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Lifetime body mass index, other anthropometric measures of obesity and risk of knee or hip osteoarthritis in the GOAL case-control study

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SUMMARY

Objective: To examine the risk of large joint osteoarthritis (OA) in those becoming overweight during early adult life, and to assess the risks associated with high body mass index (BMI) and other anthropometric measures of obesity.
Methods: BMI, waist and hip circumference were measured in the GOAL case-control study comprising hip OA cases ($n = 1007$), knee OA cases ($n = 1042$) and asymptomatic controls ($n = 1121$). Retrospective estimates of lifetime weight, body shape and other risk factors were collected using an interview-lead questionnaire. Odds ratios (ORs), adjusted OR (aOR), 95% confidence intervals (CIs) and P values were calculated using logistic regression analysis.
Results: BMI was associated with knee OA (aOR 2.68, 95% CI 2.33–3.09, P-trend < 0.001) and hip OA (aOR 1.65, 95% CI 1.46–1.87, P-trend < 0.001). Those who became overweight earlier in adulthood showed higher risks of lower limb OA (P-trend < 0.001 for knee OA and hip OA). Self-reported body shape was also associated with knee OA and hip OA, following a similar pattern to current and life-course BMI measures. Waist:hip ratio (WHR) at time of examination did not associate with OA independently of BMI, except in women-only analysis. Waist circumference was associated with lower limb OA risk.
Conclusions: Becoming overweight earlier in adult life increased the risks of knee OA and hip OA. Different distribution patterns of adiposity may be related to OA risk in women.

Introduction

Body mass index (BMI) is an established risk factor for knee osteoarthritis (OA). A recent systematic review found 36 studies on BMI and all showed a positive risk for knee OA[1]. Many studies have used the current BMI of their participants, but prospective studies have shown that BMI at baseline remains a strong risk factor[2–5], and is considered an important contributor to the causes of knee OA. Weight loss can help reduce the incidence of symptomatic knee OA[6] and its effect as a treatment of knee OA have been observed by randomised controlled trials[7]. Many studies have investigated the association between BMI and hip OA, but with conflicting results. A systematic review and meta-analysis published in 2002 concluded that moderate evidence existed to associate hip OA with obesity, with an odds ratio (OR) of approximately 2[8]. However, many studies also report no association between BMI and hip OA[2,9].

The mechanism of the association between BMI and knee and hip OA traditionally was thought to be purely biomechanical, with the excess weight inducing deleterious effects on the joints. This makes the differing associations between knee and hip OA with BMI surprising because the forces from body weight pass through the hips as well as the knees, although the different morphology of the joints might explain different abilities to withstand adverse mechanical loading. However, recent advances in adipose biology have suggested the possibility that other factors may affect the joints. Patterns of distribution of adipose tissue within the body and associations with metabolic syndrome are now known, and adipocytokines are secreted by and related to adipose tissue. The adipocytokine, leptin is related to metabolic syndrome but also has direct effects on chondrocytes[10]. Associations between hand OA and

Abbreviations: IVU, intravenous urography; BMI, body mass index; WHR, waist:hip ratio; WC, waist circumference; HC, hip circumference; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence intervals.

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obesity[11] and the increased prevalence of OA in women might favour a metabolic/hormonal contribution to OA causes, rather than a simple biomechanical mechanism. Evidence of such a factor is currently weak with associations between metabolic correlates, percentage fat and body fat distribution being non-significant after adjusting for BMI[12–16]. The Chingford study, a cohort comprised only of women, identified an association between metabolic factors (hypertension, hypercholesterolemia and blood glucose) and knee OA that was independent of obesity[17].

Studies on the distribution of adipose tissue use waist:hip ratio (WHR) which is considered a surrogate marker of the central obesity useful for determination of cardiovascular risks[18], but its value for OA research is unknown. Similarly, evidence on other obesity measures such as waist circumference (WC), hip circumference (HC), body shape and risk of knee and hip OA is sparse[4].

The aim of the current study was to assess the risk of obesity, using BMI and other related anthropometric measures, on severe knee and hip OA in the large case-control study "Genetics of Osteoarthritis and Lifestyle" (GOAL).

