EXTENDED REPORT

Life course body mass index and risk of knee osteoarthritis at the age of 53 years: evidence from the 1946 British birth cohort study

Andrew K Wills,1 Stephanie Black,1 Rachel Cooper,1 Russell J Coppack,2 Rebecca Hardy,1 Kathryn Remmes Martin,1 Cyrus Cooper,3 Diana Kuh1

ABSTRACT

Introduction The authors examined how body mass index (BMI) across life is linked to the risk of midlife knee osteoarthritis (OA), testing whether prolonged exposure to high BMI or high BMI at a particular period has the greatest influence on the risk of knee OA. Methods A population-based British birth cohort of 3035 men and women underwent clinical examination for knee OA at age 53 years. Heights and weights were measured 10 times from 2 to 53 years. Analyses were stratified by gender and adjusted for occupation and activity levels. Results The prevalence of knee OA was higher in women than in men (12.9% [n=194] vs 7.4% [n=108]). In men, the association between BMI and later knee OA was evident at 20 years (p=0.038) and remained until 53 years (OR per z-score 1.38 [95% CI 1.11 to 1.71]). In women, there was evidence for an association at 15 years (p=0.003); at 53 years, the OR was 1.89 (95% CI 1.59 to 2.24) per z-score increase in BMI. Changes in BMI from childhood in women and from adolescence in men were also positively associated with knee OA. A structured modelling approach to disentangle the way in which BMI is linked to knee OA suggested that prolonged exposure to high BMI throughout adulthood carried the highest risk and that there was no additional risk conferred from adolescence once adult BMI had been accounted for. Conclusion This study suggests that the risk of knee OA accumulates from exposure to a high BMI through adulthood.

INTRODUCTION

Regardless of study design (eg, cross-sectional, case-control or prospective cohort) or case definition, body mass index (BMI) is strongly and positively associated with knee osteoarthritis (OA) across its distribution, and there is some evidence of a relationship with disease progression. However, few studies have reported on its association with BMI at different ages, among those studies that have, most have relied on recall of body size and none has examined BMI across life from childhood to mid-adulthood. Thus, while the association between overweight and OA is considered causal through mechanical or metabolic pathways, the way in which lifetime BMI is linked with future OA remains unclear. For example, does cumulative exposure to high BMI over a prolonged period of time drive OA risk, or is there a period in life when carrying excess weight is particularly detrimental? This information is important for informing best practices on the prevention of OA and may provide an insight into pathways across life by which BMI is linked to OA.

We use a general population-based British birth cohort study to examine the relationship between lifetime BMI and knee OA at 53 years. Our aims were to: (1) determine how early in life BMI is associated with knee OA; (2) examine the influence of changes in BMI during specific periods of life; (3) assess whether prolonged exposure to high BMI throughout life increases the risk of knee OA or whether being exposed to a high BMI at a particular stage of life is the most important way in which weight affects risk; and (4) assess whether these relationships differ by gender since some studies have reported stronger associations in women.

METHODS

Study sample

The Medical Research Council National Survey of Health and Development is a socially stratified birth cohort of 2547 women and 2815 men who have been followed up since their birth in 1946. This paper uses information on knee OA that was collected when cohort members were 53 years of age and includes 5085 participants (1472 men and 1563 women). The majority (n=2989) were examined in their own homes by trained research nurses. Those who were successfully contacted were, in most respects, representative of the UK-born population of that age. Contact was not attempted for 1979 individuals who either had previously refused to take part, were living abroad, remained untraced since last contact at 43 years or had already died. Data collection received ethical approval from the Medical Research Council ethics committee, and informed consent was given by respondents at each wave.

Outcome

We used the American College of Rheumatology criteria for the clinical diagnosis of idiopathic knee OA, namely knee pain in either knee on most days for at least 1 month in the last year and at least two of the following: stiffness, crepitation, bony tenderness and bony enlargement. These items were assessed through a clinical examination conducted by a trained research nurse (see online supplementary text S1 for full details of the examination). As an indicator of functional limitations in those with knee OA, we also report the average time taken

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to complete 10 chair rises, which was performed using a standardised protocol.\textsuperscript{21}

**Exposure**

Heights and weights were measured with standardised protocols at ages 2, 4, 7, 11, 15, 36, 43 and 53 years, and were self-reported prospectively at ages 20 and 26 years. We calculated BMI (weight (kg)/height (m\(^2\))) at each age and converted these into z-scores, normalising and standardising by age and sex using the LMS method.\textsuperscript{22}

**Covariables**

The Registrar General’s classification of own occupation in adulthood at 43 years, categorised into manual and non-manual occupations, was used. To avoid reverse causation where symptoms of knee OA can cause individuals to modify their activity level, we used the level of participation in sports and recreational activities collected at age 36 years. This variable assessed the frequency and duration of participation in 27 activities (including badminton, swimming, football and jogging over the last month) split into three categories: inactive=no reported activity; less active=one to four times; more active=five or more times.

