ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 4, April 2016, pp 817–825
DOI 10.1002/art.39486

Obesity and the Relative Risk of Knee Replacement Surgery in Patients With Knee Osteoarthritis

A Prospective Cohort Study

Kirsten M. Leyland,[1] Andrew Judge,[2] M. Kassim Javaid,[2] Adolfo Diez-Perez,[3] Andrew Carr,[4] Cyrus Cooper,[2] Nigel K. Arden,[1] and Daniel Prieto-Alhambra[5]

Objective. **It is unclear what impact obesity has on the progression of knee osteoarthritis (OA) from diagnosis to knee replacement surgery. This study was undertaken to examine the relative risk of knee replacement surgery in overweight and obese patients who were newly diagnosed as having knee OA in a community setting.**

Methods. **Subjects were selected from the Information System for Development of Primary Care Research database, which compiles comprehensive clinical information collected by health care professionals for >5.5 million people in Catalonia, Spain (80% of the population). Patients newly diagnosed as having knee OA in primary care between 2006 and 2011 were included. Knee replacement was ascertained using International Classification of Diseases, Ninth Revision, Clinical Modification codes from linked hospital admissions data. Multivariable Cox regression models were fitted for knee replacement according to body mass index (BMI), and were adjusted for relevant confounders. Population proportional attributable risk was calculated.**

Results. **A total of 105,189 participants were followed up for a median of 2.6 years (interquartile range 1.3–4.2). Of these patients, 7,512 (7.1%) underwent knee replacement. Adjusted hazard ratios and 95% confidence intervals (95% CIs) for knee replacement for the World Health Organization BMI categories were 1.41 (95% CI 1.27–1.57) for overweight, 1.97 (95% CI 1.78–2.18) for obese I, 2.39 (95% CI 2.15–2.67) for obese II, and 2.67 (95% CI 2.34–3.04) for obese III compared to normal weight. The effect of BMI on risk of knee replacement was stronger among younger participants. The population attributable risk of obesity for knee OA–related knee replacement was 31.0%.**

Conclusion. **Overweight and obese patients are at >40% and 100% increased risk of knee replacement surgery, respectively, compared to patients with normal weight. This association is even stronger in younger patients. Weight reduction strategies could potentially reduce the need for knee replacement surgery by 31% among patients with knee OA.**

Osteoarthritis (OA) contributes to the global health burden due to pain and disability, the cost of treatment, and loss of work (1). The prevalence of knee OA, particularly, has been predicted to rise sharply in the future due to the aging population and the ongoing obesity epidemic (2–4). Knee replacements are a common surgical option for joint failure from end-stage disease combined with pain and/or

Supported by the IDIAP Jordi Gol Primary Care Research Institute, the Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, and the MRC Lifecourse Epidemiology Unit Southampton.

[1]Kirsten M. Leyland, DPhil, Nigel K. Arden, MBBS, FRCP, MSc, MD: University of Oxford and the Arthritis Research UK Centre for Sport, Exercise, and Osteoarthritis, Oxford, UK; [2]Andrew Judge, PhD, M. Kassim Javaid, MBBS, BMedSci, MRCP, PhD, Cyrus Cooper, MA, DM, FRCP, FFPH, FMedSci: University of Oxford, Oxford, UK, and University of Southampton, Southampton, UK; [3]Adolfo Diez-Perez, MD, PhD: FIMIM-Parc Salut Mar and Red Tematica de Envejecimiento y Fragilidad (RETICEF), Barcelona, Spain; [4]Andrew Carr, DSc, FRCS, FMedSci: University of Oxford, Oxford, UK; [5]Daniel Prieto-Alhambra, MD, PhD: University of Oxford, Oxford, UK, FIMIM-Parc Salut Mar and RETICEF, Barcelona, Spain, and GREMPAL Research Group, IDIAP Jordi Gol Primary Care Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain.

Dr. Judge has received consulting fees from Anthera Pharmaceuticals Inc. (more than $10,000) and Servier (less than $10,000) and research support from Roche. Dr. Prieto-Alhambra has received unrestricted research grants from Bioiberica SA and Amgen Spain.

Address correspondence to Daniel Prieto-Alhambra, MD, PhD, Botnar Research Centre, NDORMS, University of Oxford, Nuffield Orthopaedics Centre, Oxford OX3 7LD, UK. E-mail: Daniel.prietoalhambra@ndorms.ox.ac.uk.

Submitted for publication November 24, 2014; accepted in revised form October 20, 2015.

functional limitations. Surgery is expensive (costing £7,458 per patient in England for surgery alone), and ~20% of patients are not satisfied 1 year after surgery (5–7).

Known risk factors for progression of incident and progressive knee OA include both biomechanical and systemic/genetic factors. Local, joint-specific risk factors include abnormal joint loading, knee alignment, trauma, and obesity (8–11), and systemic factors include age, sex, ethnicity, and nutrition (3,8,12–15). Factors that have been specifically linked to progression in subjects previously diagnosed as having OA include knee alignment, low vitamin D and C levels, and obesity (11,16–19).