Methods

Study population

GOAL is a case-control study including hospital-referred hip OA cases, knee OA cases and controls, designed to investigate genetic and environmental risk factors[19–22]. All participants were unrelated Caucasians living within the Nottingham area. Cases were recruited from joint surgery lists from three Nottingham hospitals or from a large joint OA clinic and all had been referred with clinically severe OA for consideration of joint replacement surgery. Controls were recruited from intravenous urography (IVU) waiting lists at the same three hospitals and had experienced no knee or hip symptoms. For this study, the group sizes were knee OA, $n = 1042$; hip OA, $n = 1007$; controls, $n = 1121$. All participants were recruited with informed consent. Ethical approval was granted by the Nottingham City Hospital Local Research Ethics Committee (reference EC02/06).

Data collection

Data was collected in two stages; an interviewer-administered lifestyle questionnaire and a clinical examination. During the clinical examination weight (kg), height (cm), maximum WC (cm) at the natural waist or umbilicus and pelvic bone HC (cm) were measured by a trained research nurse. During the interviewer-administered questionnaire individuals estimated their weight and their body shape from a diagram (Fig. 1) at each decade of life[23]. Subjects were asked if they had been diagnosed with hypertension, stroke, heart disease; type I or type II diabetes; kidney problems, cancer, depression or thyroid diseases by their doctor. Participants were classified as having "metabolic disease" if they reported heart problems, type II diabetes, stroke or hypertension. Self-reported physical activities throughout life, smoking history and female reproductive history were also recorded.

Measurement of obesity-related variables

BMI was calculated in kg/m^2 and subjects were categorised into three groups according to WHO criteria, specifically normal ($<$25 kg/m^2), overweight ($\geq$25 and $<$30 kg/m^2) and obese ($\geq$30 kg/m^2). Prior to analysis, self-reported body shapes 6–7 and 8–9 were taken to represent approximately the WHO BMI classes of "overweight" and "obese" respectively. Individuals retrospective estimates of weight and current height were used to estimate mean BMI at three stages; 20–30's, 40–50's and at their current age. Subjects were then categorised into four groups of increasing exposure to BMI throughout life. The groups were: (1) BMI $<$25 throughout life, (2) BMI $\geq$25 only at recruitment, (3) BMI $\geq$25 from middle age (40–50's) onwards and (4) BMI $\geq$25 from 20's to 30's onwards. Similar groups were derived for self-reported overweight body shape (i.e., scale >5) throughout life (Fig. 1). Control data-derived tertiles were generated to categorise subjects for WC, HC and WHR (calculated as WC/HC).

Other variables

Major risk factors for OA were included for the adjustment purposes including age, gender, occupational risk, physical activity, smoking, female reproductive history and oestrogen exposure. Longest-held occupation was classified as manual or non-manual[24] (which was used as a surrogate for social class), and also used to estimate occupation risks. Heavy work standing ($\geq$1 h per day), lifting 25 kg ($\geq$10 times per week) or lifting 50 kg or 100 kg ($\geq$1 time per week) were score for hip OA (maximum score 3). Kneeling or squatting ($\geq$1 h per day) were added for knee OA (maximum score 5)[22]. Physical activity was measured in hours per week between the ages of 10 and 50, which was categorised into groups based upon tertiles of the control population. Smoking was categorised as never, current and ex-smoker. Exposure to oestrogen was determined as low, moderate or high derived from years of menstruation, number of pregnancies, years of HRT and contraceptive pill use; and was used in female-only analyses. Occupational exposures and female reproductive history were truncated to the age when first joint replacement took place. In average, cases were truncated 3 years earlier before the recruitment date. This was therefore used to truncate all controls.

Representativeness of GOAL

The GOAL study control group was compared to other large UK studies to assess how representative the sample group was. The other studies were Norfolk EPIC[25], the Hertfordshire cohort study (HFCS)[26], Prostate[27], British National Survey[28], British Regional Heart Survey[29] and Health Survey of England 1996[30].

