Body weight at early and middle adulthood, weight gain and persistent overweight from early adulthood are predictors of the risk of total knee and hip replacement for osteoarthritis

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Abstract

Objectives. To examine the relationships between weight at early and middle adulthood and adult weight gain and the risk of total knee and hip replacement for OA.

Methods. At baseline interview during 1990–94, 38,149 participants [mean age 54.9 (SD: 8.6) years] of the Melbourne Collaborative Cohort Study were asked to recall their weight at age 18–21 years and had their middle age height and weight measured. Total knee and hip replacement for OA between 2001 and 2009 was determined by linking the cohort records to the Australian Orthopaedic Association National Joint Replacement Registry.

Results. Greater weight and BMI at age 18–21 years and middle age, weight gain and persistent overweight during this time were associated with an increased risk of total knee and hip replacement. Middle age weight [hazard ratio (HR) per 5 kg 1.25 (95% CI 1.23, 1.27) for knee vs 1.11 (1.09, 1.14) for hip] and BMI [HR per 5 kg/m² 1.80 (1.82, 1.90) vs 1.29 (1.21, 1.37)] and adult weight gain [HR per 5 kg 1.25 (1.23, 1.28) vs 1.10 (1.07, 1.13)] were more strongly associated with the risk of total knee replacement than total hip replacement (P for heterogeneity of HRs <0.0001).

Conclusion. Greater body weight and BMI at early and middle adulthood, weight gain and persistent overweight from early to middle adulthood are risk factors for knee and hip OA. Adult weight gain confers stronger risk on knee OA than hip OA. Weight control from early adulthood and avoiding weight gain are important for the prevention of OA.

Key words: weight, body mass index, weight gain, overweight, osteoarthritis, total knee replacement, total hip replacement.

Introduction

Obesity is the most important modifiable risk factor for OA. It is strongly linked to the risk of knee OA with weight loss reducing the risk of knee OA [1–3], whereas evidence is less consistent for hip OA [4–9]. The impact of risk factors on OA, a chronic disease, is likely to have significant latency periods between the onset of exposure and disease onset: for obesity, the critical latency period is unknown. Greater early adult weight and BMI increase the risk of knee [2, 10, 11] and hip [11–13] OA defined by self-report, radiography or total joint replacement, and the associations are stronger than those for weight and BMI in middle age [10, 12, 13]. There are few studies reporting no
relationship between overweight in young adulthood and the risk of total knee replacement (TKR) for OA [14] or between early adulthood BMI and incident self-reported hip OA [10].

Adult weight gain has been associated with an increased risk of knee OA in two case-control studies [14, 15] and hip OA in four cohort studies [10, 12, 13, 16]. However, two other cohort studies reported no association between change in BMI between 20 and 49 years and knee OA [10] or between the rate of weight change between 34 and 47 years and weight change during the fourth and fifth decades of life with the risk of total hip replacement (THR) for OA [17]. No studies have reported whether weight gain is associated with the same or different risk for knee and hip OA. In terms of the cumulative exposure to overweight (BMI \( \geq 25 \text{ kg/m}^2 \)) to overweight after age 20, another case-control study showed a dose-response relationship between the duration of being overweight and the risk of knee and hip OA, with those who became overweight in early adulthood and maintained overweight during adult life having the highest risk of knee and hip OA [11].

Since weight is modifiable, understanding the associations between early adult weight and weight gain from early to middle adulthood and the risk of OA has the potential to inform people of lifestyle changes to prevent future OA. Our aim was to examine the relationship between weight, BMI, and adult weight gain and the risk of TKR and THR for OA in a longitudinal cohort study.

**Patients and methods**

**The cohort**

The Melbourne Collaborative Cohort Study (MCCS) is a prospective cohort study of 41,514 participants (24,469 women) aged between 27 and 75 years (99.3% aged 40–69 years) at baseline [18]. Participants were recruited via the electoral rolls (registration to vote is compulsory for Australian adults), advertisements and community announcements in local media, between 1990 and 1994. The study was approved by Cancer Council Victoria’s Human Research Ethics Committee.

**Body size assessment**

Height and weight were measured at baseline (1990–94) according to written protocols, using standard procedures [19]. Weight was measured to the nearest 0.1 kg using digital electronic scales and height to the nearest 1 mm using a stadiometer. BMI was calculated as weight (kilograms) divided by the square of height (metres). Since the mean age of participants at baseline was 54.9 (s.d. 8.6) years, weight and BMI at study entry were termed as weight and BMI at middle age. Participants were asked their weight between 18 and 21 years.