Obesity is an established risk factor for both the development and progression of knee OA, although some conflicting results have previously been reported in population-based studies (11,16,18–21). Cooper et al (16) found that subjects in the highest body mass index (BMI) tertile had 18.6 times the risk of incident radiographic OA compared to the lowest tertile, although BMI was not found to be a significant indicator of radiographic OA progression. Similar results were found in a population at high risk of OA, with subjects in the highest obesity group having an increased risk of radiographic OA, with a relative risk (RR) of 3.2 (95% confidence interval [95% CI] 1.7–5.9), but that study found no association between obesity and risk of progression (22). High BMI was found to be significantly associated with joint space narrowing in several studies (18,19). Obese subjects have also been found to be at increased risk of severe incident pain (RR 2.8 [95% CI 1.8–4.5]) (20). Obesity has been associated with an increased risk of surgery in a community population (23,24). Having a high BMI has been identified as a factor in reducing the mean age at which surgery is required (25) as well as increasing the expense of and complications after surgery (26,27). Coggon et al (28) found a significantly increased risk of knee surgery in obese subjects in a case–control study of UK-based subjects, where cases were identified on a surgery list and matched to non-OA patients. Weight reduction strategies have been shown to reduce functional limitations due to OA in a randomized controlled trial (29).

Understanding the effect of obesity on the risk of progression to end-stage disease is clinically important, since it is one of the few modifiable risk factors for knee OA. Although some data have shown its effect on incidence and progression, to our knowledge there are no studies showing the effect of obesity on the risk of knee replacement in a population with incident knee OA. The use of an incident population provides a more homogenous patient sample which should exclude patients with well-established symptomatic knee OA, compared to a prevalent baseline sample. It will also add useful information regarding the clinical pathway for knee OA. This study examines the association between being overweight or obese and the risk of knee replacement surgery in a large population-based study of patients newly diagnosed as having knee OA.

PATIENTS AND METHODS

Data source. Subjects were selected from the Information System for Development of Primary Care Research (SIDIAP) database (www.sidiap.org), which comprises clinical information collected by primary care professionals, pharmacy records, and hospital admissions. The database includes information on >5.5 million people in Catalonia, Spain (~80% of the population) (30).

Study design and population. A population-based cohort study was conducted. All patients registered in SIDIAP who had an incident diagnosis of knee OA (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10] code M17) between 2006 and 2011 were eligible. Subjects with a history of knee OA or replacements in either knee before January 1, 2006 were excluded from the study. Subjects with a history of inflammatory arthritis at any time point during the study and those with no recorded information on BMI were excluded in the primary analysis. OA diagnosis has previously been validated in the

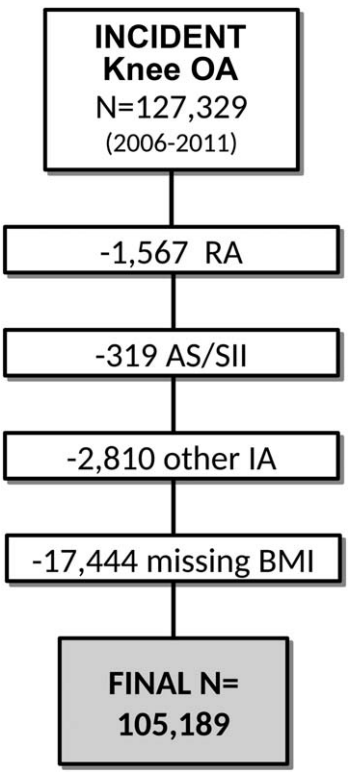

Figure 1. Flow chart of the study population. OA = osteoarthritis; RA = rheumatoid arthritis; AS = ankylosing spondylitis; SII = sacroiliitis; IA = inflammatory arthropathies; BMI = body mass index.

SIDIAP cohort using self-reported OA data from the Global Longitudinal Study of Osteoporosis in Women (GLOW) cohort (31) as well as a sensitivity analysis comparing a subset of free text notes in medical records with general practitioner (GP)–reported ICD-10 codes in the SIDIAP database (32).

Study participants were followed up from the date of knee OA diagnosis (index date) until the date they underwent elective knee replacement surgery, the date they were lost to follow-up (died or moved), or the end date of the study (December 31, 2011). The study was approved by the relevant ethics committee (Comitè d'Ètica Idiap Jordi Gol; reference number P12/72).

Measurement of BMI (main exposure). BMI measurements were obtained in primary care as part of routine clinical practice. BMI as recorded by GPs or primary care nurses in computerized records was extracted from the SIDIAP database. Index BMI was defined as the last measurement obtained in the 5 years prior to the date of diagnosis of knee OA, and was classified into the following World Health Organization categories: normal (<25 kg/m^2), overweight (25–<30 kg/m^2), obese class I (30–<35 kg/m^2), obese class II (35–<40 kg/m^2), and obese class III (≥ 40 kg/m^2). This was defined as the main study exposure.

Knee replacement surgery (study outcome). Hospital admissions for an elective knee replacement were identified from the official regional hospital admissions database (Registre de Conjunt Mínim Bàsic de Dades, Divisió de Registres de Demanda i d'Activitat, Àrea de Serveis i Qualitat, Servei Català de la Salut), which contains information on diagnoses and procedures for each hospital admission for all of the public hospitals in the region of Catalonia. After successful deterministic linkage of all of the study participants to this database using unique Catalan National Health System identifiers, we screened the hospitalizations database for the ICD-9-CM procedures code 81.54 ("Total knee replacement: Bicompartmental, Tricompartmental or Unicompartmental") to identify knee replacement surgeries. The first knee replacement date (closest to the date of diagnosis of knee OA) in the study period was the study outcome.