Statistical analysis

ORs and 95% confidence intervals (CIs) were calculated to present the relative risk of exposure. Confounding factors were adjusted for using logistic regression to generate adjusted OR (aOR). Logistic regression was performed using the variables BMI/anthropometric measures, age, gender, physical activity, metabolic disease co-morbidity, oestrogen exposure (women only), social class, smoking and occupational risks. When men and women were analysed separately, only gender and oestrogen exposure were omitted from the models. Dose–response relationships were examined whenever the data were available for graded measures and P values for linear trend are calculated. The differences in co-morbidities were assessed using the χ^2 statistic. Correlations between obesity measures were assessed by Pearson's coefficient. Anthropometric measures and BMI were included together in logistic regression models to estimate whether both independently conferred risks for OA. All analyses were performed using SPSS version 14. Statistical significance was taken when $P < 0.05$.

Results

The demographics of the GOAL study are shown in Table I. The control group had lower BMI, WC, HC, and WHR and was younger than the knee OA and hip OA groups, but contained more current smokers. The control group also had fewer subjects with self-reported metabolic diseases but more subjects with depression, kidney diseases and cancer.

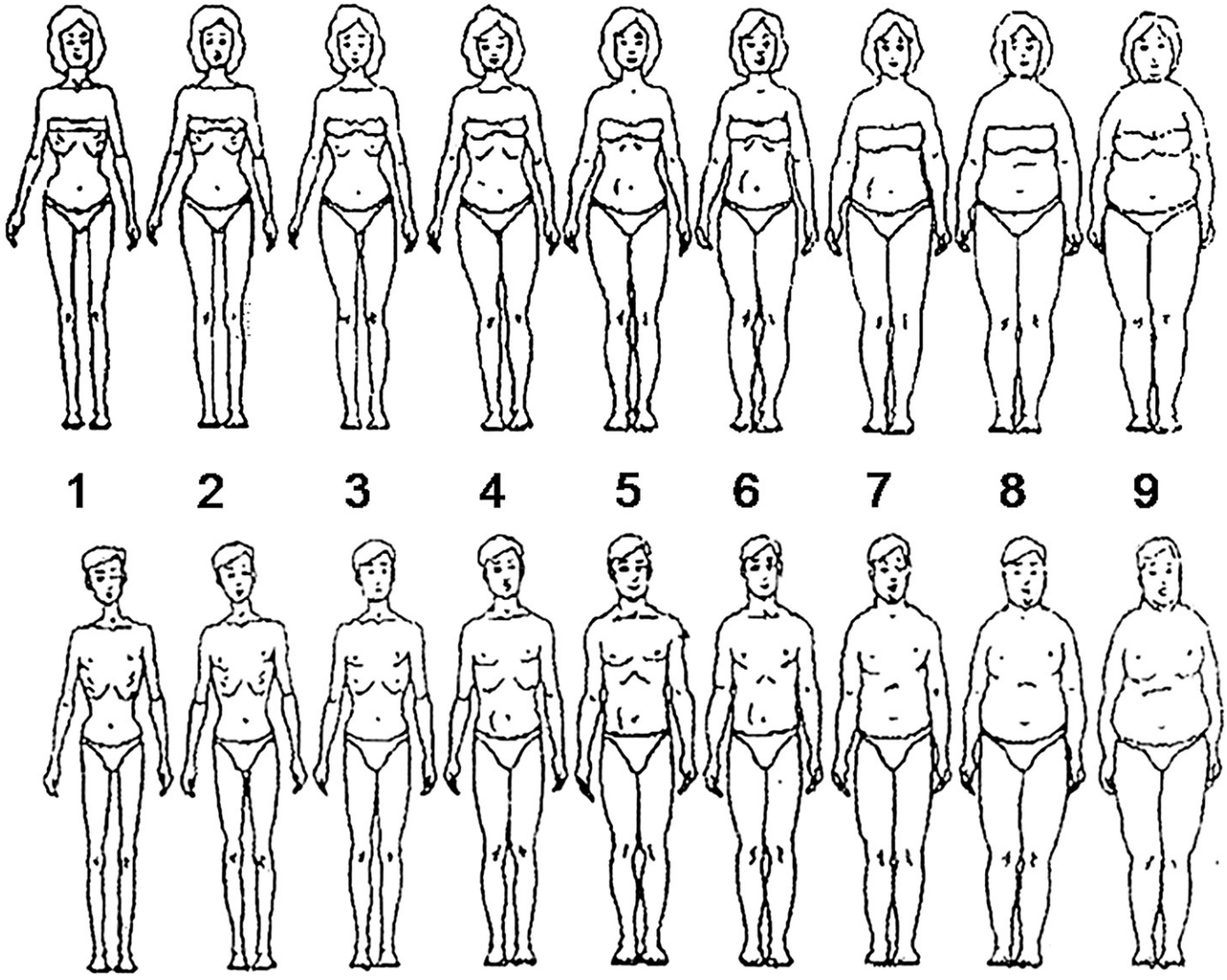

Fig. 1. Body shape diagram. Line drawing for self-assessed body shape throughout life.