**Demographic and lifestyle factors**

At baseline, information was obtained on demographic and lifestyle factors, including date of birth, country of birth (Australia, UK, Italy, Greece), smoking status (never, past, current), alcohol consumption (g/day), physical activity during leisure time (none, low, moderate, high) and highest level of education (primary school, some high or technical school, completed high or technical school, completed tertiary degree or diploma).

Between 2003 and 2007, 28,046 participants (68% of the original cohort) were followed up by face-to-face interviews. They were asked questions concerning their first joint replacement surgery: Have you ever had a hip replacement? When did you have your first hip replacement? Have you ever had a knee replacement? When did you have your first knee replacement?

**Study participants**

Of the 41,514 participants, 3365 (8%) were excluded from the current analysis because they had missing data on weight or height at study entry or recalled weight at 18–21 years; died or left Australia before 1 January 2001; reported a joint replacement performed before 1 January 2001 at MCCS follow-up; left Australia before the date of a primary joint replacement or had the first procedure being a revision surgery as recorded in the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR). Thus, 38,149 participants had data available for analysis.

**Identification of incident primary knee and hip joint replacement**

Cases were identified from the AOA NJRR. The Registry began data collection in September 1999, with staged implementation across the Australian States and Territories. Data collection commenced in Victoria in 2001, and national data on arthroplasty procedures in Australia are available from 2002 [20]. Hip and knee joint replacements are monitored with detailed information on prostheses, demographics, reasons for revisions and types of revision available. Data are collected from both public and private hospitals and validated using a sequential multi-level matching process against State and Territory Health Department unit record data. Following the validation process and retrieval of unreported records, the Registry collects an almost complete set of data relating to hip and knee replacement in Australia [21].

Identifying information for MCCS participants, including first name, last name, date of birth and gender, was provided to the AOA NJRR in order to identify those participants who had had a primary or revision joint replacement between 1 January 2001 (commencement of Victorian data collection) and 31 December 2009. The matching was performed on these data using US Bureau of the Census Record Linkage Software. Exact matches were identified and probabilistic matches were reviewed. The AOA NJRR forwarded this information to MCCS and it was added to the MCCS database. The data linkage was approved by Cancer Council Victoria’s Human Research Ethics Committee.
Research Ethics Committee and Monash University Human Research Ethics Committee.

Statistical analysis

Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% CIs for first recorded TKR and THR associated with each anthropometric measure. Follow-up for TKR and THR (i.e. calculation of person-time) began at 1 January 2001 and ended at date of first TKR or THR for OA or date of censoring. Participants were censored at either the date of first TKR or THR for indications other than OA, the date of death, the date they left Australia or end of follow-up (i.e. 31 December 2009, when ascertainment of joint replacement by NJRR was complete), whichever came first.

Height measured at study entry was used to calculate BMI at 18–21 years. Only 507 participants reported BMI at 18–21 years of ≥30 kg/m². BMI at 18–21 years was categorized as <23 kg/m² (referent category), 23 to <25 kg/m² or ≥25 kg/m², and BMI at middle age was categorized as <25 kg/m² (referent category), 25 to <30 kg/m² or ≥30 kg/m² [22].

Weight at 18–21 years and middle age were categorized into approximate sex-specific quartiles based on the analysis sample (cut-points used: at 18–21 years: 60, 66 and 72 kg (men) and 50, 54 and 60 kg (women); at middle age: 73, 80 and 87 kg (men) and 60, 66 and 75 kg (women)). Weight gain was the absolute difference between measured weight at middle age and recalled weight at 18–21 years and was categorized into approximate quartiles based on the analysis sample (cut-points used: 5.8, 12.1 and 19.5 kg). The lowest quartile was used as the referent category for weight at 18–21 years and middle age and weight gain.

Linear associations between each anthropometric variable and the risk of TKR and THR were investigated by comparing regression models with each anthropometric variable as a categorical variable and a pseudo-continuous variable (using the median value in each anthropometric category) using the likelihood ratio test. Tests for trend across categories of each anthropometric variable (calculated using each anthropometric variable as a pseudo-continuous variable) were presented only for those variables where there was no statistical evidence of a departure from a linear association with the risk of joint replacement.

To assess whether associations between each anthropometric variable and the risk of TKR and THR were modified by sex or country of birth, interaction terms between sex or country of birth and each anthropometric variable were fitted. Models with and without interaction terms were compared using the likelihood ratio test.

