Weight gain and the risk of knee replacement due to primary osteoarthritis
A population based, prospective cohort study of 225,908 individuals

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Introduction

The strong association between BMI and OA of the knee is well established 2,3. Few have however studied the effect of weight change and the effect of weight change at different ages. In a study of life course BMI and the risk of symptomatic OA, Wills et al. reported that a high BMI from early age is positively associated with later knee OA, and that this association seems to be due to prolonged exposure rather than the impact of high BMI in this particular period 4. In a previous study of the association between weight gain and the risk of total hip replacement (THR) we found that weight gain at young age was strongly associated with later THR, whereas the association in the middle aged was small or absent 5.

We wanted to study the association between weight gain and severe OA of the knee using knee replacement (KR) due to primary OA as a marker of severe OA. We also wanted to evaluate the difference in the impact of weight gain according to age, our hypothesis being that weight gain at a young age is more detrimental to the joint than weight gain at an older age.

Objective: To study the association between weight gain and the risk of knee replacement (KR) due to primary osteoarthritis (OA), and to evaluate whether the association differs by age.

Design: 225,908 individuals from national health screenings with repeated measurements of height and weight were followed prospectively with respect to KR identified by linkage to the Norwegian Arthroplasty Register. Cox proportional hazard regression was used to calculate sex-specific relative risks (RR) of KR according to change in BMI and weight, corresponding analyses were done for age categories at first screening.

Results: During 12 years of follow up, 1591 participants received a KR due to primary OA. Men in the highest quarter of yearly change in BMI had a RR of 1.5 (95% confidence interval (CI) 1.1–1.9) of having a KR compared to those in the lower quarter. For women the corresponding RR was 2.4 (95% CI 2.1–2.7). Men under the age of 20 at the first screening had a 26% increased risk for KR per 5 kg weight gain, for women the corresponding increase was 43%. At older age the association became weaker, and in the oldest it was lost.

Conclusions: Weight gain increases the risk for later KR both in men and women. The impact of weight gain is strongest in the young, at older age the association is weak or absent. Our study suggests that future OA may be prevented by weight control and that preventive measures should start at an early age.

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Body mass index
Knee replacement
Osteoarthritis

SUMMARY
Method

Population

We included participants in population based health screenings in Norway. The National Health Screening Service (now the Norwegian Institute of Public Health), performed a nationwide compulsory Tuberculosis screening during 1963–75[5], and numerous standardized cardiovascular screenings from 1974–1994[5]. In addition, population based health screenings have been performed in the city of Oslo[1], Bergen[14], Tromsø[13], and in the county of Nord-Trøndelag[8].

Exposure variables

The person’s first weight- and height-measurement was obtained from screenings performed between 1963 and 1975; the Tuberculosis screening, the Bergen Blood Pressure Study, and the Oslo Study. The person’s second weight- and height-measurement was obtained from screenings performed between 1974 and 1994; the First and Second Cardiovascular Survey of Oppland, Finnmark and Sogn og Fjordane, the Second and the Third Tromsø Study, the First Nord-Trøndelag Health Study, and the 40-year Surveys. The purpose of the Tuberculosis screening was to identify individuals with tuberculosis in the general population, and since low weight was a known predictor for the disease, standardized measurements of weight and height were included in the screening program[9]. The other studies were all performed to investigate cardiovascular risk factors. The participants received a questionnaire which included information on smoking habits, and we categorized the participants as; never smoker, former smoker, or current smoker. Their weight and height were measured by trained nurses at consultation[10–12,15–17]. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Change in body stature was expressed as change in BMI per year: the difference in BMI between the last and the first screening divided by the numbers of years between the screenings (ΔBMI/Year). We divided the cohort into sex-specific quartiles according to the ΔBMI/Year, and compared the quartiles with greater change in ΔBMI/Year with the quartile with the lowest change in ΔBMI/Year (the reference quartile). The analyses were also performed using weight change in kilograms between the two screenings.

To investigate if there was any difference between gaining weight in persons with a low BMI at the first screening compared to those with a higher BMI at the first screening, and to investigate any effect of the amount of weight gain, we performed analyses stratifying on quartiles of BMI at the first screening and on quartiles of ΔBMI/Year.

To investigate any difference in the impact of weight gain at different ages on later knee OA, the cohort was divided into strata of 20 years according to the age at the first screening.

