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

H. Apold †*, H.E. Meyer ‡§, L. Nordsletten ‖¶, O. Furnes #††, V. Baste #, G.B. Flugsrud ‖

† *Orthopaedic Department, Telemark Hospital, Skien, Norway*
‡ *Norwegian Institute of Public Health, Division of Epidemiology, Oslo, Norway*
§ *Section for Preventive Medicine and Epidemiology, University of Oslo, Norway*
‖ *Orthopaedic Department, Oslo University Hospital, Oslo, Norway*
¶ *University of Oslo, Oslo, Norway*
# *The Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway*
†† *Department of Surgical Sciences, Faculty of Medicine and Dentistry, Bergen, Norway*

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SUMMARY

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 lowest 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.

Introduction

The strong association between BMI and OA of the knee is well established[1–7]. 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[2]. 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[8].

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.

* Address correspondence and reprint requests to: H. Apold, Orthopaedic Department, Telemark Hospital, Skien 3710, Norway. Tel: 47-95-87-71-79.
E-mail addresses: Hilde.apold@medisin.uio.no, hiap@sthf.no (H. Apold), h.e.meyer@medisin.uio.no (H.E. Meyer), lars.nordsletten@medisin.uio.no (L. Nordsletten), ove.furnes@helse-bergen.no (O. Furnes), valborg.baste@helse-bergen.no (V. Baste), g.b.flugsrud@medisin.uio.no (G.B. Flugsrud).

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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[9], and numerous standardized cardiovascular screenings from 1974–1994[10]. In addition, population based health screenings have been performed in the city of Oslo[11], Bergen[12], Tromsø[13], and in the county of Nord-Trøndelag[14].

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[18]. 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 medial unicondylar 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

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Table I
Background characteristics of the cohort of 225,908 participants

	Men	Women
No.	105,190	120,718
Age at first screening*	26.6 (8.9)	26.6 (9.0)
Years between screenings*	17.3 (4.6)	17.4 (4.5)
Increase in BMI between screenings (kg/m^2)*	2.2 (2.5)	1.6 (2.9)
Increase in weight between screenings (kilos)*	7.5 (8.5)	4.6 (8.0)
Increase in ΔBMI/Year between screenings (kg/m^2/year)*	0.12 (0.14)	0.09 (0.18)
Increase in height between screenings (cm)*	0.6 (2.3)	0.3 (1.6)
Age at second screening*	44.3 (7.9)	44.5 (8.1)
Age at start follow up*	50.9 (9.3)	51.0 (9.4)
Age at operation*	65.9 (8.5)	67.9 (8.5)

* Mean (SD).

individuals (492 men and 1099 women) received their first KR for primary OA. Of these 194 were unicondylar 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 ($n = 69$), 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/m^2 (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 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

	No. of participants	Person-years	No. of KR	Events per 10,000 person-years	Age-adjusted RR (95% CI)	Adjusted RR (95% CI)*
ΔBMI/Year (kg/m^2/year)						
Men						
<0.03	28,019	337,843	157	4.65	1	1
0.03–0.12	28,786	347,291	135	3.89	1.12 (0.89–1.41)	1.29 (1.02–1.63)
0.12–0.21	25,129	303,219	101	3.33	1.15 (0.89–1.49)	1.34 (1.03–1.73)
>0.21	23,247	280,425	99	3.53	1.34 (1.03–1.75)	1.49 (1.14–1.94)
Women						
<−0.01	34,030	409,755	297	7.25	1	1
−0.01 to 0.08	29,586	356,529	214	6.00	1.03 (0.86–1.22)	1.27 (1.06–1.52)
0.08–0.18	26,830	323,376	195	6.03	1.12 (0.93–1.35)	1.41 (1.17–1.70)
>0.18	30,256	363,941	393	10.80	2.13 (1.83–2.49)	2.35 (2.01–2.74)
Weight change (kg)						
Men						
<1.5	26,333	317,412	163	5.14	1	1
1.5–6.5	27,821	335,603	142	4.23	1.08 (0.86–1.35)	1.21 (0.97–1.53)
6.5–12.5	26,935	312,867	116	3.71	1.24 (0.97–1.60)	1.40 (1.09–1.80)
>12.5	25,097	302,957	71	2.34	1.07 (0.79–1.46)	1.24 (0.91–1.69)
Women						
<0	34,129	410,761	332	8.08	1	1
0–4	29,309	353,019	247	7.00	1.09 (0.93–1.29)	1.36 (1.15–1.61)
4–9	29,469	355,149	223	6.28	1.20 (1.01–1.43)	1.45 (1.22–1.73)
>9	27,800	334,734	297	8.87	2.21 (1.87–2.60)	2.35 (1.99–2.77)