### Table 1 Demographic and anthropometric characteristics

|                        | TKR     | THR     | Without hip or knee replacement |
|------------------------|---------|---------|---------------------------------|
| **Men (n = 15300)**    |         |         |                                 |
| No. participants (%)   | 424 (3) | 365 (2) | 14 511 (95)                     |
| Age at study entry (1990–94), years | 58.8 (7.6) | 58.6 (7.7) | 55.1 (8.8)                     |
| Weight at age 18–21 years, kg | 70.5 (10.1) | 68.7 (10.0) | 67.3 (9.5)                     |
| Weight at middle age, kg   | 87.4 (13.4) | 83.2 (12.4) | 80.5 (11.6)                    |
| Weight gain, kg           | 17.0 (11.9) | 14.5 (11.4) | 13.2 (10.6)                    |
| Height at middle age, cm  | 174.0 (7.3) | 172.4 (7.0) | 172.5 (7.4)                    |
| BMI at age 18–21 years, kg/m² | 23.3 (2.8) | 23.1 (2.9) | 22.6 (2.8)                     |
| BMI at middle age, kg/m²  | 28.9 (4.0) | 28.0 (3.9) | 27.1 (3.6)                     |
| Country of birth, n (%)  | 362 (85) | 312 (85) | 10 652 (73)                    |
| Australia/UK             |         |         |                                 |
| Education, n (%)         | 225 (53) | 188 (52) | 7429 (51)                      |
| **Women (n = 22,849)**  |         |         |                                 |
| No. participants (%)     | 756 (3) | 603 (3) | 21 486 (94)                    |
| Age at study entry (1990–94), years | 58.6 (7.2) | 58.7 (7.3) | 54.4 (8.6)                     |
| Weight at age 18–21 years, kg | 56.2 (9.1) | 56.5 (7.8) | 54.8 (7.9)                     |
| Weight at middle age, kg  | 75.9 (13.5) | 70.7 (12.2) | 67.7 (12.1)                    |
| Weight gain, kg           | 19.7 (12.3) | 14.2 (11.6) | 12.9 (11.2)                    |
| Height at middle age, cm  | 159.9 (6.8) | 161.2 (6.7) | 159.9 (6.7)                    |
| BMI at age 18–21 years, kg/m² | 22.0 (3.4) | 21.8 (3.0) | 21.5 (2.9)                     |
| BMI at middle age, kg/m²  | 29.7 (5.3) | 27.3 (4.9) | 26.5 (4.8)                     |
| Country of birth          |         |         |                                 |
| Australia/UK             | 635 (84) | 542 (89) | 16 615 (77)                    |
| Education                |         |         |                                 |
| Completed high/degree/diploma | 231 (31) | 256 (42) | 8063 (38)                      |

Data presented as mean (s.d.) or n (%).
To estimate HRs for TKR and THR separately and to test for heterogeneity, Cox models based on competing risks were fitted using a data duplication method [23]. All analyses were adjusted for age at baseline, country of birth, education and sex (except for sex-specific analyses). Other potential confounding variables were included if they changed the HR of any of the anthropometric variables for either TKR or THR by $\geq 5\%$. Physical activity, smoking and alcohol consumption were added to the model. The HR changed $<5\%$, thus none of them were retained for further analysis.

Tests based on Schoenfeld residuals and graphical methods using Kaplan–Meier curves showed no evidence that proportional hazard assumptions were violated. All statistical analyses were performed using Stata 11.1/IC (StataCorp LP, College Station, TX, USA).

**Results**

Over 8.4 (6.6, 1.8) years of follow-up per person, 1180 incident TKR (424 in men and 756 in women) and 972 incident THR (365 in men and 607 in women) were identified. Study participants’ demographic and anthropometric characteristics are shown in Table 1. Weight at 18–21 years and middle age were highly correlated, $r = 0.61$ (95% CI 0.60, 0.61), and BMI at 18–21 years and middle age were moderately correlated, $r = 0.42$. Weight at 18–21 years negatively associated with weight gain, $r = -0.21$ (95% CI $-0.22, -0.20$). Most of the participants (52%) had normal weight ($\text{BMI} < 25 \text{kg/m}^2$) at 18–21 years and became overweight ($\text{BMI} \geq 25 \text{kg/m}^2$) at middle age, 35% had normal weight at both 18–21 years and middle age, 12% were overweight at both 18–21 years and middle age, only 1% were overweight at 18–21 years but had normal weight at middle age.