**Analysis**

Analyses were stratified by gender, with interactions assessed using Wald tests. We first plotted the mean lifetime BMI (z-score) in individuals with knee OA and estimated unadjusted and adjusted (controlling for activity and adult occupation) ORs for the association between BMI at each age and knee OA using logistic regression (aim 1). BMI was modelled using both standardised z-scores and raw units (kg/m\(^2\)). Z-scores allowed for a comparison of effect sizes across ages, uninfluenced by the widening distribution of BMI with age. Raw units were examined to allow for a comparison with other studies and to more directly capture the

mechanical overload hypothesis.\textsuperscript{23} There was no evidence for a departure from linearity, as tested using quadratic terms and by inspecting plots of observed versus predicted values.

We examined the influence of changes in BMI during five specific life periods (childhood: 2–7 years; childhood to adolescence: 7–15 years; adolescence to young adulthood: 15–20 years; early adulthood: 20–36 years; mid-adulthood: 36–53 years) (aim 2) by adjusting for BMI at the start of each interval. The associations are therefore conditional on size at the start of the interval, removing any of the association due to BMI tracking. This conditional variable can be interpreted as BMI change above or below that expected in our population given earlier BMI.

We used a structured modelling approach\textsuperscript{24} to provide an insight into the way in which high BMI over life is associated with knee OA (aim 3). Each individual’s lifetime BMI trajectory was simplified according to whether or not they were in the top quartile of the sex-specific BMI distribution (high BMI) at age 15, 26 and 43 years, giving eight possible trajectories. These ages approximate adolescence, early adulthood and mid-adulthood, although similar results were found in a sensitivity analysis using other ages. The top quartile, rather than overweight cut-off (>25 kg/m\(^2\)), was used to avoid zero cell counts in trajectory groups. The results were similar in a sensitivity analysis using the upper tertile (see online supplementary table S1). A saturated model was first fitted by allowing each possible trajectory to explain knee OA. Sets of model constraints were then imposed, with each corresponding to a type of life course risk model.\textsuperscript{14} In each case, the model with the constraints was tested against the saturated model using the $\chi^2$ distribution, and the p value was used as an indicator of model fit. Higher p values reflect a better model fit since they indicate that the more parsimonious (constrained) model fits the data as well as the more complex (saturated) model. The life course models considered were as follows: (1) an accumulation model where only the duration of high BMI is allowed to explain knee OA (duration);
RESULTS

At age 53 years, 302 (10.2%) individuals were classified with knee OA. The prevalence was higher in women than in men: 12.9% (n=194) versus 7.4% (n=108) (OR in women 1.84 (95% CI 1.44 to 2.36)); adjusting for BMI at age 53 years slightly attenuated this association (OR 1.76). Thirty-eight per cent of individuals with knee OA had bilateral symptoms, with little evidence of a gender difference in this proportion (p=0.1). Of individuals with knee OA, 16.2% were unable to take or complete the 10 chair rise test, compared to 4.1% of other participants (p<0.001). Those with knee OA who were able to complete 10 chair rises took, on average, 14% longer (95% CI 8.9% to 19.4%) than individuals without knee OA.

From age 36 years, women had faster BMI gains, and their BMI distribution was more positively skewed compared to men (see online supplementary figure S1). More men than women were in manual occupations (39% vs 29%, p<0.001). Women were less likely to participate in sports and recreational activities at age 36 years compared to men (% inactive: 41% vs 31%, p<0.001).

Life course BMI and knee OA

The BMI pattern among women who developed knee OA deviated from the rest of the population from 2 years such that, by age 53 years, they had a mean BMI that is 0.61 SD higher than that of women without knee OA (figure 1). The pattern was similar in men, but the accrual of extra weight began later (around 11–15 years), and the difference in BMI at 53 years between those with knee OA and those without knee OA was smaller (0.36 SD).