Body shape and BMI were significantly correlated in each decade of life (e.g., 20–30's: $r = 0.359$, $P < 0.001$; 40–50's: $r = 0.684$, $P < 0.001$ and 60's/current: $r = 0.655$, $P < 0.001$). WC and HC were also correlated with BMI ($r = 0.76$ for WC and BMI and $r = 0.86$ for HC and BMI).

BMI

The participants' current BMI was associated significantly with knee OA (aOR 2.68, 95% CI 2.33–3.09, P-trend < 0.001) and hip OA (aOR 1.65, 95% CI 1.46–1.87, P-trend < 0.001) (Fig. 2). A dose–response relationship was found both in terms of current BMI [Fig. 2(A and B)] and the duration of being overweight [Fig. 2(C and D)].

The risk of knee OA associated with current BMI appeared to be greater in women (aOR 3.23, 95% CI 2.62–3.98, P-trend < 0.001) than men (aOR 2.20, 95% CI 1.81–2.66, P-trend < 0.001). The risks for hip OA were, however, broadly similar between genders (women aOR 1.69, 95% CI 1.41–2.04, P-trend < 0.001; and men aOR 1.51, 95% CI 1.26–1.80, P-trend < 0.001).

The participants' life-course BMI was significantly associated with knee OA (aOR 1.89, 95% CI 1.71–2.09, P-trend < 0.001) and hip

Table I
Demographics of GOAL study

	Controls	Hip OA	Knee OA
$N =$	1121	1007	1042
Age (s.d.; yrs)	64.2 (8.4)	67.6 (7.1)**	68.1 (7.4)**
% Women	46.5%	50.5%	48.6%
BMI (s.d.; kg/m^2)	27.5 (4.6)	29.3 (5.2)**	31.2 (5.4)**
WC (s.d.; cm)	95.5 (12.9)	99.5 (13.5)**	102.6 (12.7)**
HC (s.d.; cm)	106.1 (9.3)	109.5 (10.8)**	112.6 (11.2)**
WHR (s.d.)	0.898 (0.079)	0.908 (0.081)*	0.911 (0.081)**
Smoking			
Never	36%	40%	44%
Ex-	44%	50%	46%
Current	20%**	10%	10%
Manual occupation	49%	54%*	61%**
Occupational Risks	38%	43%*	51%**
Metabolic diseases	48%	55%**	61%**
Depression	23%	17%**	19%*
Kidney problems	39%	6%**	6%**
Cancer	19%	9%**	8%**

The number per group, mean (s.d.) or percentage prevalence are presented. **$P < 0.01$, *$P < 0.05$ vs controls.