Table 2 shows the HRs for TKR associated with weight and BMI. Using each anthropometric variable both as a categorical and as a pseudo-continuous measure, we observed statistically significant positive linear trends in the HRs for weight and BMI at 18–21 years and middle age for both men and women ($P$ for trend <0.001). Using each anthropometric variable as a continuous measure, there was no evidence for effect modification by sex on the associations between each anthropometric variable and TKR risk. The HRs were of greater magnitude for weight and BMI at middle age compared with weight and BMI at 18–21 years.

Table 3 shows the HRs for THR associated with weight and BMI. Using each anthropometric variable both as a categorical and as a pseudo-continuous measure, we observed statistically significant positive linear trends in the HRs for weight and BMI at 18–21 years and middle age for both men and women ($P$ for trend <0.001 to 0.02). Using each anthropometric variable as a continuous measure, there was a significant difference in the HRs of

**Table 2** Hazard ratios for TKR for OA in relation to weight and BMI

| Weight at age 18–21 years, kg | Men (Cases (person-years) | HR (95% CI)$^a$ | $P$ | Women (Cases (person-years) | HR (95% CI)$^a$ | $P$ |
|-----------------------------|--------------------------|------------------|-----|-----------------------------|------------------|-----|
| <60/50                      | 47 (20 861)              | 1.00             |     | 148 (42 394)               | 1.00             |     |
| 61 to <65/50 to <54         | 96 (36 044)              | 1.19 (0.83, 1.69)|     | 157 (46 673)               | 0.95 (0.76, 1.20)|     |
| 66 to <72/54 to <60         | 104 (32 020)             | 1.32 (0.93, 1.89)|     | 219 (55 061)               | 1.19 (0.96, 1.48)|     |
| $\geq 72$/>60               | 177 (37 395)             | 1.97 (1.39, 2.80)<0.001 (trend) | | 232 (48 523)               | 1.54 (1.23, 1.92)<0.001 (trend) |     |
| Linear model (per 5)$^b$    | 424 (126 320)            | 1.16 (1.11, 1.22)<0.001 | | 756 (192 651)               | 1.14 (1.09, 1.19)<0.001 |     |
| Weight at middle age, kg    |                          |                  |     |                            |                  |     |
| <73/>>60                    | 64 (31 630)              | 1.00             |     | 69 (51 185)                | 1.00             |     |
| 73 to <80/60 to <66         | 78 (33 040)              | 1.21 (0.86, 1.68)|     | 125 (44 782)               | 2.23 (1.66, 2.99)|     |
| 80 to <87/66 to <75         | 73 (29 011)              | 1.32 (0.93, 1.86)|     | 207 (51 260)               | 3.30 (2.50, 4.33)|     |
| $\geq 87$/>75               | 209 (32 639)             | 3.48 (2.55, 4.75)<0.001 (trend) | | 355 (45 424)               | 6.67 (5.11, 8.69)<0.001 (trend) |     |
| Linear model (per 5)$^b$    | 424 (126 320)            | 1.25 (1.21, 1.30)<0.001 | | 756 (192 651)               | 1.25 (1.22, 1.28)<0.001 |     |
| BMI at age 18–21 years, kg/m$^2$ |                     |                  |     |                            |                  |     |
| <23                         | 205 (74 594)             | 1.00             |     | 515 (144 639)              | 1.00             |     |
| 23 to <25                   | 117 (30 443)             | 1.40 (1.11, 1.76)|     | 137 (28 531)               | 1.33 (1.10, 1.61)|     |
| $\geq 25$                   | 102 (21 283)             | 1.85 (1.46, 2.35)<0.001 (trend) | | 194 (49 181)               | 1.64 (1.33, 2.04)<0.001 (trend) |     |
| Linear model (per 5 kg/m$^2$)$^b$ | 424 (126 320)            | 1.51 (1.29, 1.76)<0.001 | | 756 (192 651)               | 1.37 (1.23, 1.53)<0.001 |     |
| BMI at middle age, kg/m$^2$ |                          |                  |     |                            |                  |     |
| <25                         | 68 (36 000)              | 1.00             |     | 150 (82 759)               | 1.00             |     |
| 25 to <30                   | 209 (67 712)             | 1.72 (1.31, 2.27) |     | 287 (89 767)               | 2.24 (1.83, 2.73)|     |
| $\geq 30$                   | 147 (22 608)             | 4.02 (3.00, 5.39)<0.001 (trend) | | 319 (40 125)               | 4.81 (3.94, 5.88)<0.001 (trend) |     |
| Linear model (per 5 kg/m$^2$)$^b$ | 424 (126 320)            | 1.93 (1.73, 2.15)<0.001 | | 756 (192 651)               | 1.74 (1.65, 1.85)<0.001 |     |