Confounders. The potential confounders identified a priori for this analysis were age, sex, smoking, alcohol consumption, Charlson comorbidity index (33), hip OA, polyarticular OA, and socioeconomic status. Self-reported smoking was recorded as former, current, or never. Alcohol use was divided into 3 categories based on units consumed per week: none/mild, moderate, and severe. Hip OA and polyarticular OA were recorded as present if a subject had specific ICD-10 codes recorded by their GP for hip OA (M16) or for polyarticular OA (M15). The Charlson comorbidity index was calculated using a validated algorithm (33). Socioeconomic status was evaluated using the MEDEA socioeconomic deprivation score (34), which was divided into quintiles for the analysis.

Statistical analysis. Multivariable Cox regression models were fitted to model the time from incident knee OA diagnosis to knee replacement surgery, and to estimate hazard ratios (HRs) according to the index BMI, using normal weight as the reference group. These models were adjusted for prespecified potential confounders, including age, sex, smoking, alcohol consumption, Charlson comorbidity index (33), hip OA, polyarticular OA, and socioeconomic status. A priori interac-

Table 1. Baseline characteristics of the study participants according to BMI category*

	Normal (<25 kg/m^2) (n = 11,466)	Overweight (25 to <30 kg/m^2) (n = 39,788)	Obese I (30 to <35 kg/m^2) (n = 34,657)	Obese II (35 to <40 kg/m^2) (n = 13,823)	Obese III (≥ 40 kg/m^2) (n = 5,455)	Missing BMI data (n = 17,444)
Age, mean ± SD years	68.2 ± 12.6	69.0 ± 10.7	68.5 ± 10.1	66.6 ± 10.0	63.9 ± 10.1	65.8 ± 13.1
Sex, male	3,945 (34.4)	16,018 (40.3)	11,551 (33.3)	2,932 (21.2)	787 (14.4)	6,478 (37.1)
Smoking						
Current smoker	1,973 (17.3)	5,036 (12.7)	3,858 (11.1)	1,380 (10.0)	607 (11.1)	2,165 (12.4)
Ex-smoker	691 (6.0)	3,155 (7.9)	2,647 (7.6)	792 (5.7)	236 (4.3)	839 (4.8)
Never smoker	8,373 (73.0)	30,605 (76.9)	27,404 (79.1)	11,383 (82.4)	4,514 (82.8)	9,628 (55.2)
Missing	429 (3.7)	992 (2.5)	748 (2.2)	268 (1.9)	98 (1.8)	4,812 (27.6)
Alcohol drinking						
None/mild	6,880 (60.0)	23,465 (59.0)	21,804 (62.9)	9,546 (69.1)	3,948 (72.4)	6,609 (37.9)
Moderate	2,768 (24.1)	10,819 (27.2)	8,440 (24.4)	2,631 (19.0)	849 (15.6)	2,314 (13.3)
Severe	292 (2.6)	960 (2.4)	877 (2.5)	275 (2.0)	79 (1.4)	203 (1.2)
Missing	1,526 (13.3)	4,544 (11.4)	3,536 (10.2)	1,371 (9.9)	579 (10.6)	8,318 (47.7)
Socioeconomic deprivation (MEDEA)						
1st quintile	2,767 (24.1)	8,086 (20.3)	5,920 (17.1)	2,188 (15.8)	748 (13.7)	4,210 (24.3)
2nd quintile	2,305 (20.1)	7,772 (19.5)	6,376 (18.4)	2,346 (17.0)	864 (15.8)	3,487 (20.0)
3rd quintile	2,183 (19.0)	7,673 (19.3)	6,809 (19.7)	2,647 (19.2)	987 (18.1)	3,195 (18.3)
4th quintile	1,950 (17.0)	7,623 (19.2)	7,069 (20.4)	2,927 (21.1)	1,180 (21.6)	3,000 (17.2)
5th quintile	1,704 (14.9)	6,986 (17.6)	7,115 (20.5)	3,168 (22.9)	1,432 (26.3)	2,488 (14.3)
Missing	557 (4.9)	1,648 (4.1)	1,368 (3.9)	547 (4.0)	244 (4.5)	1,064 (6.1)
Charlson comorbidity index						
0	7,049 (61.5)	23,425 (58.9)	19,415 (56.0)	7,555 (54.7)	2,802 (51.4)	12,820 (73.5)
1	3,118 (27.2)	11,559 (29.1)	10,610 (30.6)	4,306 (31.1)	1,824 (33.4)	3,428 (19.7)
2	919 (8.0)	3,539 (8.9)	3,368 (9.7)	1,482 (10.7)	596 (10.9)	880 (5.0)
3	273 (2.4)	963 (2.4)	955 (2.8)	354 (2.6)	176 (3.2)	241 (1.4)
≥ 4	107 (0.9)	302 (0.7)	309 (0.9)	126 (0.9)	57 (1.1)	75 (0.4)

* Except where indicated otherwise, values are the number (%).