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

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Table III
RR (95% CI)* for KR according to BMI at the first screening, and according to level of ΔBMI/Year

BMI at first screening (kg/m^2)	ΔBMI/Year (kg/m^2/year)			
	<0.03	0.03–0.12	0.13–0.21	>0.21
Men				
<21.3	1	0.9 (0.2–3.0)	0.9 (0.3–2.9)	1.3 (0.4–4.0)
21.3–22.9	0.9 (0.3–3.2)	2.0 (0.7–5.8)	1.9 (0.6–5.8)	3.1 (1.1–8.9)
23.0–24.8	2.4 (0.8–6.7)	2.7 (1.0–7.7)	3.6 (1.3–10.2)	4.5 (1.6–12.9)
>24.8	5.5 (2.0–15.0)	6.8 (2.5–18.6)	7.3 (2.7–20.3)	7.2 (2.6–20.0)
	<−0.01	0.01–0.08	0.09–0.18	>0.18
Women				
<20.5	1	1.1 (0.2–5.6)	1.9 (0.4–8.4)	4.8 (1.1–20.1)
20.5–22.3	3.1 (0.7–13.8)	4.5 (1.1–19.1)	6.2 (1.5–26.0)	11.1 (2.7–45.6)
22.4–24.5	7.1 (1.7–29.3)	6.7 (1.6–27.6)	10.6 (2.6–43.6)	18.8 (4.6–76.3)
>24.5	16.1 (4.0–65.1)	23.6 (5.8–95.3)	22.2 (5.5–89.9)	36.6 (9.1–147.4)

* Adjusted for age and height at first screening.

Adjusted analyses were conducted using ΔBMI/Year or weight change in kilograms as continuous variables (Table VII). Five kilograms increase in weight was associated with 26% increased risk for later KR in men aged 17–20 years at their first screening, 13% increased risk in men aged 21–40 at their first screening, whereas there was no significant association in the oldest men. The youngest women had an increased risk with 43% per weight gain of 5 kg, in those aged 21–40 the risk increased with 24% per 5 kg weight gain, and in the oldest women there was no significant association. For results of analyses using ΔBMI/Year see Table VII.

The analyses were also performed adjusting for age at start of follow up. This had little effect on the results, and the trends were the same (data not shown).

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

	Age group at first screening (years)		
	17–20	21–40	41–60
Men			
No.	32,009	62,959	10,222
Age at first screening*	18.1 (1.3)	27.8 (5.8)	45.3 (3.6)
Years between screenings*	21.0 (3.8)	15.6 (3.9)	16.3 (4.1)
Age at second screening*	39.6 (3.8)	43.8 (5.2)	62.0 (5.8)
Age at start follow up*	43.0 (1.7)	51.8 (7.1)	69.7 (3.8)
Age at operation*	53 (2.9)	65.1 (6.8)	76.1 (6.5)
Women			
No.	35,551	72,862	12,305
Age at first screening*	18.2 (1.4)	27.5 (5.8)	45.6 (3.7)
Years between screenings*	21.0 (3.7)	15.8 (3.9)	16.7 (3.8)
Age at second screening*	39.7 (3.8)	43.8 (5.4)	62.7 (5.5)
Age at start follow up*	43.1 (1.8)	51.6 (7.1)	70.1 (3.9)
Age at operation*	53.3 (2.7)	66.0 (6.5)	76.6 (4.3)

* Mean (SD).

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

Age at first screening, (years)	BMI, (kg/m^2)*	ΔBMI/Year (kg/m^2/year)*	Weight, (kg)*	Height, (cm)*
Men				
17–20	3.7 (2.6)	0.18 (0.13)	13.4 (8.8)	2.2 (3.1)
21–40	1.7 (2.2)	0.11 (0.15)	5.6 (7.0)	0.1 (1.4)
41–60	0.7 (2.0)	0.05 (0.13)	1.6 (6.1)	−0.7 (1.4)
Women				
17–20	2.2 (3.3)	0.10 (0.16)	6.8 (8.9)	1.0 (1.5)
21–40	1.5 (2.7)	0.09 (0.18)	4.2 (7.3)	0.2 (1.4)
41–60	0.6 (2.7)	0.03 (0.18)	0.7 (6.9)	−1.0 (1.7)

* Mean (SD).