$^a$Models adjusted for age, country of birth and education and stratified by sex. Models with weight at 18–21 years or weight at middle age also adjusted for height at middle age. $^b$Test for heterogeneity in the HRs between men and women, for weight at age 18–21 years ($P = 0.18$), weight at middle age ($P = 0.49$), BMI at age 18–21 years ($P = 0.49$) and BMI at middle age ($P = 0.13$).
BMI at middle age by sex ($P = 0.004$): the association between BMI at middle age and THR risk was stronger for men than for women. The magnitude of HRs was moderately greater for weight and BMI at middle age than weight and BMI at 18–21 years in men, while the magnitude of HRs was similar for these measures in women. Table 4 shows the HRs for TKR and THR associated with weight gain. For TKR, using weight gain as a

### Table 3 HRs for THR for OA in relation to weight and BMI

| Weight at age 18–21 years, kg | Men | | | Women | | |
|---|---|---|---|---|---|---|
| **Cases (person-years)** | **HR (95% CI)** | **P** | **Cases (person-years)** | **HR (95% CI)** | **P** |
| <50 to <60 | 60 (20 861) | 1.00 | 85 (42 394) | 1.00 |
| 61 to <66/50 to <70 | 91 (36 044) | 0.97 (0.70, 1.36) | 135 (46 673) | 1.36 (1.03, 1.79) |
| 66 to <72/54 to <60 | 84 (32 020) | 0.97 (0.68, 1.37) | 201 (55 061) | 1.67 (1.28, 2.17) |
| ≥72/≥60 | 130 (37 395) | 1.42 (1.01, 2.01) | 0.02 (trend) | 186 (48 523) | 1.78 (1.35, 2.34) | <0.001 (trend) |
| Linear model (per 5 kg)$^b$ | 365 (126 320) | 1.11 (1.05, 1.18) | <0.001 | 607 (192 651) | 1.11 (1.06, 1.17) | <0.001 |

| Weight at middle age, kg | Men | | | Women | | |
|---|---|---|---|---|---|---|
| <73/≤60 | 68 (31 630) | 1.00 | 100 (51 185) | 1.00 |
| 73 to <80/≤66 to <70 | 89 (33 040) | 1.39 (1.01, 1.92) | 149 (44 782) | 1.67 (1.30, 2.16) |
| 80 to <87/≤66 to <75 | 91 (29 011) | 1.76 (1.27, 2.44) | 171 (51 260) | 1.68 (1.30, 2.16) |<0.001 (trend) |
| ≥87/>75 | 117 (32 639) | 2.22 (1.59, 3.09) | <0.001 (trend) | 187 (45 242) | 2.16 (1.67, 2.78) | <0.001 (trend) |
| Linear model (per 5 kg)$^b$ | 365 (126 320) | 1.15 (1.10, 1.20) | <0.001 | 607 (192 651) | 1.10 (1.06, 1.13) | <0.001 |

| BMI at middle age, kg/m$^2$ | Men | | | Women | | |
|---|---|---|---|---|---|---|
| <23 | 198 (74 594) | 1.00 | 432 (144 639) | 1.00 |
| 23 to <25 | 84 (30 443) | 1.01 (0.78, 1.31) | 108 (28 531) | 1.30 (1.05, 1.61) |<0.001 (trend) |
| ≥25 | 83 (21 283) | 1.55 (1.20, 2.01) | 0.004 (trend) | 67 (19 481) | 1.36 (1.05, 1.76) | 0.003 (trend) |
| Linear model (per 5 kg/m$^2$)$^b$ | 365 (126 320) | 1.37 (1.15, 1.62) | <0.001 | 607 (192 651) | 1.28 (1.12, 1.45) | <0.001 |

| BMI at middle age, kg/m$^2$ | Men | | | Women | | |
|---|---|---|---|---|---|---|
| <25 | 80 (36 000) | 1.00 | 215 (82 759) | 1.00 |
| 25 to <30 | 195 (67 172) | 1.37 (1.06, 1.78) | 248 (69 767) | 1.42 (1.18, 1.71) |<0.001 (trend) |
| ≥30 | 90 (22 606) | 2.06 (1.51, 2.81) | <0.001 (trend) | 144 (40 125) | 1.68 (1.35, 2.08) | <0.001 (trend) |
| Linear model (per 5 kg/m$^2$)$^b$ | 365 (126 320) | 1.50 (1.32, 1.72) | <0.001 | 607 (192 651) | 1.24 (1.15, 1.35) | <0.001 |

$^a$Models adjusted for age, country of birth and education and stratified by sex. Models with weight at age 18–21 years or weight at middle age also adjusted for height at middle age. $^b$Test for heterogeneity in HRs between men and women, for weight at age 18–21 years ($P = 0.09$), weight at middle age ($P = 0.88$), BMI at age 18–21 years ($P = 0.45$) and BMI at middle age ($P = 0.004$).