Table 2. Baseline characteristics of the study participants as recorded by primary care physicians*

	No knee replacement (n = 97,677)	Knee replacement (n = 7,512)	*P*
Age, mean ± SD years	68.0 ± 10.9	70.2 ± 7.7	<0.001
Sex, male	32,979 (33.8)	2,254 (30.0)	<0.001
BMI, mean ± SD kg/m^2	30.6 ± 5.1	32.0 ± 5.0	<0.001
BMI categories			
Normal/underweight	11,039 (11.3)	427 (5.7)	
Overweight	37,438 (38.3)	2,350 (31.3)	
Obese I	31,792 (32.6)	2,865 (38.1)	
Obese II	12,475 (12.8)	1,348 (17.9)	
Obese III	4,933 (5.1)	522 (7.0)	
Time from BMI measurement, median (IQR) years†	2.4 (0.8–4.1)	1.6 (0.4–3.1)	
Smoking			
Current smoker	12,233 (12.5)	621 (8.3)	<0.001
Ex-smoker	7,070 (7.2)	451 (6.0)	
Never smoker	75,961 (77.8)	6,318 (84.1)	
Missing	2,413 (2.5)	122 (1.6)	
Alcohol drinking			
None/mild	60,713 (62.2)	4,930 (65.6)	<0.001
Moderate	23,839 (24.4)	1,668 (22.2)	
Severe	2,347 (2.4)	136 (1.8)	
Missing	10,778 (11.0)	778 (10.4)	
Socioeconomic deprivation (MEDEA)			
1st quintile (least deprived)	18,400 (18.8)	1,309 (18.2)	0.004
2nd quintile	18,162 (18.6)	1,501 (20.8)	
3rd quintile	18,834 (19.3)	1,465 (20.3)	
4th quintile	19,255 (19.7)	1,494 (20.7)	
5th quintile (most deprived)	18,968 (19.4)	1,437 (19.9)	
Missing	4,058 (4.2)	306 (4.1)	
Hip OA	4,729 (4.8)	320 (4.3)	0.023
Polyarticular OA	6,894 (7.1)	750 (10.0)	<0.001
Charlson comorbidity index			
0	55,855 (57.2)	4,391 (58.5)	<0.001
1	29,098 (29.8)	2,319 (30.9)	
2	9,268 (9.5)	636 (8.5)	
3	2,584 (2.7)	137 (1.8)	
≥4	872 (0.9)	29 (0.4)	

* Except where indicated otherwise, values are the number (%). IQR = interquartile range.
† Median time between index body mass index (BMI) measurement and date of incident osteoarthritis (OA) diagnosis.

tions for age and sex were tested, and the median age of the population was used to categorize subjects into younger and older age categories.

Missing values for socioeconomic status, smoking, and alcohol drinking were imputed using multiple imputation with chained equations for the primary analysis (35). There were no missing values for the other confounders.

In a secondary analysis, Cox regression models using multiple imputation with chained equations were used in order to check for potential bias introduced by the missing index BMI values. Ten data sets with imputed BMI values as well as other missing variables were produced based on all available covariates, the outcome, and the Nelson-Aalen estimator of the baseline hazard. Due to a significant interaction with age being identified during the analysis, a post hoc analysis was performed repeating the secondary analysis using age instead of follow-up time to knee replacement as the time scale. This was done in order to produce age-specific HRs for each BMI group.

Population proportional attributable risk was calculated using the standard formula (36) and the reported population statistics from the EPISER study, a random age- and sex-stratified health survey representative of the entire Spanish population, which found a 41.3% prevalence of obesity in a population of patients with knee OA in Spain (ref. 37 and Carmona L: personal communication). All analyses were performed using Stata version 12.0 for Mac and version 13.0 for Windows.

RESULTS

A total of 127,329 subjects were diagnosed as having incident knee OA during the study period. After exclusion for a history of inflammatory arthritis, 122,633 were eligible for the analysis (Figure 1). At least one BMI measurement was recorded for 105,189 (86%) of the 122,633 patients, and these patients became the primary study population. The demographic characteristics of subjects with and those without baseline BMI measurements are shown in Table 1.

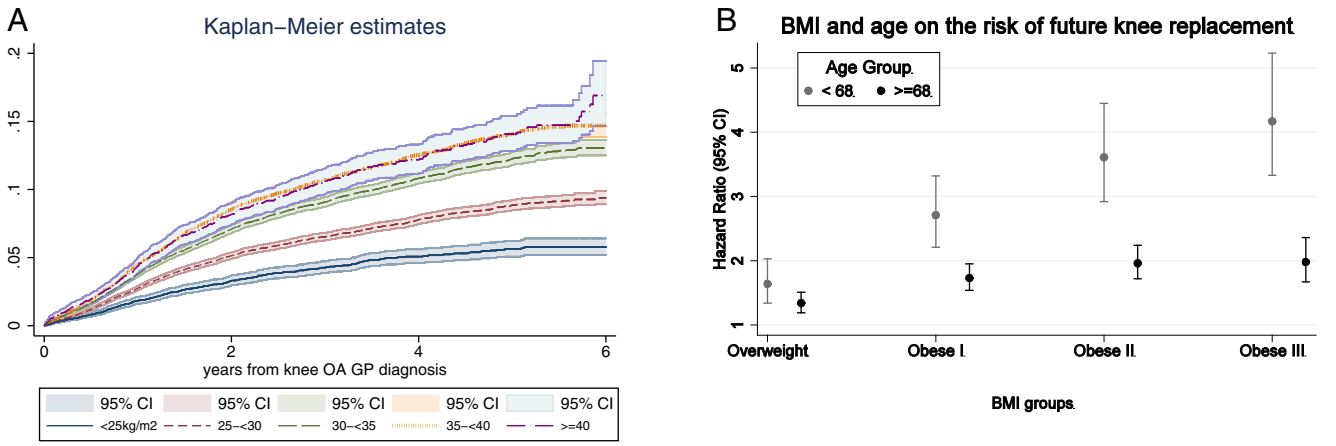

Figure 2. Effects of body mass index (BMI) and age on the risk of knee replacement. **A,** Unadjusted Kaplan-Meier estimates showing the predicted unadjusted cumulative probability of knee replacement according to BMI in subjects newly diagnosed as having knee osteoarthritis (OA). GP = general practitioner. **B,** Effect of the interaction between BMI and age group on the risk of future knee replacement. Circles show the adjusted hazard ratio; error bars show the 95% confidence interval (95% CI).