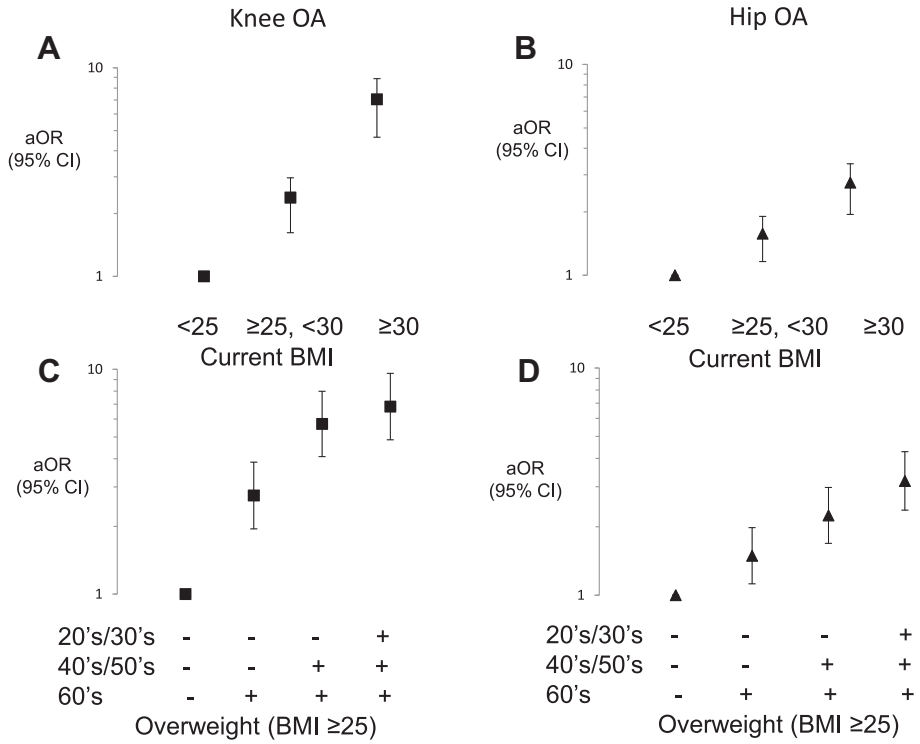

Fig. 2. BMI and risks of OA. Participants' current and self-assessed life-course BMIs were stratified and used to calculate aOR (95% CI). Current BMI and risks of (A) knee OA and (B) hip OA. Self-reported overweight (≥25) throughout life and risks of (C) knee OA and (D) hip OA. The results are adjusted for age, gender, social class, occupation, physical activity, metabolic diseases and smoking.

OA (aOR 1.46, 95% CI 1.34–1.60, P-trend < 0.001), with earlier increases in BMI conferring greater risk [Fig. 2(C and D)]. The risks of knee OA appeared greater in women (aOR 2.33, 95% CI 1.98-2.75, P-trend < 0.001) than in men (aOR 1.55, 95% CI 1.36–1.77, P-trend < 0.001). The risks of hip OA were similar between genders (women aOR 1.46, 95% 1.29–1.65, P-trend < 0.001; and men aOR 1.39, 95% CI 1.21–1.59, P-trend < 0.001).

Body shape

Similar dose–response association was observed with the self-reported body shapes (Fig. 3). The risks of knee OA associated with shape in age 60's appeared stronger in women (aOR 2.67, 95% CI 2.12–3.34, P-trend < 0.001) than in men (aOR 1.36, 95% CI 1.56–2.38, P-trend < 0.001). The risks of hip OA were similar between women (aOR 1.60, 95% CI 1.30–1.97, P-trend < 0.001) and men (aOR 1.43, 95% CI 1.17–1.75, P-trend $= 0.001$).

The risks of knee OA associated with large body shape through life were also greater in women (aOR 1.98, 95% CI 1.65–2.37, P-trend < 0.001) than in men (aOR 1.53, 95% CI 1.31–1.79, P-trend < 0.001). The risks of hip OA were similar between women (aOR 1.49, 95% CI 1.26–1.75, P-trend < 0.001) and men (aOR 1.37, 95% CI 1.18–1.58, P-trend < 0.001).