### Table 4 HRs for TKR and THR for OA in relation to weight gain from age 18 to middle age

| Weight gain | Men | | | Women | | |
|---|---|---|---|---|---|---|
| **Cases (person-years)** | **HR (95% CI)** | **P** | **Cases (person-years)** | **HR (95% CI)** | **P** |
| TKR | | | | | | |
| <5.8 kg | 70 (29 607) | 1.00 | 77 (50 230) | 1.00 |
| 5.8 to <12.1 kg | 74 (32 406) | 1.25 (0.89, 1.74) | 140 (48 808) | 2.30 (1.73, 3.05) |<0.001 (trend) |
| 12.1 to <19.5 kg | 112 (32 791) | 2.05 (1.50, 2.80) | 177 (46 447) | 3.01 (2.29, 3.96) |<0.001 (trend) |
| ≥19.5 kg | 168 (31 516) | 3.62 (2.68, 4.89) | <0.001 (trend) | 362 (47 186) | 6.22 (4.83, 8.01) | <0.001 (trend) |
| Linear model (per 5 kg)$^b$ | 424 (126 320) | 1.24 (1.19, 1.29) | <0.001 | 756 (192 651) | 1.26 (1.23, 1.29) | <0.001 |

| THR | | | | | | |
|---|---|---|---|---|---|---|
| <5.8 kg | 72 (29 067) | 1.00 | 137 (50 230) | 1.00 |
| 5.8 to <12.1 kg | 94 (32 406) | 1.42 (1.04, 1.95) | 148 (48 808) | 1.31 (1.03, 1.66) |<0.001 (trend) |
| 12.1 to <19.5 kg | 91 (32 791) | 1.47 (1.07, 2.02) | 147 (46 447) | 1.37 (1.06, 1.75) |<0.001 (trend) |
| ≥19.5 kg | 108 (31 516) | 2.06 (1.49, 2.83) | <0.001 (trend) | 175 (47 166) | 1.70 (1.35, 2.15) | <0.001 (trend) |
| Linear model (per 5 kg)$^b$ | 365 (126 320) | 1.13 (1.08, 1.19) | <0.001 | 607 (192 651) | 1.08 (1.05, 1.12) | <0.001 |

$^a$Models adjusted for age, weight at age 18–21 years, height at middle age, country of birth and education and stratified by sex. $^b$Test for heterogeneity in the HRs between men and women, for hip replacement ($P = 0.21$) and knee replacement ($P = 0.39$).
pseudo-continuous measure, we observed a significant positive linear trend in the HRs for both men and women, where the increased risk per 5 kg weight gain was approximately 1.2 fold. Similar findings, with increased risk of 1.1 fold per 5 kg weight gain, were observed for THR. There was no evidence of effect modification by sex.

Table 5 compares the HRs for TKR and THR in relation to weight, BMI and weight gain. While the magnitude of associations of weight and BMI at 18–21 years was similar for TKR and THR, weight and BMI at middle age and weight gain had stronger associations with the risk of TKR than risk of THR (P for heterogeneity of HRs <0.0001).

Table 6 shows the HRs for TKR and THR associated with the level of obesity (determined by BMI). Men and women who were overweight at middle age, regardless of their weight at 18–21 years, had increased risks of TKR and THR than those with normal weight at both 18–21 years and middle age. Being overweight at both 18–21 years and middle age conferred the highest risk to TKR and THR. Men who were overweight at 18–21 years, even if they were of normal weight at middle age, still had an increased risk of TKR than those with normal weight at both 18–21 years and middle age.