Participants were followed up for a median of 2.6 years (interquartile range 1.3–4.2). During this time, 7,512 (7.1%) of these subjects underwent knee replacement surgery, equivalent to an annual incidence rate of 2.46 per 100 person-years (95% CI 2.39–2.50).

Baseline characteristics of the study participants who underwent knee replacement and those who did not undergo knee replacement during the follow-up period are shown in Table 2. Participants who underwent knee replacement surgery were on average older and more likely to be female, obese, and to have polyarticular OA. Conversely, those undergoing knee replacement were less likely to be smokers or severe alcohol drinkers, and had a lower Charlson comorbidity index.

The risk of knee replacement increased with BMI, with unadjusted incidence rates of surgery ranging from 1.35 per 100 person-years (95% CI 1.22–1.48) in patients with a normal weight to 3.49 per 100 person-years (95% CI 3.20–3.80) in patients whose weight was categorized as obese grade III (Figure 2A and Table 3). Corresponding adjusted HRs were 1.41 (95% CI 1.27–1.57) for overweight, 1.97 (95% CI 1.78–2.18) for obese I, 2.39 (95% CI 2.15–2.67) for obese II, and 2.67 (95% CI 2.34–3.04) for obese III compared to normal-weight patients (Table 3).

A sensitivity analysis that included subjects with missing index BMI values using imputed BMI values showed very similar results to the main study findings. Adjusted HRs for the association between BMI and risk of knee replacement were 1.40 (95% CI 1.26–1.54), 1.93 (95% CI 1.75–2.13), 2.36 (95% CI 2.12–2.62), and 2.67 (95% CI 2.36–3.02) for overweight, obese I, obese II, and obese III, respectively.

A significant interaction between BMI and age on the risk of knee replacement ($P < 0.001$) was found (Figure 2B), with a higher relative hazard associated with

Table 3. Number and incidence rate of knee replacement according to baseline BMI, and results from Cox regression models*

WHO BMI category	No. (%) undergoing knee replacement	Knee replacement incidence rate (per 100 person-years) (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)†
Normal	427 (3.7)	1.35 (1.22–1.48)	Reference	Reference
Overweight	2,350 (5.9)	2.10 (2.02–2.19)	1.57 (1.42–1.74)	1.41 (1.27–1.57)
Obese I	2,865 (8.3)	2.97 (2.86–3.08)	2.21 (2.00–2.45)	1.97 (1.78–2.18)
Obese II	1,348 (9.8)	3.48 (3.30–3.67)	2.60 (2.33–2.90)	2.39 (2.15–2.67)
Obese III	522 (9.6)	3.49 (3.20–3.80)	2.60 (2.29–2.95)	2.67 (2.34–3.04)

* BMI = body mass index; WHO = World Health Organization; 95% CI = 95% confidence interval; HR = hazard ratio.
† Adjusted for age, sex, smoking, alcohol drinking, hip osteoarthritis (OA), polyarticular OA, and Charlson comorbidity index.

Table 4. Association between BMI (WHO categories) and knee replacement risk, stratified by age*

BMI WHO category	Age <68 years at the time of knee OA diagnosis		Age ≥68 years at the time of knee OA diagnosis	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)†	Unadjusted HR (95% CI)	Adjusted HR (95% CI)†
Normal	Reference	Reference	Reference	Reference
Overweight	1.90 (1.55–2.34)	1.64 (1.34–2.03)	1.43 (1.27–1.61)	1.34 (1.19–1.51)
Obese I	3.21 (2.62–3.93)	2.71 (2.21–3.32)	1.89 (1.68–2.13)	1.73 (1.54–1.95)
Obese II	4.19 (3.40–5.16)	3.61 (2.92–4.45)	2.19 (1.92–2.50)	1.96 (1.72–2.24)
Obese III	4.48 (3.58–5.61)	4.17 (3.33–5.23)	2.24 (1.89–2.66)	1.98 (1.67–2.36)

* BMI = body mass index; WHO = World Health Organization; HR = hazard ratio; 95% CI = 95% confidence interval.
† Adjusted for age, sex, smoking, alcohol drinking, hip osteoarthritis (OA), polyarticular OA, and Charlson comorbidity index.

obesity among younger patients (<68 years), with adjusted HRs of 1.64 (95% CI 1.55–2.34), 2.71 (95% CI 2.21–3.32), 3.61 (95% CI 2.92–4.45), and 4.17 (95% CI 3.33–5.23) for overweight, obese I, obese II, and obese III, respectively, compared to normal weight. Detailed results for age-stratified analyses are shown in Table 4. No significant interaction was found with sex (*P* for interaction 0.45). A post hoc analysis using age as the time scale found adjusted HRs of 1.64 (95% CI 1.48–1.82), 2.53 (95% CI 2.29–2.81), 3.68 (95% CI 3.30–4.11), and 2.17 (95% CI 1.95–2.43) for overweight, obese I, obese II, and obese III, respectively, compared to normal weight.

