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Association between overweight and obesity and risk of clinically diagnosed knee, hip, and hand osteoarthritis: a population-based cohort study.

Running Head : Overweight/obesity and the risk of developing osteoarthritis

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ABSTRACT

[248/250 words]

Objective: Previous cohorts have reported associations between overweight/obesity and knee and hand osteoarthritis (OA). However, no data on the effect of these on the OA burden are available. We aimed to analyse the effect of overweight and obesity on the incidence of routinely diagnosed knee, hip, and hand OA.

Methods:

Design: population-based cohort

Setting: primary care records from the SIDIAP database (>5.5 million subjects) covering >80% of the population of Catalonia, Spain.

Participants: ≥40 years old with no OA on 01/01/2006 and with body mass index (BMI) data available. Follow-up: from 01/01/2006 to 12/31/2010, loss to follow-up, or death.

Measures: BMI World Health Organization categories (exposure), and incident clinical diagnoses of knee, hip, or hand OA (ICD-10 codes).

Results

1,764,061 subjects were observed for a median (inter-quartile range) of 4.45 (4.19 to 4.98) years. Incidence rates (per 1000 PY) of knee, hip and hand OA ranged from 3.7 (3.6 to 3.8), 1.7 (1.7 to 1.8) and 2.6 (2.5 to 2.7) amongst normal-weight, to 19.5 (19.1 to 19.9), 3.8 (3.7 to 4.0) and 4.0 (3.9 to 4.2) in the grade II obese respectively.

Compared to normal-weight subjects, being overweight or obese increased the risk of OA at all three sites, especially at the knee: overweight and (grade I, II) obesity increased knee OA risk by a factor of 2, 3.1 and 4.7 fold respectively.

Conclusions

Both overweight and obesity increase the risk of hand, hip, and knee OA, especially for the latter, with a dose-response gradient with increasing BMI.

Obesity and osteoarthritis (OA) are two interconnected health care problems affecting a large proportion of the adult population worldwide. The increasing weight of the population will lead to nearly 1.3 billion and 573 million adults overweight and obese respectively by 2030 [1]. Moreover, OA increases as the population ages [2] representing a leading cause of chronic pain and disability among older people [3].

There is extensive evidence supporting obesity as one of the major risk factors for knee OA [4-7,8], independent of the method of assessment used [9]. To a lesser extent there are reports associating obesity with hand OA [10,8] and more conflicting results are found regarding hip OA [6,7,11,8]. The mechanical overload of the weight-bearing joint or the activation of metabolic factors contributing to the joint damage have both been proposed as possible mechanisms to explain how weight increases the risk of knee or hand OA [12].

Nevertheless the limited treatments for OA make prevention of modifiable risk factors, such as obesity, a key target for public health and medical interventions today. Consequently, the aim of this study is to analyse the effect of obesity on the incidence of symptomatic knee, hip and hand OA, using a large population database.

PATIENTS AND METHODS

Study design and setting:

We conducted a population-based cohort study using routinely collected data from the Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP) database (http://www.sidiap.org).

Data source:

SIDIAP gathers clinical information as recorded by general practitioners (GP) and primary care nurses including prescriptions, events (ICD-10 codes) and measurements (such as body mass index, blood pressure, or spirometry results amongst others collected using structured spreadsheets) during routine practice. It covers >5.5 million people (a representative >80% of the population of Catalonia, Spain) registered with one of the 3,414 GPs working in any of the 274 primary care practices run by the Catalan Institute of Health (ICS for its acronym in Catalan [15].

The Spanish (and by extension, the Catalan) healthcare system is of universal coverage, and GPs are, as in the British NHS, gatekeepers to any other medical or allied healthcare professional attention with the exception of Accident and Emergency rooms.

Participants:

Eligible participants were all subjects aged at least 40 years old without a history of diagnosed OA in primary care records at index joint on 1st January 2006 and with at least one measurement of BMI coded in the primary care computerized records (SIDIAP database)

Study period:

Participants were observed from study initiation (1st January 2006) or from the date when they registered at any of the primary health care practices covered by the SIDIAP (whatever came

last) to the earliest of the following: end of the study (31st December 2010), transfer out of catchment area, or death.