To examine the influence of potential secondary OA on our findings, we repeated the analyses after excluding cases who had reported ever seeing a doctor about a knee injury on the limb diagnosed as having OA. We extended this by additionally excluding those with unilateral OA. Stata (V.10.1) was used for all analyses.

(2) an accumulation model that is similar to (1) but additionally allows the effect of high BMI to vary by age of exposure (duration and age); and (3) period models where each period is separately allowed to explain knee OA risk. Online supplementary text S2 gives the algebraic formulation of each model.

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FIGURE 2 Odds ratios (OR) for knee osteoarthritis in men (filled markers) and women (open markers) per z-score increase in body mass index (BMI) at each age (A) and per kg/m² increase in BMI (B). Adjusted for activity levels and occupation (manual/non-manual). Evidence for a sex interaction using BMI z-scores at ages 15 years (p=0.035) and 53 years (p=0.025) and weak evidence at ages 36 years (p=0.051) and 43 years (p=0.089). Evidence for sex interaction using nonstandardised BMI at age 15 years (p=0.043).

FIGURE 3 Association (OR) between conditional body mass index (BMI) change (per z-score increase) and knee osteoarthritis in infancy (2–7 years), childhood/adolescence (7–15 years), adolescence to young adulthood (15–20 years), early adulthood (20–36 years) and mid-adulthood (36–53 years) in men (filled markers) and women (open markers). Each period of BMI change is adjusted for BMI at the beginning of the interval. Adjusted for activity levels and occupation (manual/non-manual). Sex interactions: 7–15 years: p=0.088; 15–20 years: p=0.035; 20–36 years: p=0.012.
On the normalised and standardised scale, the association between BMI and knee OA was 39% (p=0.035), 31% (p=0.051), 28% (p=0.089) and 37% (p=0.025) stronger in women than in men at ages 15, 36, 43 and 53 years, respectively (figure 2A). However, with the exception of the gender interaction at 15 years (p=0.043), these gender differences were almost entirely removed when raw BMI units (kg/m²) were used (figure 2B).

These results were qualitatively similar after removing cases of suspected secondary knee OA due to a knee injury (see online supplementary text S4.1). The associations between BMI and knee OA were larger but had a similar pattern across age and gender after further exclusion of unilateral knee OA (see online supplementary text S4.1).

### Conditional BMI change

In men, conditional BMI gain from 15 to 20 years was associated with a higher risk of knee OA (figure 3), but there was no evidence of an association with gains in adulthood. However, adult BMI gains were important after excluding suspected secondary OA and unilateral knee OA (see online supplementary figures S4 and S7). In women, BMI increases from childhood to adolescence (7–15 years) and in adulthood were positively associated with knee OA (figure 3).

### Life course models of knee OA risk

Tests of life course models suggested that there was no additional benefit from including an early BMI measure (15 years) once adult BMI has been accounted for, so we restricted these tests to BMI exposures at 26 and 43 years to increase statistical power. In men, the most parsimonious model with the most support (highest p value) included a single term for high BMI at 43 years (table 1), suggesting that BMI in mid-adulthood was most important in explaining knee OA risk. However, there was still strong support for an accumulation model (duration of exposure). In women, the accumulation (duration and age of exposure) model had the most support, with a high BMI at 43 years having a stronger association with knee OA (OR 2.64 (95% CI 1.80 to 3.87)) than a high BMI at 26 years (OR 1.51 (95% CI 1.02 to 2.24)).

### DISCUSSION

Our study showed a linear relationship between BMI and midlife knee OA that was detectable around puberty in female subjects and in early adulthood in male subjects and persisted through life. While these associations appear to have their origins through BMI gains in childhood and adolescence, comparisons of different life course models suggest that the accumulation or duration of exposure in adult life is the main way by which high BMI influences knee OA risk. This implies that having a high BMI in childhood or adolescence is not independently associated with knee OA over and above that acting through BMI in adulthood.

### Strengths and limitations

A key strength of this study is its prospective and longitudinal design, which allowed for a detailed examination of the influence of lifetime BMI on knee OA and minimised bias from recall, regression dilution and reverse causality, particularly with regards to associations at younger ages where many studies have relied on recall.6–12 However, with prevalent rather than incident cases, there is the possibility of some reverse causation bias at later ages. While knee OA might lead to reductions in habitual activity and increased BMI, thereby inflating our associations, it is also possible that some individuals with known OA will reduce their weight to manage their condition, attenuating these associations.