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 ΔBMI/Year in 225,908 Norwegian men and women

ΔBMI/Year (kg/m^2/year)	No. of participants	Person-years	No. of KR	Events per 10,000 person-years	Adjusted RR 95% CI*
Men					
17–20 years					
<0.03	3589	43,347	5	1.15	1
0.04–0.12	8178	98,795	9	0.91	1.2 (0.4–3.6)
0.13–0.21	9921	119,822	9	0.75	1.1 (0.3–3.4)
>0.22	10,319	124,594	22	1.77	2.6 (0.9–7.2)
21–40 years					
<0.03	19,267	232,298	114	4.91	1
0.04–0.12	17,814	214,883	98	4.56	1.3 (1.0–1.7)
0.13–0.21	13,766	166,041	78	4.70	1.5 (1.1–2.0)
>0.22	12,107	145,974	70	4.80	1.4 (1.1–1.9)
41–60 years					
<0.03	5463	62,197	38	6.11	1
0.04–0.12	2794	33,613	28	8.33	1.4 (0.9–2.3)
0.13–0.21	1442	17,356	14	8.07	1.3 (0.7–2.4)
>0.22	821	9858	7	7.10	1.1 (0.5–2.5)
Women					
17–20 years					
<−0.01	8539	103,170	8	0.78	1
−0.02 to 0.08	9185	110,970	6	0.54	0.9 (0.3–2.7)
0.09–0.18	8472	102,346	15	1.47	2.7 (1.1–6.4)
>0.19	9353	112,869	53	4.70	7.5 (3.6–16.0)
21–40 years					
<−0.01	20,427	246,069	176	7.15	1
−0.02 to 0.08	17,323	17,323	131	75.62	1.3 (1.1–1.7)
0.09–0.18	16,125	194,328	130	6.69	1.5 (1.2–1.9)
>0.19	18,974	228,121	283	12.41	2.4 (1.9–2.9)
41–60 years					
<−0.01	5064	60,517	113	18.67	1
−0.02 to 0.08	3078	36,780	77	20.94	1.2 (0.9–1.6)
0.09–0.18	2233	26,702	50	18.73	1.1 (0.8–1.5)
>0.19	1929	22,950	57	24.84	1.3 (1.0–1.8)

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

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

	No. of KR	RR/0.1 kg/m^2/year (95% CI)*	RR/5 kg (95% CI)*
Men			
17–20 years	45	1.26 (1.08–1.49)	1.26 (1.09–1.45)
21–40 years	360	1.09 (1.03–1.15)	1.13 (1.06–1.21)
41–60 years	87	1.12 (0.98–1.29)	1.12 (0.95–1.31)
Women			
17–20 years	82	1.4 (1.33–1.53)	1.43 (1.33–1.55)
21–40 years	720	1.16 (1.13–1.20)	1.24 (1.19–1.29)
41–60 years	297	1.06 (1.00–1.12)	1.06 (0.99–1.15)

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

KR. Accordingly; caution should be exercised when comparing rates across age categories. However, the effect within age categories would be small. The mean age of the participants at start of follow up was however 50.9 (SD 9.4), and this is an age where only a small proportion of the population is expected to have undergone joint replacement. The completeness of reporting of primary KR's to the Norwegian Arthroplasty Register is estimated to be 99%; the number of undetected events in the study population within the follow-up period is therefore likely to be insignificant[19]. During the period of follow up data from the Norwegian Arthroplasty Register shows an increasing number of KR's performed in Norway; from 995 in 1994 to 3254 in 2005. This change in the number of performed KR's probably reflects that KR was a relative new procedure in the 90ties. Not every hospital in Norway performed the procedure in the early part of our follow up, and the indication for whom to operate may have changed as the procedure has become more common. Data from the Nordic arthroplasty registers indicate that there is a tendency to operate on younger patients now than it was in the early years of the registers[20]. These changes in indication and provision of the procedure might have biased our results. To elaborate on this we performed the analyses including only those operated after 2000. This had only minor effects on the results, with the same trends (data not shown).

The mean age at start of follow up was 50.9 years (SD 9.4), and at end of follow up 62.3 years (SD 8.4). This is an age group where the estimated need for joint replacement of the knee has not yet reached its peak. Culliford *et al.* estimated the 10-year risk for undergoing a total KR to be 1.1 % (95% CI 0.8–2.4) for a female at age 50, and 0.6% (95% CI 0.4–0.9) for a man at the same age[21]. At the age of 70 the risk had increased to 5.2% (95% CI 4.4–6.1) for men and 4.4% (95% CI 3.6–5.3) for women. One could argue that we have studied risk factors for early, severe OA of the knee, and it may be that the risk factors would be different if we had followed the population until older age.