The impact of body fat distribution on OA risk

Although greater WC and HC were associated with risk for knee OA and hip OA, the association was weaker than that with BMI (Table II). After adjustment for BMI and other confounders, no increased risks for OA were found from WHR or HC. In women-only analysis, the risk for hip OA was associated with WHR (aOR 1.31, 95% CI 1.06–1.62, P-trend $= 0.013$), but not the risk for knee OA (aOR 1.05, 95% CI 0.84–1.33, P-trend $= 0.666$), and neither was related to OA in men. Smaller risks than those from BMI were observed from WC in knee OA and also hip OA (Table II). In women-only analysis the risk of knee OA was associated with increasing WC (aOR 1.53, 95% CI 1.20-1.96, P-trend $= 0.001$) as was the risk of hip OA (aOR 1.49, 95% CI 1.18-1.89, P-trend $= 0.001$), where in men the adjusted risks were close to unity.

Co-morbidities

Self-reported co-morbidities were used to classify participants as having a metabolic disease. Metabolic disease was associated with increasing BMI ($P < 0.001$) and WHR ($P < 0.001$) as well as knee OA ($P < 0.001$). The control group had higher prevalence of cancer, depression and kidney problems (Table I).

Representativeness of GOAL

The control group of GOAL was compared to other large UK studies, to assess how representative GOAL was. Major demographics are summarised in Table III, and the GOAL control group was broadly similar to these studies for age range, BMI and smoking status.

Discussion

We have undertaken an epidemiological analysis of obesity-related variables in a large case-control data set (GOAL) derived from the Nottingham region. It was observed that being overweight or obese was strongly associated with knee OA and hip OA. A trend for greater risk for knee and hip OA with increasing duration of being overweight was also found. Women consistently showed more risk for knee OA from obesity than men. The WHR was only related independently to the risk in hip

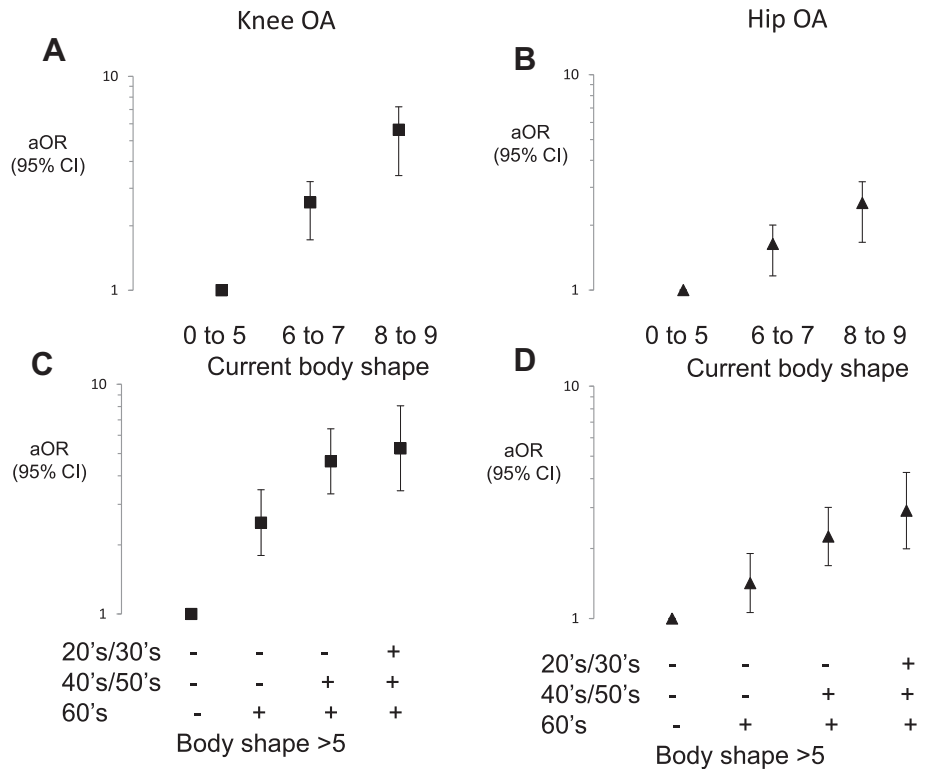

Fig. 3. Self-assessed body shape and risks of OA. Participants' self-assessed body shape on an ascending scale (0–9) was stratified and used to calculate aOR (95% CI). Current body shape and risks of (A) knee OA and (B) hip OA. Self-reported large body shape (>5) throughout life and risks of (C) knee OA and (D) hip OA. The results are adjusted for age, gender, social class, occupation, physical activity, metabolic diseases and smoking.