We used the American College of Rheumatology criteria for a symptom-based diagnosis of knee OA. While we did not assess radiographic change and have no data on reliability, there is good evidence to suggest that those with well-defined symptoms also have structural changes on radiographs.26 Furthermore, the internal validity of our case classification is supported by the reduced physical performance among cases and by the similar effect sizes we saw compared to other studies that used radiographic criteria.27 It thus seems unlikely that our findings would be qualitatively different if radiographic criteria were used. Lastly our results should be generalisable to a similarly aged UK population.28

### Comparison with other studies and interpretation

Despite differences in populations, confounders considered and case definition, the effect size and linearity of the association between adult BMI and knee OA were similar to previous prospective studies1 6–8 10 15 16 39–52 (online supplementary table S2 reports associations in BMI categories). Several studies have reported associations between BMI at age 20 or 30 years and later knee OA7–10; however, with the exception of one case-control study of women, which found a weak association at

### Table 1  Adult life course models testing the way in which exposure to high BMI (top quartile) in adulthood might affect later life knee OA

<table>
<thead>
<tr>
<th>BMI trajectory</th>
<th>BMI (kg/m²)</th>
<th>Life course models (test of fit against the saturated model*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1=high</td>
<td>Median</td>
<td>Accumulation (duration)†</td>
</tr>
<tr>
<td>26 Years</td>
<td>26 Years</td>
<td>26 Years</td>
</tr>
<tr>
<td>Men</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>26.0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>23.7</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>27.1</td>
</tr>
<tr>
<td>Women</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>24.8</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>22.6</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>26.2</td>
</tr>
</tbody>
</table>

*The saturated model allows each BMI trajectory to affect the likelihood of knee OA. The model that differs the least from the saturated model in terms of explaining knee OA is the one with most support. Hence, larger p values indicate a better model (highlighted in boldface).
†Accumulation (duration): this model assumes that the effect of a high BMI is the same at each age, that is, it is only the amount of time exposed that is important (see online supplementary text S2).
‡Accumulation (duration and age): this model is the same as the duration model but also allows the effect of having a high BMI to differ at each age, that is, exposure time and age of exposure are allowed to influence the likelihood of knee OA (see online supplementary text S2).
§Period: These models allow exposure to affect knee OA at one age only. BMI, body mass index; OA, osteoarthritis.
school-leaving age, none has examined BMI at earlier ages. Our findings of associations in childhood for women and in young adulthood for men are thus new.

Conditional BMI gains in periods coinciding with steep adolescent rises in BMI (15–20 years in men and 7–15 years in women) were associated with an elevated risk of knee OA. Although excessive weight during these periods may result in mechanical alteration to the knee joint, it is also possible that the relationship is a consequence of an underlying metabolic predisposition to both adiposity and OA.

Whichever of these potential mechanisms is at play, our findings support the hypothesis that knee OA risk accumulates from prolonged exposure to high BMI throughout adulthood, with a high BMI in mid-adulthood carrying a slightly greater risk in women. Our sensitivity analysis excluded individuals with a previous knee injury and restricted to cases with bilateral involvement. Associations were generally stronger among this subset, supporting such an accumulation model for this particular disorder. The inclusion of cases of knee OA where BMI is not a component cause would dilute any attempt to disentangle the role of lifetime BMI among cases where it is a necessary component; this is possibly also reflected in the associations between weight gain and OA that, while evident in women, were only evident among the bilateral OA cases in men. No other studies have attempted to disentangle how BMI over life is related to knee OA using the methods employed here, although there is support for an accumulation model from studies that have shown a relationship between early adult BMI and knee OA after adjustment for later weight.

The higher risk conferred by adult BMI in women was explained by the scale and functional form of the BMI exposure in the sense that a z-score increase in women represents a larger shift in raw units of BMI than in men, as visible in an earlier study, and that the distribution of BMI is more skewed in women. It would be interesting to see whether the sex differences reported in studies that used distributional units of BMI would remain when continuous units of kilograms per meter squared are used. Women had a higher prevalence of knee OA, similar to that reported in population-based cohort studies and in primary care. Differences in BMI were unable to explain these gender-specific prevalence; reproductive hormone status presents one possible mechanism.

