.v2i0.17470
- 380 26. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence.
381 *CMAJ : Canadian Medical Association journal = journal de l'Association medicale*
382 *canadienne* 2006;174(6):801-9. doi: 10.1503/cmaj.051351 [published Online First:
383 2006/03/15]
- 384 27. Wang Y, Simpson JA, Wluka AE, Teichtahl AJ, English DR, Giles GG, et al. Is physical activity
385 a risk factor for primary knee or hip replacement due to osteoarthritis? A prospective
386 cohort study. *The Journal of rheumatology* 2011;38(2):350-7. doi:
387 10.3899/jrheum.091138 [published Online First: 2010/10/19]
- 388 28. Cheng Y, Macera CA, Davis DR, Ainsworth BE, Troped PJ, Blair SN. Physical activity and
389 self-reported, physician-diagnosed osteoarthritis: is physical activity a risk factor?
390 *Journal of clinical epidemiology* 2000;53(3):315-22. [published Online First:
391 2000/04/13]

- 392 29. McAlindon TE, Wilson PW, Aliabadi P, Weissman B, Felson DT. Level of physical activity
393 and the risk of radiographic and symptomatic knee osteoarthritis in the elderly: the
394 Framingham study. *The American journal of medicine* 1999;106(2):151-7. [published
395 Online First: 1999/05/07]
- 396 30. Ageberg E, Engstrom G, Gerhardsson de Verdier M, Rollof J, Roos EM, Lohmander LS.
397 Effect of leisure time physical activity on severe knee or hip osteoarthritis leading to
398 total joint replacement: a population-based prospective cohort study. *BMC*
399 *musculoskeletal disorders* 2012;13:73. doi: 10.1186/1471-2474-13-73 [published
400 Online First: 2012/05/19]
- 401 31. Felson DT, Niu J, Clancy M, Sack B, Aliabadi P, Zhang Y. Effect of recreational physical
402 activities on the development of knee osteoarthritis in older adults of different
403 weights: the Framingham Study. *Arthritis and rheumatism* 2007;57(1):6-12. doi:
404 10.1002/art.22464 [published Online First: 2007/02/03]
- 405 32. Hannan MT, Felson DT, Anderson JJ, Naimark A. Habitual physical activity is not associated
406 with knee osteoarthritis: the Framingham Study. *The Journal of rheumatology*
407 1993;20(4):704-9. [published Online First: 1993/04/01]
- 408 33. Urquhart DM, Soufan C, Teichtahl AJ, Wluka AE, Hanna F, Cicuttini FM. Factors that may
409 mediate the relationship between physical activity and the risk for developing knee
410 osteoarthritis. *Arthritis Research & Therapy* 2008;10(1):203-03. doi: 10.1186/ar2343

34. Felson DT, Niu J, Clancy M, Sack B, Aliabadi P, Zhang Y. Effect of recreational physical activities on the development of knee osteoarthritis in older adults of different weights: the Framingham Study. *Arthritis Rheum* 2007;57 doi: 10.1002/art.22464
35. Hootman JM, Macera CA, Helmick CG, Blair SN. Influence of physical activity-related joint stress on the risk of self-reported hip/knee osteoarthritis: a new method to quantify physical activity. *Preventive medicine* 2003;36(5):636-44. [published Online First: 2003/04/12]
36. Soutakbar H, Lamb SE, Scammell BE, Hodgson L, Edwards KL, Silman AJ. The differential influence of high levels of physical activity on knee OA in overweight and obese men and women. *Osteoarthritis and cartilage* 2018;26:S11-S12. doi: <https://doi.org/10.1016/j.joca.2018.02.040>

Table 1: Participants' characteristics data at baseline

Baseline	Men	Women
Subject, N (eligible knees)	702 (1173)	965 (1628)
Age, year, mean (SD)	58.69 (8.97)	59.60 (8.49)
BMI, kg/m², 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)	1157 (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)
Marital Status N (%): Married; Never married	571 (81.3); 58 (8.3)	621 (64.4); 95 (9.8)

Table 2: 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 3: The effect of physical activity, BMI and their interactions on incident radiographic knee OA.

Incident radiographic knee OA <i>Adjusted odds ratio¹ (95% confidence interval)</i>						
Gender	Activity (quartiles ²)		Active vs. Inactive ³	BMI ⁴ (odds ratio per Kg/m ²)	Effect of BMI by Physical Activity group (odds ratio per Kg/m ²)	
Men	2 nd	0.94 (0.48-1.86) <i>p</i> = 0.88	1.91 (1.20-3.04) <i>p</i> = 0.006	1.06 (1.00-1.11) <i>p</i> = 0.031	BMI in active group	1.07 (1.01-1.13) <i>p</i> = 0.01
	3 rd	1.32 (0.68-2.53) <i>p</i> = 0.40			BMI in inactive group	1.04 (0.99-1.10) <i>p</i> = 0.09
	4 th	2.37 (1.23-4.54) <i>p</i> = 0.009				
Women	2 nd	1.17 (0.78-1.77) <i>p</i> = 0.42	1.11 (0.80-1.54) <i>p</i> = 0.504	1.15 (1.11-1.18) <i>p</i> < 0.001	BMI in active group	1.15 (1.11-1.18) <i>p</i> < 0.001
	3 rd	1.40 (0.94-2.09) <i>p</i> = 0.09			BMI in inactive group	1.14 (1.11-1.17) <i>p</i> < 0.001
	4 th	1.42 (0.93-2.17) <i>p</i> = 0.10				