OA in women, whereas WC showed a wider association with the disease.

The patterns of risk observed here are consistent with previous studies showing BMI as an independent risk factor for knee OA (reviewed in Ref.[1]). Previous studies estimating risk for hip OA either found no association or else reported smaller risks than in knee OA. Here we also observed smaller estimates for hip OA risk when compared to knee OA. Our findings also support the

Table II
Risks of OA related to measures of obesity

Categories	Controls	Knee OA			Hip OA		
	N	*N*	Univariate	Adjusted†	*N*	Univariate	Adjusted†
BMI							
1	347	99	1	1	194	1	1
2	488	375	2.70 (2.08–3.51)**	2.33 (1.75–3.10)**	419	1.57 (1.26–1.95)**	1.51 (1.19–1.92)**
3	286	567	6.94 (5.33–9.05)**	7.48 (5.45–10.27)**	394	2.49 (1.97–3.14)**	2.54 (1.93–3.35)**
			P-trend < 0.001			*P*-trend < 0.001	
WHR							
1	373	308	1	1	303	1	1
2	375	327	1.06 (0.86–1.31)	0.89 (0.66–1.21)	332	1.09 (0.88–1.35)	1.08 (0.82–1.43)
3	372	402	1.31 (1.07–1.61)*	1.18 (0.76–1.83)	371	1.23 (1.00–1.51)	1.40 (0.95–2.05)
			P-trend = 0.862			*P*-trend = 0.106	
WC							
1	374	144	1	1	230	1	1
2	370	323	2.27 (1.78–2.89)**	1.44 (1.03–1.99)*	325	1.43 (1.14–1.78)**	1.38 (1.02–1.85)*
3	377	575	3.96 (3.14–5.00)**	1.59 (1.05–2.39)*	452	1.95 (1.57–2.41)**	1.45 (0.98–2.13)
			P-trend = 0.007			*P*-trend = 0.013	
HC							
1	370	142	1	1	216	1	1
2	365	283	2.02 (1.58–2.59)**	1.18 (0.87–1.61)	318	1.49 (1.19–1.87)**	1.16 (0.89–1.53)
3	386	617	4.17 (3.30–5.25)**	1.26 (0.86–1.85)	473	2.10 (1.69–2.60)**	1.06 (0.74–1.51)
			P-trend = 0.134			*P*-trend = 0.346	

The risks for lower limb OA conferred by measures of obesity are presented, to investigate whether any measures are independent risk factors. Risks for knee OA and hip OA are presented using the lowest category of BMI, WHR, WC and HC as reference. OR (95% CI) and aOR (95% CI) are presented.
**$P < 0.01$, *$P < 0.05$.
† Adjusted for age, gender, social class, occupation risks, physical activity, smoking, metabolic diseases and BMI (or WHR when BMI is dependent variable).

Table III
Comparison between GOAL and other case-control studies

	GOAL controls	HSE 1996	British National Survey	Prostate cancer controls	HFCS	Norfolk EPIC
Male						
Mean age/range	66.2 (45–81)	65–74	55–64	68.3 (44–77)	66	65–74
Mean BMI	27.7	27	N/C	N/C	26.8	26.7
Never smoked %	27	18	31	25	32	N/C
Ex-smoker %	54	60	49	58	51	N/C
Current smoker %	19	22	20	17	17	N/C
Female						
Mean age/range	61.8 (45–81)	65–74	55–64	N/C	65.5	65–74
Mean BMI	27.3	27.3	N/C	N/C	26.7	26.6
Never smoked %	45	36	52	N/C	60	N/C
Ex-smoker %	32	40	27	N/C	29	N/C
Current smoker %	27	24	21	N/C	11	N/C

A comparison of demographics between GOAL and other large UK studies. HSE – Health Survey of England; N/C – not compared to GOAL.

prospective studies where increasing BMI earlier in life was a risk factor for knee OA[31,32]. Also, our findings support those from Lohmander *et al.* where WHR and other measures of obesity were poorly associated with OA once BMI had been accounted for[4].