Variables:

Study exposure**:** The BMI coded by health care professionals in kg/m^2 during the study period was the main study exposure. Values of BMI <10 or >60 were assumed as typing errors and not used for the current analyses. When more than one measurement was available, the closest to index date (1st January/2006) was used. Patients were classified according to the World Health Organization definitions in: normal (BMI below 25 kg/m$^{2)}$, overweight (BMI 25 or over and below 30 kg/m^2), obese grade I (BMI 30 or above and below 35 kg/m^2), and obese grade II (BMI 35 kg/m^2 or above).

Study outcomes**:** Incident clinical diagnoses of OA as registered by general practitioners during the study period (1 January 2006 to 31 December 2010) were identified using a previously validated list of ICD-10 codes: knee OA (M17, M17.0, M17.1, M17.2, M17.3, M17.4, M17.5 and M17.9), hip OA (M16, M16.0, M16.1, M16.2, M16.3, M16.4, M16.5, M16.6, M16.7 and M16.9) and hand OA (M15.1, M15.2, M18, M18.0 to M18.5 and M18.9). OA coding within SIDIAP has been validated against self-reported OA in the Global Longitudinal Study of Osteoporosis in Women (GLOW) population-based cohort [13], as well as by reviewing free text and x-ray reports collected in primary care records [14].

Statistical analyses:

Age (in 5-year groups) and gender-specific incidence rates (IRs) and 99% Confidence Intervals (99%CIs) for each of the outcomes identified in the study period were estimated assuming a Poisson distribution.

Cox regression modelling was used to compute age and gender-adjusted hazard ratios (HRs) and

99%CIs for an incident clinical diagnosis of knee, hip, and hand OA according to BMI (continuous, per kg/m^2 increase) and BMI category (using normal weight as a reference group). Age-specific adjusted rate ratios (RRs) for overweight, obese grade I and obese grade II compared to normal-weight were calculated using Poisson regression.

All the statistical analyses were carried out using STATA SE for Mac V.12.0.

Ethical approval:

Scientific approval was obtained from the SIDIAP Scientific Committee, and ethics approval was granted by the relevant board (CEIC IDIAP Jordi Gol) with certificate number P14/153. Patient consent was not required as only anonymised retrospective data was used for this study, and no patient or GP contact was required.

RESULTS

Baseline characteristics

A total of 1,764,061 (54.0%) out of 3,266,826 potentially eligible subjects registered in SIDIAP had data on BMI, and were therefore included in the study. Compared to the source population, the included participants (i.e. with BMI data available) were slightly older (64.1 versus 62.4 years) and more likely to be women (54.2% versus 51.8%).

Eligible subjects were categorized into the following BMI categories: 446,034 (25.3%) normal-weight, 742,258 (42.1%) overweight, 409,714 (23.2%) grade I obesity, and 166,055 (9.4%) grade II obesity. Baseline characteristics of subjects according to their BMI category are shown in table 1.

Incidence rates of knee, hip, and hand OA in the study population

Participants were observed for a median (IQR) of 4.45 (4.19 to 4.98) years. Incidence rates are reflected in figures 1, 2 and 3. During this period, 83,469 incident cases with knee OA were identified with crude-incidence rates of 9.1, 99%CI (9.0 to 9.2) per 1,000 person-years at risk respectively, 27,701 incident cases with hip OA were identified with crude-incidence rates of 2.9 (2.8 to 2.9) per 1,000 person-years at risk respectively and 30,909 incident cases with hand OA were identified with a crude-incidence rates of 3.2 (3.2 to 3.3) per 1,000 person-years at risk respectively. Incidence rates of knee, hip and hand OA for each BMI category are represented in table 2.

The incidence rates for knee and hip OA increased since the age of 40 years old with a special increase at the age of 55-60 and 70 to 75 years old respectively (figures 1 and 2)

Association of BMI and knee, hip and hand OA:

The incidence of knee, hip, and hand OA increased with increasing BMI, with a greater increase for knee OA (figures 1-3). The adjusted HR for the effect of BMI on OA is reported in table 3.

In the fitted survival model, age increased the risk of OA similarly at all three sites (knee, hand and hip) whereas female gender increased the risk mostly in hand OA.