Endpoint

By using the national 11-digit personal identification code we were able to link the data from the health screenings with the data on performed KR's from the Norwegian Arthroplasty Register. The Norwegian Arthroplasty Register was established by the Norwegian Orthopaedic Association, and started to include information on KR’s from January 1994[14]. The operating orthopedic surgeon submits a standardized form to the register for each joint replacement performed. The form contains information on the diagnosis that lead to the operation, any previous KR or other surgery performed in the joint, the type of implant used, and information on how the procedure is performed.

The event was defined as the first recorded KR for the diagnosis of primary OA, either a total knee joint replacement with or without a patella button, or a unicompoundal KR.

Data on death and emigration was collected from the Norwegian Registry of Vital Statistics.

The start of follow up in this study was set to January 1st, 1994, the date the Norwegian Arthroplasty Register started registration of KR’s. End of follow up was set to February 1st, 2006.

Exclusion

A total of 271,537 individuals had repeated measurements of weight and height. Of these 225,908 (83.2%) were eligible for the study. We excluded individuals younger than 16 years at the initial screening (n = 29,764) and older than 80 years at start of follow up (n = 3856). We also excluded individuals who had information in the register about revision surgery, but no information on primary surgery (n = 127), individuals with irregularities in the registry data (n = 2), and individuals who according to the Norwegian Registry of vital statistics had died or emigrated before start of follow up (n = 11,880).

Statistical methods

Descriptive statistics was provided as means, standard deviation (SD) and occurrence per 10,000 person-years. Person-years were calculated as number of years form start of follow up until event, or censoring. The analyses were performed as a survival study using the Cox proportional hazard regression method, calculating hazard ratios (hereafter called relative risks (RR)) with a 95% confidence interval (CI) for having a KR.

Censoring occurred for KR performed for other diagnosis than primary osteoarthritis (OA), for death, for emigration, and at end of follow up.

The analyses regarding ΔBMI/Year and weight change were adjusted for age, BMI and height at the first screening, and for smoking habits at the second screening. ΔBMI/Year was in addition analyzed separately for age groups (17–20, 21–40 and 41–60 years). All analyses were given gender specific. Since the age at start of follow up varied among those in the same age group at first screening, the analyses were also performed adjusting for age at start of follow up.

We performed analyses stratified on BMI at the first screening and on different levels of ΔBMI/Year; e.g., comparing those who had a high BMI at the first screening and a large weight gain with those who had a low BMI at the first screening and a small weight gain per time.

We inspected Log minus log curves for each of the covariates, and the visual inspection showed approximately parallel lines indicating that the proportional hazard assumption of the Cox model was satisfied. The numbers of included individuals in the tables may vary slightly due to some missing values. The analyses were performed using the statistical program package SPSS version 19 (SPSS Inc., Chicago, IL).

The study was approved by The Norwegian Data Protection Authority, and the Regional Committee for Medical and Health Research Ethics South East.

Results

105,190 men and 120,718 women were included in the study. The mean age at first screening was 26.6 (SD 8.9) years, at second screening 44.4 (SD 8.0) years, at start of follow up 50.9 (SD 9.4) years, and at end follow up 62.3 (SD 8.4) years (for sex-specific numbers see Table I). During the 12 years of follow up, 1591
individuals (492 men and 1099 women) received their first KR for primary OA. Of these 194 were unicompartmental and 1397 were total KRs. Censoring occurred for 328 individuals because they received a KR for another condition than primary OA. The main indications for surgery in these cases were rheumatoid arthritis (n = 108), sequel after meniscal injury (n = 68), or sequel after previous fracture (n = 55). A total of 22,599 individuals were censored because they died or emigrated during follow up.

**Analyses of the total population**

The mean time between the two screenings was 17.3 years (SD 4.5). The mean increase in BMI between the screenings was 1.9 kg/m² (SD 2.8), the mean weight change was 6.0 kg (SD 8.4), and the change in height was 0.5 cm (SD 2.0) (for sex-specific numbers see Table I).

Men in the highest quartile of ΔBMI/Year had a 49% increased risk for having a KR compared to those in the quartile with the lowest ΔBMI/Year (Table II). Women in the highest quartile of ΔBMI/Year had more than doubled the RR of later KR compared to women in the lowest quartile. There was a dose–response relationship between change in ΔBMI/Year and later KR in both men and women. The analyses were also performed using weight change in kilograms (Table II). The results followed the same trends as observed when using ΔBMI/Year except for men in the upper quartile were the results were only borderline significant.