An analysis of population proportional attributable risk using the Spanish EPISER population prevalence data (41.3% obesity in subjects with clinical knee OA) showed that the need for knee replacement would be reduced by 31.0% if patients moved from the obese BMI category into the normal or overweight category, assuming a direct causality between BMI and progression to knee replacement (ref. 37 and Carmona L: personal communication).

DISCUSSION

In this cohort of >100,000 patients with an incident diagnosis of knee OA in primary care, 2.5% required a knee replacement each year. This study demonstrated that index BMI (at the time of diagnosis of knee OA) was predictive of knee replacement, with a 40% increased risk in overweight patients, and an almost 2.7-fold higher risk in patients whose weight was categorized as obese III compared to patients of normal weight. This association was independent of age, sex, lifestyle factors (smoking and alcohol drinking), socioeconomic status, and comorbidities. The observed association was even higher in younger patients (<68 years old), with a 64% increased risk in the overweight group, and an almost 4.5-times higher need for knee replacement among patients whose weight was classified as obese III compared to those of normal weight. According to these data, the need for knee replacement in the population of patients recently diagnosed as having knee OA could be reduced by >30% if none of the subjects affected were obese.

Both mechanical and metabolic pathways have been suggested for the effect of obesity on incidence and progression of OA (11,38). Mechanical loading can be exacerbated by local factors, such as alignment, which may explain differences in prevalence rates for hip and knee OA (11). Metabolic factors such as hyperlipidemia or hyperglycemia, which are linked to inflammation, play a role in the effect of obesity on the onset of knee OA, and might also be involved in the progression to end-stage disease (39–41).

In studies using general population cohorts (not specifically diagnosed as having OA), obesity (defined as a BMI of ≥30 kg/m^2) was associated with a 10-fold higher risk of knee replacement (24), and a relative risk of 2.4 (95% CI 2.0–2.8) for the need for surgery based on pain, function, and clinical assessment (23). A Swedish study found similar results using a lower BMI cutoff (≥25 kg/m^2), with an RR of 6.9 for women and 4.4 for men compared to subjects with a normal BMI (42). In studies using the Canadian joint registry, overweight subjects (BMI of 25.0–29.9 kg/m^2) were found to have a 3.2-fold risk of knee replacement, with up to an 18.7-fold risk in subjects classified as obese group II (BMI 35.0–39.9 kg/m^2) compared to subjects with a normal BMI (≤25.0 kg/m^2) (43). However, all of those studies aggregated the effect of obesity on both incident knee OA onset and knee surgery and failed (or did not attempt) to disentangle the impact of being overweight or obese on progression to joint failure following a diagnosis of knee OA.

Previous studies of obesity and progression have produced mixed evidence, with only a few significant associations found, but primarily borderline or no significant

relationship between obesity and progression (21). There are several differences in the present study that may explain our significant results. Previous studies have primarily used structural markers for progression, such as joint space narrowing, osteophytes, and/or Kellgren/Lawrence grade (16,18,19,21), while joint replacement as a surrogate marker of end-stage disease, as used in the present study, involves some level of increased pain and disability.

Changulani et al found that among patients undergoing knee surgery, those who were morbidly obese (BMI $\geq$40 kg/m^2) were a mean of 13 years younger than patients with a normal BMI (25). This result is consistent with the findings of the present study showing a stronger effect size of surgery in younger patients. A post hoc analysis, producing age-specific HRs, showed slightly higher results than the original analysis for subjects in the overweight, obese group I, and obese group II categories. In a case–control study of OA patients listed for surgery, Coggon et al calculated that 23.6% of knee replacements might be avoided if all overweight/obese patients reduced their weight by 5 kg or until their BMI was in the normal range (28). Weight reduction strategies have been shown to improve function in older patients with symptomatic knee OA. Miller et al (29) found that subjects following a strict calorie-controlled diet and exercise program showed a mean 8.7% loss in body weight over 6 months and had significantly higher self-reported physical function than the control group at follow-up (29).

Potential limitations of this study include the lack of individual validation of exposure or events. Nevertheless, SIDIAP has been widely used for the study of the epidemiology of OA in the past, and it has been shown to collect reliable information on the coding of this disease (32,44). The use of knee replacement as a marker of joint failure has several limitations, e.g., indications for surgery often include aspects of both structural and pain and/or functional limitations, as well as health care planning and GP/surgeon decisions. A knee replacement also implies a willingness to have surgery (45). However, knee replacement is a very relevant outcome in terms of health care resource use and patients' quality of life, two undeniably important aspects of the care of patients with knee OA. An additional limitation was that due to the small number of underweight subjects, they were included in the normal BMI group for the analyses. A potential bias exists due to missing index BMI data (for 14.2% of subjects); however, a sensitivity analysis using multiple imputation showed no significant difference from the primary complete case analysis, suggesting a low risk of selection bias.

In the calculation of population proportional attributable risk, the underlying assumption is that BMI is causally associated with progression to knee replacement, and that there is no unmeasured confounding or bias in the exposed and unexposed subjects. BMI is one of the strongest risk factors for knee OA progression and has strong causal evidence. Both the prevalence data and risk (HR) used to calculate the attributable risk were derived from comparable populations.