After categorization into WHO-recommended groups, and compared to those with normal weight (<25kg/m^2), those with overweight had an excess risk of OA, especially at the knee. This excess risk continued increasing as the BMI increased, being more pronounced for knee OA in subjects with grade 2 obesity (>35kg/m^2); these subjects were 4.7 fold more frequently diagnosed with knee OA compared to subjects with BMI <25kg/m^2.

The observed associations between overweight/obesity and the risk of knee, hip were present throughout all the participant ages (40 years or older) (Figures 1, 2 respectively). However, the excess risk of OA associated with obesity varied at different ages for knee OA while this association was more constant (unmodified by age) for hip OA, (Figure 4).

DISCUSSION

Principal findings:

Our study confirms that the incidence of OA mostly affects the knee in our population, compared to the other joint sites, reaching a maximum incident rate of 19.5 per 1,000 persons-year for subjects with grade II obesity compared to the 3.7 per 1,000 persons-year for normal-weight subjects. Obesity seemed to increase the risk in all three joint sites, including the hip, but the greatest increase was reported for knee. The effect of obesity on knees was more pronounced at younger ages, which could be useful for public health messaging.

We found a positive association between overweight and obesity with the risk of developing OA at the knee, hip and hand. The excess risk found was greater for subjects with grade II obesity, who were 4.7 times more likely to develop knee OA compared to subjects with normal-weight.

Strengths and weaknesses of the study:

Our main strength is the large population included in this study, which allows us to easily extrapolate our results using a clinically relevant outcome. Moreover, to our knowledge this is the first study to analyse the impact of obesity on osteoarthritis using routinely collected data from primary care. However, this study must be also interpreted in the light of certain limitations; the main outcome was based on symptomatic OA and no information was collected regarding radiographic OA. However, there is strong evidence that obesity is associated with radiographic OA [7], which suggests that our results would remain unchanged. Moreover, SIDIAP does not contain information on the side of the joint affected (joint site (eg, knee) was considered as a whole and nearly 46% of the subjects had missing information on their BMI. The missing BMI could be a source of bias, however the BMI registration in Spain is part of the

recommended health check programme called PAPPs required by the government in order to give funding to the primary health cares [16], hence it is not always linked to a more pathological population but maybe to a population that more frequently uses primary health care resources. Moreover, we compared the BMI distribution of the population in our study with another large national study carried out in Spain, where the trends of the BMI were analysed on over 11,000 subjects and found similar percentages of obesity between 2008-2010 [17], witch reinforces the representativeness of our population. Conversely, we analysed the IR of knee, hip and hand OA in those subjects with missing BMI and found a lower IR of OA in this population (Unadjusted IR 2.98 per 1000persons-year for knee, IR 1.03 per 1000 persons-year for hip and IR 1.33 per 1000 persons-year for hand OA), although we do not think that this invalidates the association between BMI and OA at the different sites found in this study, this may limit its representativeness. Another limitation to be considered is the lack of information on incident overweight subjects during the study period; the information on BMI relied on the available data on the SIDIAP database and given that periodic BMI registering is quite uncommon we were not able to account for this.

Despite previous validation of the data collected in the SIDAP database, [13] and due to the retrospective nature of this study, the possibility of misclassification and registration biases should be considered. Finally, we did not collect information on occupation, physical activity or previous injuries, which could have influenced our results. Previous studies have shown an increased risk with manual labour occupations and OA [18], while physical activity has been found to have an unclear association with OA [6]

Strength and weaknesses in relation with other studies

Overweight and obesity have been previously identified as a risk factor for developing OA. This

association has been especially reported for knee [4-8] and hand OA [10], with more inconsistent results for hip OA [6,7,8,11]. Our results confirm these previous findings for knee and hand OA and extend what has been previously published regarding hip OA [11]; compared to those subjects with normal-weight, our overweight and grade II obese population had a 46 and a 93% excess risk of hip OA respectively. Some previous studies [6-8] did not find an association between BMI and hip OA which could be due to the low number of subjects with hip OA included (compared to the 27,701 cases found in our population), the self-reported OA [6-7] (compared to our routinely collected data by primary health care professionals) or the selection of a rather healthy and younger population [6-8], leading to an underestimation of this association. Among the studies that did analyze the association between obesity and OA through a life-course approach [19-23], early and middle adulthood [19, 20, 22, 23] and up to the age of 60 years old [20, 22, 23] were identified as periods in life where there was an excess risk of OA for obese and overweight subjects. Furthermore, another previous study based on data from the National Health Interview Survey in the US [24] found that the incidence of knee OA peaked in those subjects aged 55 to 64 years old and was higher among obese subjects. Our results are consistent with these findings; compared to the normal-weight subjects those with obesity (grade I and II) had an excess risk of OA that varied with age, especially at the knee.