The use of BMI as a marker of body composition can be debated. However, Lohmander *et al.* found that all measures of overweight (BMI, waist circumference, percentage of body fat, waist-hip ratio and weight) were significantly associated with severe knee OA, and the strongest gradient was observed for BMI[22]. There are some limitations to the use of change in BMI per year as exposure variable. We have no information on how each person's body stature evolved between the two screenings, e.g., whether the person gained weight rapidly the first year, or if the person had an evenly distributed weight gain throughout the whole period. To elaborate on this the analyses were also performed using weight change in kilograms between the two screenings, and in general the results followed the same pattern as for ΔBMI/Year.

We lack information on possible confounders like family history of OA, malalignment, pregnancies, physical activity at work, and at leisure. Physical activity was measured at some of the screenings, but due to the use of different questionnaires it was not possible to summarize it into one variable applicable for this study. It could be that the young weight gainers are more physically active than the old. However there is a strong relationship between low physical activity and obesity[23], and since high level of physical activity among the overweight is unlikely, it is not considered a major cause of knee OA in this group. We have previously identified a deleterious effect of the combination of high levels of BMI and strenuous activity at work on the risk of later KR (article submitted). Information on work activity would have been valuable.

Severe obesity is a relative contraindication to surgery, and this may have introduced a bias. If so, such a bias would presumably lead to an underestimation of the association between weight gain and KR, and it would be independent of age group at first screening, and not distort the association between age, weight gain and later KR. Since we studied only those with severe disease that needs KR, one could postulate that we have studied weight gain as a risk factor for progression, but it may also be that those who gained weight had more pain, and therefore more often needed joint replacement surgery, meaning that weight gain is associated with increased pain, not with OA progression. There are, however, studies that show a strong association between radiographic severity of OA and knee pain, this indicates that most of the patients receiving a joint replacement have severe OA[24].

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.

Death as competing risk is a possible bias when estimating the probability of having a KR, but would less likely influence on the association between weight change and KR. We did investigate any difference in mortality in the different quartiles of weight change, finding only moderate differences in the same age group, however caution should be made when comparing results across age groups.

One could hypothesize that an elevated BMI leads to increased joint wear, and earlier manifestation of symptomatic OA. Alternatively it could be postulated that symptomatic OA enforces a sedentary lifestyle, resulting in an increased BMI. In our investigation the mean time between the last weight and height measurements and the joint surgery was 17.2 years (SD 5.3). Such a long interval makes reverse causation between sedentary lifestyle and weight gain due to OA symptoms unlikely. Other studies have similarly shown that obesity precedes the development of OA of the knee[25].

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.*[2]. They found that the risk accumulated for those with a high BMI throughout adulthood. 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[26]. 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

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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 total knee and THRs[27]. 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[28]. 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[3]. 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[4]. They suggested that a BMI over 25 kg/m^2 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[8]. 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[29]. 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

1. Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Body mass index in young men and the risk of subsequent knee and hip osteoarthritis. Am J Med 1999;107(6):542–8.
2. Wills AK, Black S, Cooper R, Coppack RJ, Hardy R, Martin KR. Life course body mass index and risk of knee osteoarthritis at the age of 53 years: evidence from the 1946 British birth cohort study. Ann Rheum Dis 2011;71:655–60.
3. Manninen P, Riihimaki H, Heliovaara M, Suomalainen O. Weight changes and the risk of knee osteoarthritis requiring arthroplasty. Ann Rheum Dis 2004;63:1434–7.
4. Dawson J, Juszczak E, Thorogood M, Marks SA, Dodd C, Fitzpatrick R. An investigation of risk factors for symptomatic osteoarthritis of the knee in women using a life course approach. J Epidemiol Community Health 2003;57:823–30.
5. Holmberg S, Thelin A, Thelin N. Knee osteoarthritis and body mass index: a population-based case-control study. Scand J Rheumatol 2005;34:59–64.
6. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. Ann Intern Med 1992;116:535–9.
7. Nicholls AS, Kiran A, Javaid MK, Hart DJ, Spector TD, Carr AJ, *et al.* Change in body mass index during middle age affects risk of total knee arthroplasty due to osteoarthritis: a 19-year prospective study of 1003 women. Knee 2012;19:316–9.
8. Apold H, Meyer HE, Espehaug B, Nordsletten L, Havelin LI, Flugsrud GB. Weight gain and the risk of total hip replacement a population-based prospective cohort study of 265,725 individuals. Osteoarthritis Cartilage 2011;19:809–15.
9. Waaler HT. Height, weight and mortality. The Norwegian experience. Acta Med Scand Suppl 1984;679:1–56.
10. Tverdal A, Hjellvik V, Selmer R. Heart rate and mortality from cardiovascular causes: a 12 year follow-up study of 379,843 men and women aged 40–45 years. Eur Heart J 2008;29:2772–81.
11. Leren P, Askevold EM, Foss OP, Froili A, Grymyr D, Helgeland A, *et al.* The Oslo study. Cardiovascular disease in middle-aged and young Oslo men. Acta Med Scand Suppl 1975;588:1–38.
12. Mo R, Lund-Johansen P, Omvik P. The Bergen Blood Pressure Study: definition of hypertensive and normotensive families based on 27 years' follow-up. Blood Press 1992;1:230–9.
13. The Tromsø Study. http://tromsoundersokelsen.no.
14. The Nord-Trøndelag Health Study. http://www.ntnu.no/hunt/english.
15. Tverdal A, Stensvold I, Solvoll K, Foss OP, Lund-Larsen P, Bjartveit K. Coffee consumption and death from coronary heart

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disease in middle aged Norwegian men and women. BMJ: Br Med J 1990;300:566–9.
16. Thelle DS, Foorde OH, Try K, Lehmann EH. The Tromsoo heart study. Methods and main results of the cross-sectional study. Acta Med Scand 1976;200:107–18.
17. Midthjell K, Kruger O, Holmen J, Tverdal A, Claudi T, Bjorndal A, *et al*. Rapid changes in the prevalence of obesity and known diabetes in an adult Norwegian population. The Nord-Trondelag Health Surveys: 1984–1986 and 1995–1997. Diabetes Care 1999;22:1813–20.
18. Furnes O, Espehaug B, Lie SA, Vollset SE, Engesaeter LB, Havelin LI. Early failures among 7,174 primary total knee replacements: a follow-up study from the Norwegian Arthroplasty Register 1994–2000. Acta Orthop Scand 2002;73:117–29.
19. Espehaug B, Furnes O, Havelin LI, Engesæter LB, Vollset SE, Kindseth O. Registration completeness in the Norwegian Arthroplasty Register. Acta Orthop 2006;77:49–56.
20. Robertsson O, Bizjajeva S, Fenstad AM, Furnes O, Lidgren L, Mehnert F, *et al*. Knee arthroplasty in Denmark, Norway and Sweden. Acta Orthop 2010;81:82–9.
21. Culliford DJ, Maskell J, Kiran A, Judge A, Javaid MK, Cooper C, *et al*. The lifetime risk of total hip and knee arthroplasty: results from the UK general practice research database. Osteoarthritis Cartilage 2012;20:519–24.
22. Lohmander LS, Gerhardsson M, Rollof J, Nilsson PM, Engstrom G. Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass. A population-based prospective cohort study. Ann Rheum Dis 2008. ard.
23. Ching PL, Willett WC, Rimm EB, Colditz GA, Gortmaker SL, Stampfer MJ. Activity level and risk of overweight in male health professionals. Am J Public Health 1996;86:25–30.
24. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P, *et al*. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. BMJ 2009;339:b2844.
25. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, *et al*. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. Arthritis Rheum 1997;40:728–33.
26. Helminen HJ, Hyttinen MM, Lammi MJ, Arokoski JP, Lapvetelainen T, Jurvelin J, *et al*. Regular joint loading in youth assists in the establishment and strengthening of the collagen network of articular cartilage and contributes to the prevention of osteoarthrosis later in life: a hypothesis [Review] [129 Refs]. J Bone Miner Metab 2000;18:245–57.
27. Wang Y, Wluka AE, Simpson JA, Giles GG, Graves SE, de Steiger RN, *et al*. 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. Rheumatology (Oxford) 2013;52:1033–41.
28. Nawaz H, Chan W, Abdulrahman M, Larson D, Katz DL. Self-reported weight and height: implications for obesity research. Am J Prev Med 2001 May;20(4).
29. Lobstein T, Baur L, Uauy R, IASO International OT. Obesity in children and young people: a crisis in public health. Obes Rev 2004;5(Suppl l):104.

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