Gender differences in the risk for knee OA conferred by BMI were evident in our study, and have been reported by other groups[33]. Hip OA risks conferred by BMI and body shape did not appear to vary between genders. Our estimate of oestrogen exposure did not greatly alter the risks, although it was compiled from self-reported medical histories which will lack some degree of accuracy.

The literature mostly suggests that body fat distribution is not associated with OA[14–16,34], independently of BMI, as with our global observations of WHR. Numerically, WHR did not vary greatly between cases and controls, despite the differences achieving statistical significance. However, in women-only analyses, associations were found between WHR and OA, which may indicate a gender difference in obesity-related risk. Some recent studies have observed a BMI-independent association between knee OA and WC[4,35], which we also report here and which appears to be restricted to the female cases. Patients with OA displayed increased prevalence of metabolic diseases, although these were self-reported during the interview. In other studies, patients with knee OA were more likely to have metabolic syndrome, although the association may not be independent of confounders[36]. The Chingford study, however, identified an association between metabolic factors (hypertension, hypercholesterolemia, and blood glucose) and knee OA in women that was independent of obesity[17]. The metabolic and endocrine actions of adipose tissue, such as leptin production, may contribute to OA, possibly to a greater extent in women. However, little is known at present about any potential mechanisms. In addition to metabolic diseases, the GOAL control group also had higher prevalence of depression, cancer and kidney problems, which is likely to be due to their recruitment from hospital IVU lists.

The GOAL case-control study was designed for the purpose of OA risk factor characterisation and is sufficiently powered to investigate association with genes and lifestyle/clinical risk factors[19–22]. The GOAL study group appears to be representative of other large UK studies. The BMI of the GOAL control group was comparable to that of other control groups in a number of UK case-control and cohort studies suggesting that there were not substantial biases during selection. GOAL is also a retrospective study with most of the cases having already undergone joint replacements, therefore, measures of BMI, WC and HC are subsequent to disease. The data used for the analysis of life-course BMI are estimates of weight within each decade of life, which may be subject to recall bias and error, and the BMI was calculated using height, as measured in the study, which means that some calculated BMIs will be overestimates due to subjects losing height with age. However, this effect is probably minimal and will occur across the whole data set. All measures of obesity were classified into three groups, minimising the effects of small inaccuracies on the analyses. Another limitation in this analysis is the ability to accurately measure WC and HC. It is particularly difficult to determine HC in larger individuals. It also gives no indication to the type of fat, subcutaneous or visceral.

In conclusion obesity, as measured by BMI, is a major risk factor for OA, with the extent of the risk differing due to the affected joint, duration of exposure and possibly gender. Here WHR was not an independent risk factor for lower limb OA, after accounting for BMI.

Contributions

Conception and design of study: Kate Holliday, Daniel McWilliams, Kenneth Muir, Rose Maciewicz, Weiya Zhang, Michael Doherty.

Acquisition of data: Kate Holliday.

Analysis and interpretation of data: Kate Holliday, Daniel McWilliams, Kenneth Muir, Rose Maciewicz, Weiya Zhang, Michael Doherty.

Drafting and important revisions: Kate Holliday, Daniel McWilliams, Kenneth Muir, Rose Maciewicz, Weiya Zhang, Michael Doherty.

Final approval: Kate Holliday, Daniel McWilliams, Kenneth Muir, Rose Maciewicz, Weiya Zhang, Michael Doherty.

Daniel McWilliams (dan.mcwilliams@nottingham.ac.uk) and Michael Doherty (michael.doherty@nottingham.ac.uk) take responsibility for the integrity of this work.

Competing interests

Rose Maciewicz owns stocks in AstraZeneca UK and is named on a patent application for a gene associated with OA. No other authors have competing interests to declare.

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