The strengths of this research include the nature of the data, since SIDIAP contains data collected in routine practice conditions, minimizing potential sources of observer bias and Hawthorne effect. In addition, it covers >80% of the local population, making this study population very representative. The use of an incident population provides a more meaningful interpretation of the results of our study, by helping clarify part of the clinical pathway by examining the time from diagnosis of disease by a GP to the need for surgery in this patient population. These data are also rare in that they combine primary care record and hospital admission information for all study participants.

The present study showed a higher HR in younger patients (median age of <68 years) for surgery compared to older patients. There are several possible explanations for this result. The first is that younger patients are becoming obese earlier in life, which is shifting the progression of knee OA earlier in life, and possibly the speed of progression. Due to the relatively short follow-up time (median 2.6 years), we may be identifying more patients with quickly progressing disease, who may be younger. Another possible explanation is that this is the result of a cohort effect between the older and younger patients, either due to a "healthy" patient effect, where older patients have other and more complex comorbidities in addition (and possibly related) to their obesity, a variation of health-seeking behaviors between age groups, or differences specifically related to willingness to undergo surgery (45).

Our findings demonstrate that being overweight or obese is a strong independent predictor of the clinical progression of knee OA, from disease onset/diagnosis to joint failure and subsequent knee replacement. Overweight subjects have a >40% increased risk of surgery, and obese subjects have a more than doubled risk when compared to subjects of normal weight. Although being overweight or obese at the time of diagnosis by a GP is a significant risk factor for knee replacement, this should not be confused with the reported great benefit that overweight and obese patients derive from surgery once they have progressed to end-stage disease (46).

This relative risk is much higher in younger subjects. Knee replacement surgeries could be reduced by 31% in the Spanish population if patients were not in the obese BMI range. These results could encourage patients recently diagnosed as having knee OA to lose weight, as well as inform future trials on the effect of a weight reduction program on the progression of knee OA.

ACKNOWLEDGMENTS

We gratefully thank all of the health professionals involved in registering data in computerized medical records for the Information System for Development of Primary Care Research (SIDIAP). We also thank the Catalan Health Service (Government of Catalonia) for the linkage and provision of hospital admissions data (Registre de Conjunt Mínim Bàsic de Dades [CMBD], Divisió de Registres de Demanda i d'Activitat, Àrea de Serveis i Qualitat, Servei Català de la Salut). This article was not prepared in collaboration with personnel from the CMBD, and does not necessarily reflect their opinions or views. Data quality and accuracy are the responsibility of the authors alone. We would also like to sincerely thank the EPISER study group for providing additional population level data for this analysis.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Prieto-Alhambra had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Leyland, Diez-Perez, Carr, Arden, Prieto-Alhambra.

Acquisition of data. Prieto-Alhambra.

Analysis and interpretation of data. Leyland, Judge, Javaid, Cooper, Prieto-Alhambra.

REFERENCES

1. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380:2197–223.
2. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2010;18:24–33.
3. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly: the Framingham Osteoarthritis Study. Arthritis Rheum 1987;30:914–8.
4. Jinks C, Jordan K, Croft P. Osteoarthritis as a public health problem: the impact of developing knee pain on physical function in adults living in the community: (KNEST 3). Rheumatology (Oxford) 2007;46: 877–81.
5. National Joint Registry. National Joint Registry for England and Wales: summary report to the 2nd annual report. September 2005. URL: http://www.njrcentre.org.uk/NjrCentre/Portals/0/Documents/England/Reports/NJR_AR_2%28s%29.pdf.
6. Baker PN, van der Meulen JH, Lewsey J, Gregg PJ. The role of pain and function in determining patient satisfaction after total knee replacement: data from the National Joint Registry for England and Wales. J Bone Joint Surg Br 2007;89:893–900.
7. Dakin H, Gray A, Fitzpatrick R, Maclennan G, Murray D. Rationing of total knee replacement: a cost-effectiveness analysis on a large trial data set. BMJ Open 2012;2:e000332.
8. Garstang SV, Stitik TP. Osteoarthritis: epidemiology, risk factors, and pathophysiology. Am J Phys Med Rehabil 2006;85 Suppl: S2–11.
9. Lane NE, Brandt K, Hawker G, Peeva E, Schreyer E, Tsuji W, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. Osteoarthritis Cartilage 2011;19:478–82.
10. Roos EM. Joint injury causes knee osteoarthritis in young adults. Curr Opin Rheumatol 2005;17:195–200.
11. Sharma L, Lou C, Cahue S, Dunlop DD. The mechanism of the effect of obesity in knee osteoarthritis: the mediating role of malalignment. Arthritis Rheum 2000;43:568–75.
12. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol 2007;34:172–80.
13. Muraki S, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M, et al. Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. Osteoarthritis Cartilage 2009;17:1137–43.
14. Van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989; 48:271–80.
15. Zhang Y, Xu L, Nevitt MC, Aliabadi P, Yu W, Qin M, et al. Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: the Beijing Osteoarthritis Study. Arthritis Rheum 2001; 44:2065–71.
16. Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000;43:995–1000.
17. McAlindon TE, Felson DT, Zhang Y, Hannan MT, Aliabadi P, Weissman B, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. Ann Intern Med 1996; 125:353–9.
18. Ledingham J, Regan M, Jones A, Doherty M. Factors affecting radiographic progression of knee osteoarthritis. Ann Rheum Dis 1995;54:53–8.
19. Schouten JS, van den Ouweland FA, Valkenburg HA. A 12 year follow up study in the general population on prognostic factors of cartilage loss in osteoarthritis of the knee. Ann Rheum Dis 1992;51:932–7.
20. Jinks C, Jordan K, Croft P. Disabling knee pain–another consequence of obesity: results from a prospective cohort study. BMC Public Health 2006;6:258.
21. Belo JN, Berger MY, Reijman M, Koes BW, Bierma-Zeinstra SM. Prognostic factors of progression of osteoarthritis of the knee: a systematic review of observational studies. Arthritis Rheum 2007;57:13–26.
22. Niu J, Zhang YQ, Torner J, Nevitt M, Lewis CE, Aliabadi P, et al. Is obesity a risk factor for progressive radiographic knee osteoarthritis? Arthritis Rheum 2009;61:329–35.
23. Judge A, Welton NJ, Sandhu J, Ben-Shlomo Y. Modeling the need for hip and knee replacement surgery. Part 1. A two-stage cross-cohort approach. Arthritis Rheum 2009;61:1657–66.
24. Liu B, Balkwill A, Banks E, Cooper C, Green J, Beral V. Relationship of height, weight and body mass index to the risk of hip and knee replacements in middle-aged women. Rheumatology (Oxford) 2007;46:861–7.
25. Changulani M, Kalairajah Y, Peel T, Field RE. The relationship between obesity and the age at which hip and knee replacement is undertaken. J Bone Joint Surg Br 2008;90:360–3.