**Discussion**

In a large cohort of men and women, we found that greater body weight and BMI at early and middle adulthood, weight gain and persistent overweight from early to middle adulthood are all risk factors for TKR and THR for OA, with weight and BMI at middle age and adult weight gain conferring greater risk at the knee than the hip. Weight and BMI at middle age appeared to be stronger predictors of TKR and THR than weight and BMI at early

**Table 5** Relationships of weight, BMI and weight gain with risk of TKR and THR for OA

|                      | TKR                                           | THR                                           |
|----------------------|------------------------------------------------|------------------------------------------------|
|                      | HR (95% CI)                                   | P                                             | HR (95% CI)                                   | P for heterogeneity of HRs |
| Weight and BMI at 18–21 years |                          |                                                |                                                |                           |
| Weight at 18–21 years (per 5 kg) | 1.15 (1.11, 1.19)                          | <0.001                                        | 1.12 (1.08, 1.16)                          | <0.001          | 0.20          |
| BMI at 18–21 years (per 5 kg/m²) | 1.44 (1.31, 1.57)                          | <0.001                                        | 1.30 (1.17, 1.43)                          | <0.001          | 0.13          |
| Weight and BMI at middle age |                          |                                                |                                                |                           |
| Weight at middle age (per 5 kg) | 1.25 (1.23, 1.27)                          | <0.001                                        | 1.11 (1.09, 1.14)                          | <0.001          | <0.0001       |
| BMI at middle age (per 5 kg/m²) | 1.80 (1.72, 1.89)                          | <0.001                                        | 1.29 (1.21, 1.37)                          | <0.001          | <0.0001       |
| Weight gain (per 5 kg) | 1.25 (1.23, 1.28)                          | <0.001                                        | 1.10 (1.07, 1.13)                          | <0.001          | <0.0001       |

*aModel adjusted for age, country of birth, education and height at middle age, stratifying by sex. bModel adjusted for age, country of birth and education, stratifying by sex. cModel adjusted for age, country of birth, education, height at middle age and weight at 18–21 years, stratifying by sex.

**Table 6** HRs for TKR and THR for OA in relation to obesity level at age 18–21 years and middle age

|                      | Men                             | Women                            |
|----------------------|---------------------------------|----------------------------------|
|                      | Cases (person-years)            | HR (95% CI)                      | Cases (person-years)            | HR (95% CI)                      |
| Total knee replacement|                                 |                                  |                                 |                                  |
| Normal/normal        | 61 (34 524)                     | 1.00                             | 146 (79 842)                     | 1.00                             |
| Normal/overweight    | 261 (70 512)                    | 2.29 (1.66, 2.92)                | 506 (93 326)                     | 2.93 (2.43, 3.53)                |
| Overweight/normal    | 7 (1477)                       | 2.79 (1.28, 6.11)                | 4 (2915)                        | 0.79 (0.29, 2.15)                |
| Overweight/overweight| 95 (19 806)                    | 3.02 (2.18, 4.18)                | 100 (16 566)                     | 3.78 (2.91, 4.90)                |
| Total hip replacement |                                 |                                  |                                 |                                  |
| Normal/normal        | 75 (34 524)                     | 1.00                             | 207 (79 846)                     | 1.00                             |
| Normal/overweight    | 207 (70 511)                    | 1.44 (1.10, 1.88)                | 333 (93 327)                     | 1.47 (1.23, 1.76)                |
| Overweight/normal    | 5 (1477)                       | 1.63 (0.66, 4.04)                | 8 (2915)                        | 1.12 (0.55, 2.26)                |
| Overweight/overweight| 78 (19 806)                    | 2.03 (1.47, 2.80)                | 59 (16 566)                     | 1.74 (1.30, 2.34)                |

Normal defined as BMI <25 kg/m²; overweight defined as BMI ≥25 kg/m². *Models adjusted for age, country of birth and education and stratified by sex.
adulthood. The relationship between middle age BMI and THR risk was stronger for men than women.

Weight and BMI in early adulthood have been associated with the risk of knee and hip OA [2, 10–13]. We also found that weight and BMI at 18–21 years increased the risk of TKR and THR for OA. This suggests that exposure to greater weight during young adulthood is an important contributor to knee and hip OA and thus, weight control from young adulthood is beneficial for the prevention of OA. Previous studies have shown a stronger association of early adulthood weight and BMI than middle age weight and BMI with the risk of OA [10, 12, 13]. For 1180 men of the Johns Hopkins Precursors Study, measured BMI at 20–29 years was more predictive of future self-reported knee OA than self-reported BMI at 30–39 or 40–49 years [10]. In the Nurses’ Health Study of 93,442 women, self-reported BMI at 18 years was a stronger predictor of self-reported THR for OA than self-reported current BMI [12]. Self-reported data may be subject to recall bias and error, introducing misclassification of BMI category and OA status. A cohort study of 1.2 million people showed that BMI measured at age 18–25 years was more strongly associated with the risk of THR for OA ascertained by the Norwegian Arthroplasty Register than BMI measured between 55 and 59 years [13]. However, this study did not compare the effect of young adulthood BMI with that of middle age BMI in the same individuals. In contrast, we found stronger associations of weight and BMI measured at middle age with the risk of TKR and THR ascertained by the AOA NJRR than those of recalled weight and BMI at 18–21 years. Whether young adult weight or middle age weight has a stronger impact on OA risk warrants further investigation. Although there is evidence for an association between early adult weight and the risk of OA, it is unclear whether this is a direct association or an indirect association via later life weight.