- Odds ratios were adjusted for age, gender and injury
- 4th Quartile includes individuals with the highest PASE scores.
- Active: PASE ≥200; Inactive: PASE <200
- BMI (Kg/m²): body mass index was used as continuous variable

472

473

474

475

476 **Table 4:** The effect of physical activity, BMI and their interactions on incident symptomatic knee OA.

Incident symptomatic knee OA <i>Adjusted odds ratio¹ (95% confidence interval)</i>						
Gender	Activity ² (quartiles)		Active vs. Inactive ³	BMI ⁴ (odds ratio per Kg/m ²)	Effect of BMI by Physical Activity group (odds ratio per Kg/m ²)	
Men	2 nd	1.03 (0.41-2.58) <i>p</i> = 0.93	1.18 (0.56-2.46) <i>p</i> = 0.65	1.07 (0.99-1.16) <i>p</i> = 0.06	BMI in active group	1.09, (0.99-1.17) <i>p</i> = 0.053
	3 rd	0.53 (0.17-1.65) <i>p</i> = 0.27			BMI in inactive group	1.07, (0.99-1.16) <i>p</i> = 0.084
	4 th	1.47 (0.55-3.92) <i>p</i> = 0.43				
Women	2 nd	1.27 (0.66-2.45) <i>p</i> = 0.46	1.12 (0.68-1.82) <i>p</i> = 0.64	1.11 (1.06-1.16) <i>p</i> < 0.001	BMI in active group	1.12, (1.07-1.17) <i>p</i> < 0.001
	3 rd	1.74 (0.94-3.22) <i>p</i> = 0.07			BMI in inactive group	1.11, (1.06-1.16) <i>p</i> < 0.001
	4 th	1.61 (0.83-3.11) <i>p</i> = 0.15				

477 1. Odds ratios were adjusted for age, gender and injury

478 2. 4th Quartile includes individuals with the highest PASE scores.