When entering ΔBMI/Year, and weight change in kilograms as continuous variables, men had an RR of 1.11 (95% CI 1.07–1.17) per 0.1 unit of ΔBMI/Year, and an RR of 1.11 (95% CI 1.05–1.17) per 5 kg of weight gain. For women the corresponding figures were 1.18 (95% CI 1.15–1.37) and 1.22 (95% CI 1.18–1.26).

We tested for possible interaction between BMI at screening, and ΔBMI/Year. There was an interaction between ΔBMI/Year and BMI at the first screening for women (P = 0.01), not for men (P = 0.83), and no interaction was found for BMI at screening and absolute weight change. To investigate this interaction we stratified on BMI at the first screening, and the RR estimates for ΔBMI/Year followed the same pattern in all the different BMI-groups as in the non-stratified analyses (data not shown).

There was a trend for increasing RR for KR for both men and women with increasing BMI at the first screening and with higher levels of ΔBMI/Year (Table III).

**Analyses according to age at first screening**

The cohort was divided into groups according to the age at their first screening. The mean time between the two screenings was 17.3 (SD 4.5) years, somewhat longer in the youngest age group (Table IV). For age specific changes in BMI, ΔBMI/Year, weight, and height see Table V.

There was no statistically significant association between change in ΔBMI/Year and the risk of having a KR in the youngest age group of men, although the point estimate suggested a more than doubled risk (Table VI). In men aged 21–40 at their first screening, there was an increase in the RR of 40% in the quartile with the greatest change in ΔBMI/Year compared to the quartile with the lowest change, whereas in the oldest age group of men there was no association. For women in the youngest age group those in the highest quartile of ΔBMI/Year had over seven times the risk of needing a KR compared to those with the lowest change. In the age group 21 to 40 at screening the risk was doubled in the highest quartile of ΔBMI/Year compared to those in the lowest quartile. In the oldest age group the association was lost (Table VI).

**Table I**

Background characteristics of the cohort of 225,908 participants

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>105,190</td>
<td>120,718</td>
</tr>
<tr>
<td>Age at first screening*</td>
<td>26.6 (8.9)</td>
<td>26.6 (9.0)</td>
</tr>
<tr>
<td>Years between screenings</td>
<td>17.3 (4.6)</td>
<td>17.4 (4.5)</td>
</tr>
<tr>
<td>Increase in BMI between screenings (kg/m²)</td>
<td>2.2 (2.5)</td>
<td>1.6 (2.9)</td>
</tr>
<tr>
<td>Increase in weight between screenings (kilos)</td>
<td>7.5 (8.5)</td>
<td>4.6 (8.0)</td>
</tr>
</tbody>
</table>

* Mean (SD).

**Table II**

Age-adjusted and RR of KR due to primary OA according to ΔBMI/Year, and weight change in a Norwegian cohort of 105,190 men and 120,718 women