Implications

The importance of weight control throughout life as a means of primary prevention of knee OA is emphasised by our finding that BMI is associated with later knee OA as early as 11 years in women and 20 years in men, and by the suggestion that risk from a high BMI accumulates through adulthood. It is further emphasised by the tendency of BMI to track from childhood to adulthood, meaning that weight control interventions that start earlier in life may be more effective. However, our results also suggest that an individual can stop accumulating risk by reducing weight at any stage in adulthood.

Being overweight is a major factor in the aetiology of knee OA—the increase in knee OA risk per unit increase in BMI is similar to that reported for mortality from vascular disease (Prospective, 2009 479/ id). Our findings extend our understanding of this relationship by highlighting the role of lifetime BMI in knee OA risk. Rising secular patterns of obesity (particularly in children), combined with our ageing population, mean that the prevalence of knee OA is likely to rise in future generations. Future research into the mechanisms of knee OA in obesity and into the effectiveness of weight control across life in preserving musculoskeletal health are essential to best inform how to tackle these trends.

Acknowledgements

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Ethics approval

This study was conducted with the approval of the Medical Research Council ethics committee.

Provenance and peer review

Not commissioned; externally peer reviewed.

REFERENCES

**Supplementary material**

**S1 Clinical knee examination protocol:**

The clinical knee examination was conducted with the participant in a seated position, with their legs stretched out in front resting on another chair. Protocol dictated that the examination could be conducted over leggings, tights or most trousers, although trousers rolled up above the knee so long as to not restrict movement was preferred. Nurses were instructed to examine the knee for evidence of crepitus, bony tenderness, bony enlargement and evidence of varus or valgus knee alignment in the following ways.

Crepitus (passive) was assessed with the nurse placing a left hand over the knee cap and the right hand holding the ankle at the front, flexing the knee from full extension to a 90° flexion. The left hand was to feel for a grating sensation during the movement and again as the knee is straightened to full extension. Any palpated grating was designated as crepitus.

Bony tenderness was assessed via palpation of the antero-medial and antero-lateral joint margins with the left and right thumbs as the knee was flexed at 90°. Bony tenderness is considered present when, at uniform pressure, tenderness of the joint margin at the level of the patella but medial or lateral to it is noted by participant expression of discomfort.

Bony enlargement was assessed via palpation around the circumference of the knee joint margin for evidence of craggy cold hard swelling representing osteophyte from the femoral condyles or tibule plateau.

**S2. Additional details on the structured modelling approach used to test life course risk models:**

Models compared when using the structured life course modelling approach (1)

Fully saturated model:

$$\text{Log odds(knee OA)} = \alpha + \beta_1 \text{BMI}_1 + \beta_2 \text{BMI}_2 + \beta_3 \text{BMI}_3 + \theta_{12}\text{BMI}_1\text{BMI}_2 + \theta_{23}\text{BMI}_2\text{BMI}_3 + \theta_{13}\text{BMI}_1\text{BMI}_3 + \theta_{123}\text{BMI}_1\text{BMI}_2\text{BMI}_3$$

Compared with:

1) Adolescent period model

$$\text{Log odds(knee OA)} = \alpha + \beta_1 \text{BMI}_1$$

constraints: $\beta_2=\beta_3=0$; $\theta_{12}=\theta_{23}=\theta_{13}=\theta_{123}=0$

2) Early adulthood period model

$$\text{Log odds(knee OA)} = \alpha + \beta_2 \text{BMI}_2$$

constraints: $\beta_1=\beta_3=0$; $\theta_{12}=\theta_{23}=\theta_{13}=\theta_{123}=0$

3) Mid adulthood period model

$$\text{Log odds(knee OA)} = \alpha + \beta_3 \text{BMI}_3$$

constraints: $\beta_1=\beta_2=0$; $\theta_{12}=\theta_{23}=\theta_{13}=\theta_{123}=0$
4) Accumulation model: summed score (assuming similar effects sizes at each age)
\[
\text{Log odds(knee OA)} = \alpha + \beta \sum_j \text{BMI}_j
\]
constraints: \( \beta_1 = \beta_2 = \beta_3; \theta_{12} = \theta_{23} = \theta_{13} = \theta_{123} = 0 \)

5) Accumulation model: mutually adjusted (allowing for differences in effect size at each age)
\[
\text{Log odds(knee OA)} = \alpha + \beta_1 \text{BMI}_1 + \beta_2 \text{BMI}_2 + \beta_3 \text{BMI}_3
\]
constraints: \( \beta_1 \neq \beta_2 \neq \beta_3; \theta_{12} = \theta_{23} = \theta_{13} = \theta_{123} = 0 \)

Notes:
BMI=Body mass index (top quartile); 1=at age 15 years; 2=at age 26 years; 3=at age 43 years

S3 BMI distribution in the 1946 British Birth cohort study.