479 3. Active: PASE ≥200; Inactive: PASE <200

480 4. BMI (Kg/m²): body mass index was used as continuous variable

481

482

483

484

485

486

487

488

489

490

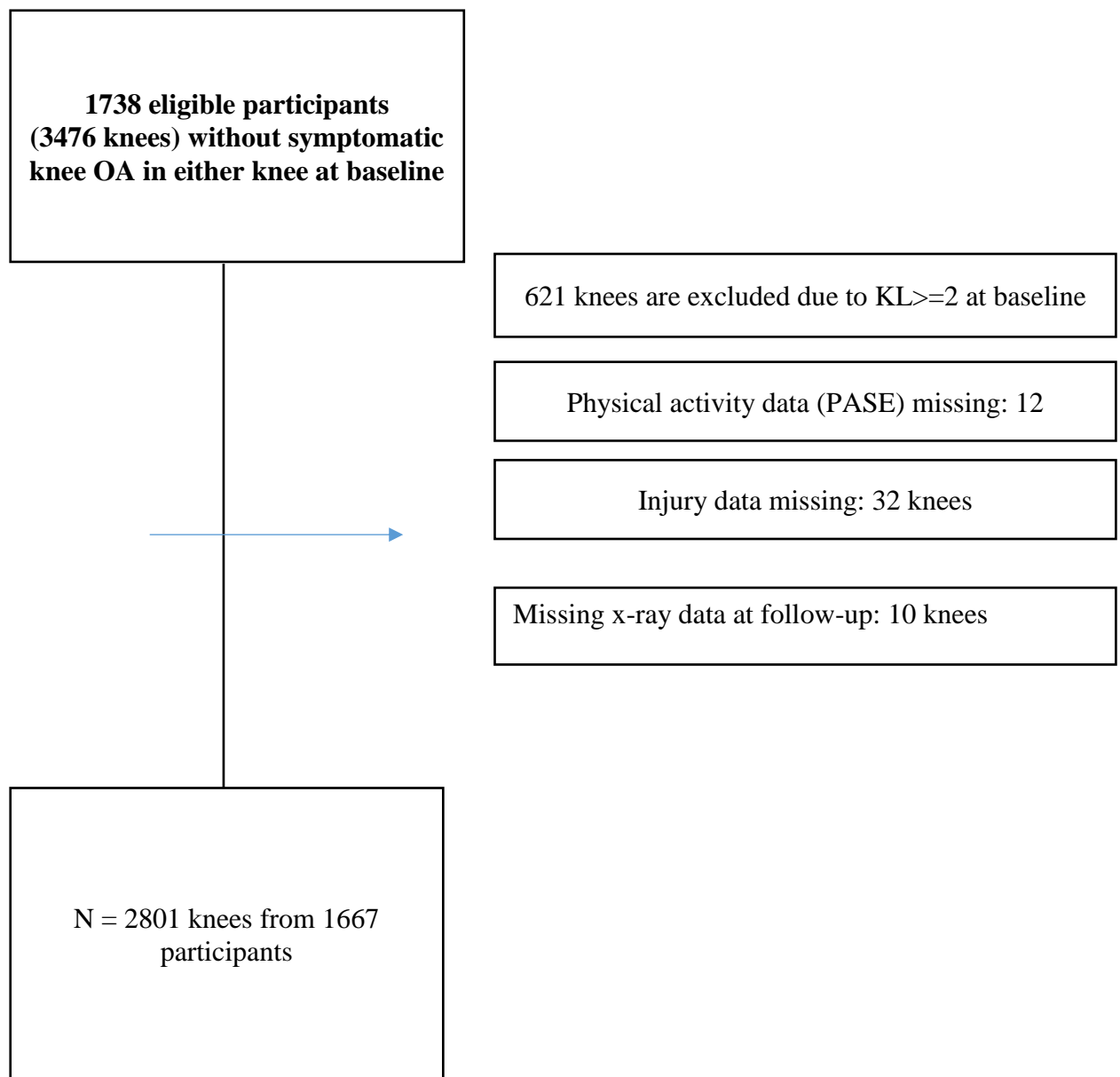
491 **Supplementary 1:**

492 The PASE covers three domains of physical activity, which are leisure activities, household activities
493 and occupational activities. Leisure physical activity was evaluated based on the number of days/week
494 (frequency: never, seldom (1-2 days), sometimes (3-4 days), often (5-7 days), don't know) and
495 hours/day (<1 hr, 1hr - <2hr, 2-4hr, >4 hr, don't know) spent on the following activities 1: sitting; 2:
496 walking; 3: light sport/recreation; 4: moderate sport/recreation; 5: strenuous sport/recreation; 6: muscle
497 strength/endurance. Six different group of household activities (light housework, heavy housework,
498 home repairs, lawn work/yard care, outdoor gardening, caring for another person) were scored using
499 four categories of 1: no; 2: yes; 3: don't know; 4: refused to answer.

500 Occupational physical activity has been evaluated based on the four sub-categories: Category 1: mainly
501 sitting; Category 2: mainly sitting or standing but including some walking activities; Category 3:
502 walking and handling of different items which are not heavier than 50 pounds; Category 4: walking and
503 handling of items which are heavier than 50 pounds.

Gender specific quartiles categories of PASE score		
	Men	Women
1 st Quartile (reference category)	0-120	1-108
2 nd Quartile	121-175	109-154
3 rd Quartile	176-250	155-208
4 th Quartile	251-526	209-408

Suplimentary file 2: Participants included in this project



530

531

532

533

534

535 **Supplementary file 3:** The effect of physical activity, BMI and their interactions on the progression of
 536 JSN.

Progression of joint space narrowing Adjusted odds ratio ¹ (95% confidence interval)						
Gender	Activity (quartiles ²)		Active vs. Inactive ³	BMI ⁴ (odds ratio per Kg/m ²)	Effect of BMI by Physical Activity group (odds ratio per Kg/m ²)	
Men	2 nd	0.74 (0.35-1.57) <i>p</i> = 0.44	2.50 (1.51-4.15) <i>p</i> = 0.001	1.07 (1.01-1.14) <i>p</i> = 0.01	BMI in active group	1.09, (1.03- 1.15) <i>p</i> = 0.004
	3 rd	1.55 (0.79-3.05) <i>p</i> = 0.19			BMI in inactive group	1.05, (0.99-1.12) <i>p</i> = 0.08
	4 th	2.37 (1.16-4.80) <i>p</i> = 0.01				
Women	2 nd	0.98 (0.62-1.55) <i>p</i> = 0.94	1.07 (0.74-1.57) <i>p</i> = 0.69	1.11 (1.08-1.16) <i>p</i> < 0.001	BMI in active group	1.12, (1.08- 1.16) <i>p</i> < 0.001
	3 rd	1.26 (0.81-1.97) <i>p</i> = 0.29			BMI in inactive group	1.11, (1.08- 1.15) <i>p</i> < 0.001
	4 th	1.14 (0.70-1.84) <i>p</i> = 0.59				

537 1. Odds ratios were adjusted for age, gender and injury

538 2. 4th Quartile includes individuals the with highest PASE scores.

539 3. Active: PASE ≥200; Inactive: PASE <200

540 4. BMI (Kg/m²): body mass index was used as continuous variable