<table>
<thead>
<tr>
<th>ΔBMI/Year (kg/m²/year)</th>
<th>No. of participants</th>
<th>Person-years</th>
<th>No. of KR</th>
<th>Events per 10,000 person-years</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Adjusted RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.03</td>
<td>28,019</td>
<td>337,843</td>
<td>157</td>
<td>4.65</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0.03–0.12</td>
<td>28,786</td>
<td>347,291</td>
<td>135</td>
<td>3.89</td>
<td>1.12 (0.89–1.41)</td>
<td>1.29 (1.02–1.63)</td>
</tr>
<tr>
<td>0.12–0.21</td>
<td>25,129</td>
<td>303,219</td>
<td>101</td>
<td>3.33</td>
<td>1.15 (0.89–1.49)</td>
<td>1.34 (1.03–1.73)</td>
</tr>
<tr>
<td>&gt;0.21</td>
<td>22,247</td>
<td>280,425</td>
<td>99</td>
<td>3.53</td>
<td>1.34 (1.03–1.75)</td>
<td>1.49 (1.14–1.94)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.01</td>
<td>34,030</td>
<td>409,755</td>
<td>297</td>
<td>7.25</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0.01 to 0.08</td>
<td>29,586</td>
<td>356,529</td>
<td>214</td>
<td>6.00</td>
<td>1.03 (0.86–1.22)</td>
<td>1.27 (1.06–1.52)</td>
</tr>
<tr>
<td>0.08–0.18</td>
<td>26,830</td>
<td>323,376</td>
<td>195</td>
<td>6.03</td>
<td>1.12 (0.93–1.35)</td>
<td>1.41 (1.17–1.70)</td>
</tr>
<tr>
<td>&gt;0.18</td>
<td>30,256</td>
<td>363,941</td>
<td>393</td>
<td>10.80</td>
<td>2.13 (1.83–2.49)</td>
<td>2.35 (2.01–2.74)</td>
</tr>
<tr>
<td><strong>Weight change (kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>26,333</td>
<td>317,412</td>
<td>163</td>
<td>5.14</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1.5–6.5</td>
<td>27,821</td>
<td>335,603</td>
<td>142</td>
<td>4.23</td>
<td>1.08 (0.86–1.35)</td>
<td>1.21 (1.05–1.53)</td>
</tr>
<tr>
<td>&gt;6.5</td>
<td>26,935</td>
<td>312,867</td>
<td>116</td>
<td>3.71</td>
<td>1.24 (0.97–1.60)</td>
<td>1.40 (1.06–1.80)</td>
</tr>
<tr>
<td>&gt;12.5</td>
<td>25,097</td>
<td>302,957</td>
<td>71</td>
<td>2.34</td>
<td>1.07 (0.79–1.46)</td>
<td>1.24 (0.91–1.69)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0</td>
<td>34,129</td>
<td>410,761</td>
<td>332</td>
<td>8.08</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0–4</td>
<td>29,309</td>
<td>353,019</td>
<td>247</td>
<td>7.00</td>
<td>1.09 (0.93–1.29)</td>
<td>1.36 (1.15–1.61)</td>
</tr>
<tr>
<td>4–9</td>
<td>28,460</td>
<td>355,149</td>
<td>224</td>
<td>6.28</td>
<td>1.20 (1.01–1.43)</td>
<td>1.45 (1.22–1.73)</td>
</tr>
<tr>
<td>&gt;9</td>
<td>27,800</td>
<td>334,734</td>
<td>297</td>
<td>8.87</td>
<td>2.21 (1.87–2.60)</td>
<td>2.35 (1.99–2.77)</td>
</tr>
</tbody>
</table>

* Adjusted for age, BMI, and height at first screening, and for smoking habits at second screening.

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For results of analyses using 

in those aged 21 gest women had an increased risk with 43% per weight gain of 5 kg, there was no signiﬁcant association in the men aged 21

later KR in men aged 17

grams increase in weight was associated with 26% increased risk for

RR (95% CI)

Table III

Discussion

We found a dose–response relationship between the amount of weight gain and the risk of needing a KR for primary OA. Dividing the population into age groups according to the age at the ﬁrst screening we found an association between weight gain and later KR in the youngest and those less than 40 years at their ﬁrst screening. For those older than 40 years at screening an association was not evident.

Table IV

Background characteristics of the cohort of 225,908 participants according to age at ﬁrst screening

Table V

Change in BMI, ∆BMI/Year, weight and height for the 225,908 participants according to age at ﬁrst screening

Strength and weaknesses

This is to our knowledge the ﬁrst study using information on measured weights at health screenings to show an association between weight gain at different ages and later severe knee OA leading to joint replacement. The very large number of participants from unselected Norwegian cohorts is a major strength of the study. The numbers of events are particularly large in the older age groups, lending the analysis a high statistical power to detect a possible effect of weight gain in the old.

We do not have complete information on KR’s performed before the start of follow up, and some may erroneously have been classiﬁed as not operated. This would probably most often be the case in the oldest age groups leading to an underestimation of the risk of

Table VI

Relative risk of KR due to primary OA according to ∆BMI/Year in 225,908 Norwegian men and women

Adjusted RR 95% CI

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However, Lohmander et al. (2014) demonstrated that the risk factors would be different if we had followed the participants in the study for a longer period. They studied risk factors for early, severe OA of the knee, and it may be that the risk factors for OA are different in younger age groups. Data from the Nordic arthroplasty registers indicate that the risk of severe OA has increased over time. In 1994, the risk of severe OA was 5.0% (95% CI 4.4-5.6), and in 2005, it had increased to 5.2% (95% CI 4.4-6.1). The increase in the risk of severe OA is likely due to changes in lifestyle, such as weight gain, which is a known risk factor for OA. Weight gain has been associated with increased pain, not with OA progression. There are, however, no studies that show a strong correlation between weight gain and knee OA severity.

Severe obesity is a relative contraindication to surgery, and death as competing risk is a possible bias when estimating the risk. Osteoarthritis and Cartilage (2014), http://dx.doi.org/10.1016/j.joca.2014.03.002

Since a substantial proportion of individuals older than 80 years may have medical conditions making them unfit for surgery, and may not receive a KR even if they have severe symptomatic OA, individuals older than 80 at start of follow up were not included.