Figure S1. Median BMI and 10th, 25th, 75th and 90th centiles of BMI in males (dashed line) and females (solid line).
S4. Influence of secondary knee OA on findings:

S4.1 Results after excluding individuals who had reported seeing a GP for an acute knee injury (suspected secondary knee OA):

To examine the influence of secondary knee OA on the patterns of associations with BMI, and in particular on the sex differences, we repeated the analysis after excluding individuals who had reported consulting a Dr about a knee injury, if that knee injury was on the same limb as that diagnosed with OA. Under these criteria, 134 (44%) out of the original 302 with knee OA were suspected of having secondary knee OA and were removed from the analyses, leaving 51 male and 117 female knee OA cases.

Figures S2 and S3 show that after excluding suspected secondary OA, the results were qualitatively similar to those presented in the main paper, both in terms of the pattern of associations over life and the sex interactions. The sex interactions were weaker, mainly due to a loss of power. Figure S4 also shows that conditional BMI gain in adulthood is now more important compared to the group including suspected secondary OA.

Figure S2. Lifetime BMI z-score in men (left) and women (right) (solid line) among those with knee OA at age 53 after excluding those who had reported seeing a Dr about a knee injury to the limb in which OA was diagnosed. The shaded area is the 95% CI and the dashed line represents the BMI pattern in individuals without knee OA at age 53 years.
Figure S3. Adjusted* odds ratios (OR) for knee OA in men (filled markers) and women (open markers) after excluding suspected secondary knee OA. The left panel plots the associations per z-score increase in BMI and the right panel per raw unit (kg/m²) increase.

*Adjusted for activity levels and adult occupation (manual/ non manual)

Weak evidence for a sex interaction using standardised BMI at age 15 (p=0.1), 36 (p=0.055) and 43 years (p=0.089).

No evidence for a sex interaction using unstandardised BMI (kg/m²)

Figure S4. Adjusted* association (odds ratio) between conditional BMI change (per z-score increase) and knee OA in men (filled markers) and women (open markers) after excluding suspected secondary knee OA. The conditional BMI change intervals are infancy (2 to 7 years), childhood/adolescence (7 to 15 years), adolescence to young adulthood (15 to 20y), early adulthood (20 to 36y) and mid-adulthood (36 to 53y). Each period of BMI change is adjusted for BMI at the beginning of the interval.

*adjusted for activity levels and occupation (manual/ non manual).

Sex interactions: 20 to 36y: p=0.033.
S4.2 Additional exclusion of those with unilateral knee OA.

Previous studies have reported shown stronger associations between BMI and bilateral knee OA than unilateral knee OA (Davis., 1988). We reran models after excluding individuals with suspected secondary OA (as above – see 2.1) and/or unilateral knee OA. There were 32 (1.1%) men and 64 (2.5%) women with bilateral knee OA and no evidence of a knee injury to both joints.

The associations (point estimates of effect) were generally larger although power was diminished due to the small sample number of knee OA cases (figure S6). Figure S7 also shows that conditional BMI gain in adulthood is now important in this subset.

Figure S5. Lifetime BMI z-score in men (left) and women (right) among those with bilateral knee OA and no previously reported acute knee injury (solid line) at age 53. The shaded area is the 95% CI and the dashed line represents the BMI pattern in individuals without knee OA at age 53 years.
Figure S6. Adjusted* odds ratios (OR) for bilateral knee OA in men (filled markers) and women (open markers). The left panel plots the associations per z-score increase in BMI and the right panel per raw unit (kg/m$^2$) increase.

*adjusted for activity levels and occupation (manual/ non manual).
No evidence for a sex interaction using either scale of BMI (P>0.1).