26. Baker P, Petheram T, Jameson S, Reed M, Gregg P, Deehan D. The association between body mass index and the outcomes of total knee arthroplasty. J Bone Joint Surg Am 2012;94:1501–8.
27. Dowsey MM, Liew D, Choong PF. Economic burden of obesity in primary total knee arthroplasty. Arthritis Care Res (Hoboken) 2011;63:1375–81.
28. Coggon D, Reading I, Croft P, McLaren M, Barrett D, Cooper C. Knee osteoarthritis and obesity. Int J Obes Relat Metab Disord 2001;25:622–7.
29. Miller GD, Nicklas BJ, Davis C, Loeser RF, Lenchik L, Messier SP. Intensive weight loss program improves physical function in older obese adults with knee osteoarthritis. Obesity (Silver Spring) 2006;14:1219–30.
30. Garcia-Gil M, Hermosilla E, Prieto-Alhambra D, Fina F, Rosell M, Ramos R, et al. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). Inform Prim Care 2011;19:135–45.
31. Prieto-Alhambra D, Nogues X, Javaid MK, Wyman A, Arden NK, Azagra R, et al. An increased rate of falling leads to a rise in fracture risk in menopausal women with self-reported osteoarthritis: a prospective multinational cohort study (GLOW). Ann Rheum Dis 2013;72:911–7.
32. Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Ann Rheum Dis 2013;73: 1659–64.
33. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–9.
34. Reyes C, Garcia-Gil M, Elorza JM, Mendez-Boo L, Hermosilla E, Javaid MK, et al. Socio-economic status and the risk of developing hand, hip or knee osteoarthritis: a region-wide ecological study. Osteoarthritis Cartilage 2015;23:1323–9.
35. Royston P. Multiple imputation of missing values: update. Stata J 2005;5:188–201.
36. Kirkwood BR, Sterne JA. Essential medical statistics. 2nd ed. London: Wiley-Blackwell; 2003.
37. Fernandez-Lopez JC, Laffon A, Blanco FJ, Carmona L. Prevalence, risk factors, and impact of knee pain suggesting osteoarthritis in Spain. Clin Exp Rheumatol 2008;26:324–32.
38. Felson DT, Neogi T. Osteoarthritis: is it a disease of cartilage or of bone? [editorial]. Arthritis Rheum 2004;50:341–4.
39. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. J Rheumatol 1995;22:1118–23.
40. Sowers MR, Karvonen-Gutierrez CA. The evolving role of obesity in knee osteoarthritis. Curr Opin Rheumatol 2010;22: 533–7.
41. Yoshimura N, Muraki S, Oka H, Tanaka S, Kawaguchi H, Nakamura K, et al. Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. Osteoarthritis Cartilage 2012;20:1217–26.
42. Lohmander LS, Gerhardsson de Verdier 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 2009;68:490–6.
43. Bourne R, Mukhi S, Zhu N, Keresteci M, Marin M. Role of obesity on the risk for total hip or knee arthroplasty. Clin Orthop Relat Res 2007;465:185–8.
44. Bolibar B, Fina Aviles F, Morros R, Garcia-Gil Mdel M, Hermosilla E, Ramos R, et al. [SIDIAP database: electronic clinical records in primary care as a source of information for epidemiologic research]. Med Clin (Barc) 2012;138:617–21.
45. Hawker GA, Wright JG, Badley EM, Coyte PC. Perceptions of, and willingness to consider, total joint arthroplasty in a population-based cohort of individuals with disabling hip and knee arthritis. Arthritis Rheum 2004;51:635–41.
46. Judge A, Batra RN, Thomas GE, Beard D, Javaid MK, Murray DW, et al. Body mass index is not a clinically meaningful predictor of patient reported outcomes of primary hip replacement surgery: prospective cohort study. Osteoarthritis Cartilage 2014; 22:431–9.