Weight gain according to age

The explanation of the increased risk in those gaining weight at young age may be that their joint suffered a high load for more years than those who gained weight later in life. The association between life course BMI and symptoms of knee OA at the age of 53 was investigated by Will et al. They found that the risk of severe OA was 5.0% (95% CI 4.4-6.1). The duration of exposure through adult life rather than susceptible-age best captured the association between BMI and knee OA in their cohort. This concurs with our findings. Another possible explanation for the great impact of weight gain at young age could be that the cartilage is susceptible to damage by increased loading more in the young than in the middle aged and old. Animal studies have shown that cartilage during maturation responds to loading with changes in its collagen architecture. Regular loading has a positive effect, but there is a threshold where the tissue’s ability to adapt is exceeded. It is possible that the human cartilage has different thresholds to loading during life, and that

Table VII

Adjusted RR of KR due to primary OA per 0.1 unit of ΔBMI/Year, and per 5 kilo increase in weight

<table>
<thead>
<tr>
<th>No. of KR</th>
<th>RR/0.1 kg/m²/year (95% CI)</th>
<th>RR/5 kg (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17–20 years</td>
<td>45</td>
<td>1.26 (1.08–1.49)</td>
</tr>
<tr>
<td>21–40 years</td>
<td>360</td>
<td>1.09 (1.03–1.15)</td>
</tr>
<tr>
<td>41–60 years</td>
<td>87</td>
<td>1.12 (0.98–1.29)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17–20 years</td>
<td>82</td>
<td>1.43 (1.33–1.55)</td>
</tr>
<tr>
<td>21–40 years</td>
<td>720</td>
<td>1.24 (1.19–1.29)</td>
</tr>
<tr>
<td>41–60 years</td>
<td>297</td>
<td>1.06 (1.00–1.12)</td>
</tr>
</tbody>
</table>

* Adjusted for age, BMI, and height at first screening, and for smoking habits at second screening.
overweight at young age may therefore increase the risk of OA more than overweight at older age. We would have needed more measurements on each participant to evaluate the duration vs the susceptible-age hypothesis in our study. Wang et al. found that weight gain was associated with later knee and THRs. They used recalled weight at age 18–21, and measured weight at baseline (mean age 54 years). They found that middle-aged weight was more strongly associated with later joint replacement than weight at young age, but the weight at young age was based upon recollection, and this may have led to an underestimation. Studies have shown that individuals with a high BMI tend to under-report their weight and over-report their height. In our study body weight and height were measured in a standardized way at a consultation, circumventing the problems with self-reported weight and height.

Manninen et al. used information on recalled weight at age 20, 30 and 50 years in patients who had undergone total knee replacement (TKR) and compared them to sex and age matched controls. They found that gaining weight after the age of 20 years led to an increased risk of TKR, the effect of a shift from normal to overweight led to a higher risk for TKA compared to constant overweight. The findings concur with our study. Dawson et al. performed a case–control study with women on the waiting list for KR. They suggested that a BMI over 25 kg/m² before the age of 40 increased the risk for KR markedly, and suggested future studies to investigate weight gain at different ages.

In previous studies of the same cohort we investigated the association between weight gain and later THR for primary OA. We found an association between weight gain and later THR in the young, in the older age groups the association was weak, or absent. The trend is thus similar for weight gain and later KR and weight gain and later THR.

Conclusion

Our study suggests that gaining weight is detrimental to the knee joint. The effect of weight gain was more pronounced in women than in men and at a young age than at middle age. The obesity epidemic is severely affecting the young population. Our findings indicate that it is particularly important to prevent early weight gain to hinder the development and progression of severe knee OA.

Author contributions

H. Apold; conception and design of the study, analysis and interpretation of the data, drafted the manuscript.
HE. Meyer; conception and design of the study, analysis and interpretation of the data, revised the manuscript for important intellectual content.
L. Nordsletten; obtaining funding, conception and design of the study, revised the manuscript for important intellectual content.
O. Furnes; conception and design of the study, revised the manuscript for important intellectual content.
V. Baste; statistical expertise, revised the manuscript for important intellectual content.
GB. Flugsrud; conception and design of the study, analysis and interpretation of the data, revised the manuscript for important intellectual content.
All the authors have given their final approval of the version submitted.
H. Apold and GB Flugsrud take responsibility for the integrity of the work as a whole.

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Conflict of interest

The authors have no conflict of interest.

STROBE statement

We adhered to the strengthening of reporting of observational studies in epidemiology guidelines for cohort studies.

References