Figure S7. Adjusted* association (odds ratio) between conditional BMI change (per z-score increase) and bilateral knee OA in infancy (2 to 7 years), childhood/adolescence (7 to 15 years), adolescence to young adulthood (15 to 20y), early adulthood (20 to 36y) and mid-adulthood (36 to 53y) in men (filled markers) and women (open markers). Each period of BMI change is adjusted for BMI at the beginning of the interval.

*adjusted for activity levels at age 36 and occupation (manual/ non manual).
No evidence for a sex interaction (p>0.1) for any intervals.
Table S1. Adult life course models for the way in which exposure to high BMI (top tertile) in adulthood might affect later life knee OA.

<table>
<thead>
<tr>
<th>BMI trajectory</th>
<th>BMI (kg/m²)</th>
<th>Knee OA</th>
<th>Life course models (test of fit against the saturated model*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median N (%)</td>
<td>n (%)</td>
<td>Accumulation (duration)†</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26y 43y</td>
<td>26y 43y</td>
<td>26y 43y</td>
<td>26y 43y</td>
</tr>
<tr>
<td>0 0</td>
<td>21.6 23.8</td>
<td>703 (56.0)</td>
<td>5.97</td>
</tr>
<tr>
<td>1 0</td>
<td>25.2 25.3</td>
<td>132 (10.5)</td>
<td>7.58</td>
</tr>
<tr>
<td>0 1</td>
<td>23.1 27.9</td>
<td>137 (10.9)</td>
<td>8.03</td>
</tr>
<tr>
<td>1 1</td>
<td>26.5 29.5</td>
<td>283 (22.6)</td>
<td>10.25</td>
</tr>
<tr>
<td>Women</td>
<td></td>
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<tr>
<td>26y 43y</td>
<td>26y 43y</td>
<td>26y 43y</td>
<td>26y 43y</td>
</tr>
<tr>
<td>1 0</td>
<td>23.8 23.9</td>
<td>153 (11.5)</td>
<td>11.76</td>
</tr>
<tr>
<td>0 1</td>
<td>21.9 28.0</td>
<td>141 (10.6)</td>
<td>17.02</td>
</tr>
<tr>
<td>1 1</td>
<td>25.6 30.1</td>
<td>291 (22.0)</td>
<td>24.39</td>
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</table>

*The saturated model allows each BMI trajectory to affect the likelihood of knee OA. The model that differs least from the saturated model in terms of explaining knee OA is the one with most support. Hence, large p-values indicate a good model (highlighted in bold).
† Accumulation (duration): this model assumes that the effect of having a high BMI is the same at each age, i.e. it is only the amount of time exposed that is important. (see text S1)
‡ Accumulation (duration and age): this model is the same as the duration model but also allows the effect of having high BMI to differ at each age, i.e, exposure time and age of exposure are allowed to influence the likelihood of knee OA (see text S1).
|| Period: These models allow the exposure to affect knee OA at one age only.
S5: Gender interactions and effect size using WHO criteria for overweight and obese.

As a comparison with previous studies we report associations between WHO categories of BMI (2) and knee OA (Table S1). We did this from 20 to 53 years because the guidelines are for adult BMI.

Table S2. Adjusted odds ratio (OR)* for knee OA in men and women per category increase in BMI (<25kg.m\(^2\); 25-30kg.m\(^2\); >30kg.m\(^2\)) at each age in adulthood, 95% CI and test of gender differences (p(sex)).

<table>
<thead>
<tr>
<th>Age</th>
<th>Men</th>
<th>Women</th>
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<tr>
<td></td>
<td>n</td>
<td>OR</td>
</tr>
<tr>
<td>20</td>
<td>&lt;25kg/m(^2)</td>
<td>2165</td>
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<tr>
<td></td>
<td>25-30kg/m(^2)</td>
<td>1.75</td>
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<tr>
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<td>&gt;30kg/m(^2)</td>
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<td>2392</td>
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<td>1.15</td>
</tr>
<tr>
<td></td>
<td>&gt;30kg/m(^2)</td>
<td>2.51</td>
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<td>&lt;25kg/m(^2)</td>
<td>2633</td>
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<td>25-30kg/m(^2)</td>
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<td>1.60</td>
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<tr>
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<td>&gt;30kg/m(^2)</td>
<td>2.44</td>
</tr>
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* adjusted for activity and occupation.
Reference List