Emerging evidence suggests adult weight gain increases the risk of knee and hip OA [10, 12–16], where weight gain is from young adulthood and over decades. We also found linear associations between weight gain and the risk of knee and hip OA. While cumulative exposure to overweight increases the risk of OA [11, 14], one study showed a stronger association of a shift from normal BMI to overweight than constant overweight between 20 and 50 years with the risk of TKR for OA [14]. In contrast, we found the strongest association for constant overweight from early to middle adulthood, rather than a shift from normal to overweight, with the risk of TKR and THR. The absolute weight change within the categories of a shift from normal BMI to overweight and persistent overweight may differ between studies, which may explain the discrepant findings. Our findings suggest that weight gain over decades, as well as cumulative exposure to overweight, have adverse effects on the health of weight-bearing joints and the development or progression of OA. Thus, weight control and prevention of weight gain from early adulthood through middle age are important for the prevention of knee and hip OA.

In our study, middle age weight and BMI and adult weight gain were associated with a stronger risk for TKR than for THR. Whilst previous studies have shown stronger and more consistent evidence for the association of obesity with knee OA than hip OA [9, 24–26], none have examined the relationships with both knee and hip OA in the same population. Both mechanical and metabolic mechanisms have been implicated in the association between obesity and OA [27, 28]. The site differences for the association between obesity or weight gain and OA may be driven by biomechanical mechanism, where excess weight increases joint loading thus resulting in deleterious effects on weight-bearing joints. This mechanism may be more evident at the knee, since different morphologies and functions of the hip and knee joints may confer different abilities to withstand adverse mechanical loading. The site differences may also be affected by metabolic factors, which may have stronger effects on knee OA than hip OA. This is supported by a cohort study reporting that metabolic syndrome increased the risk of knee OA but not hip OA, although the association was attenuated after adjustment for BMI [29].

We found a stronger association between middle age BMI and the risk of THR in men than in women. This supports previous studies that showed greater association between BMI and risk of THR for OA in men than in women [13] or a weak association in men but no association in women [24]. The reason for the gender difference is unclear, but it may relate to variation in hormonal factors or anatomical hip structure. Alternatively, men are more likely to work in occupations that are associated with increased risk of hip OA; this may have confounded the associations we observed.

We had almost a complete record of TKR and THR since 2001 with the AOA NJRR as few participants left the country. However, we do not have complete and reliable joint replacement data before 2001. Although we excluded participants who reported a joint replacement prior to 2001, this information may be unreliable and is only available for 68% of the original cohort. Thus, some misclassification of joint replacement status might have occurred. As this is likely to be non-differential in relation to weight measurement, it may have resulted in underestimation of the strength of any observed associations. Furthermore, obese participants and those with weight gain were more likely to have TKR or THR soon after baseline, prior to 2001. Assessment of TKR and THR between 2001 and 2009 may have led to greater underestimation of the overall incidence of TKR and THR for obese participants and those with weight gain and have diluted the observed associations. Our study participants were asked at 40–69 years to recall their weight at 18–21 years. Self-report of past weight over a similar period to our study has shown moderate to strong correlation with measured weight (correlation coefficients range from 0.64 to 0.95), and these correlations are modified by sex and current weight [30–34]. However, the reliability of self-reported past weight is generally supported in epidemiologic studies [30, 32, 33]. The number of cases was
small for some of our analyses, particularly for the group who were overweight at 18–21 years but had normal BMI at middle age (Table 6); thus, some associations may not have been detected because of low statistical power. In addition, the information on potential confounding variables was only collected at study entry and might not be relevant to the time period we studied.

In conclusion, greater weight and BMI at early and middle adulthood, weight gain and persistent overweight from early adulthood predict TKR and THR for OA. Adult weight gain is more strongly associated with the risk of knee OA than hip OA. These findings suggest that weight control from young adulthood, in particular avoiding excessive weight gain during adulthood, is important in preventing the development or progression of OA in later life.

Rheumatology key messages

- Greater early adult weight and adult weight gain increase the risk of knee and hip OA.
- Adult weight gain confers stronger risk on knee OA than hip OA.

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