Meaning of the study and implications of current findings:

Obesity is a modifiable risk factor and correctly identifying the population with a higher risk of OA, such as the one identified by our study, could help prevention strategies to reduce the symptomatology or even the future progression of OA. Despite that interventions aiming to reduce the clinical outcomes of OA have proven to be effective [25,26], changes in peoples

lifestyles and habits are not easy to implement. By identifying the age at which obesity would more seriously influence the risk of OA, healthcare providers could focus prevention strategies on a narrower target population (i.e. middle adulthood).

Unanswered questions and future research

The mechanism through which obesity increases the risk of OA has not yet been fully elucidated and falls outside the scope of this study. Whether the peak excess risk observed in middle adulthood for knee and hand OA reflects the pathogenic pathways involved in the appearance of OA at the different sites (eg due to the increase in metabolic disorders such as diabetes or due to menopause [27,28]) should be investigated in future research.

Conclusions:

Both overweight and obesity increase the risk of hand, hip, and knee OA, especially for the latter, with a dose-response gradient with increasing BMI. Health care providers should implement prevention tools, especially focused on these ages, in order to reduce the risk of developing OA at these sites.

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Ethical approval: This study was approved by the relevant ethics committee (Comitè d'Ètica IDIAP Jordi Gol) with reference number P12/72.

REFERENCES

1- Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond) 2008;32:1431-7.

2- 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 2014;73:1659-64.

3- Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis 2001;60:91-7.

4- Jiang L, Tian W, Wang Y, Rong J, Bao C, Liu Y, et al. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2012;79:291-7.

5- 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.

6- Mork PJ, Holtermann A, Nilsen TI. Effect of body mass index and physical exercise on risk of knee and hip osteoarthritis: longitudinal data from the Norwegian HUNT Study. J Epidemiol Community Health 2012;66:678-83.

7- Reijman M, Pols HA, Bergink AP, Hazes JM, Belo JN, Lievense AM, et al. Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: the Rotterdam Study. Ann Rheum Dis 2007;66:158-62.

8- Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. BMC Musculoskelet Disord 2008;9:132.

9- Lohmander LS, Gerhardsson de Verdier M, Rollof J, Nilsson PM, Engström 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.

10- Yusuf E, Nelissen RG, Ioan-Facsinay A, Stojanovic-Susulic V, DeGroot J, van Osch G et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis 2010;69:761-5.

11-Jiang L, Rong J, Wang Y, Hu F, Bao C, Li X, et al. The relationship between body mass index and hip osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2011;78:150-5.

12-King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res 2013;138:185-93.

13-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 postmenopausal women with self-reported osteoarthritis: a prospective multinational cohort study (GLOW). Ann Rheum Dis 2013;72:911–7.

14- 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 2014;73:1659-64.

15-Garcia-Gil M del 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 2012;19:135–45.

16- Maiques Galán A, Brotons Cuixart C, Villar Álvarez F, Navarro Pérez J, Lobos-Bejarano JM, Ortega Sánchez-Pinilla R, et al. Recomendaciones preventivas cardiovasculares. Aten Primaria. 2012;44 Supl 1:3-15.

17- Gutiérrez-Fisac JL, León-Muñoz LM, Regidor E, Banegas J, Rodríguez-Artalejo F. Trends in obesity and abdominal obesity in the older adult population of Spain (2000-2010). Obes Facts. 2013;6(1):1-8.

18- Sulsky SI, Carlton L, Bochmann F, Ellegast R, Glitsch U, Hartmann B, et al. Epidemiological evidence for work load as a risk factor for osteoarthritis of the hip: a systematic review. PLoS One 2012;7(2):e31521.

19- 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;107:542-8.

20- Holliday KL, McWilliams DF, Maciewicz RA, Muir KR, Zhang W, Doherty M. Lifetime body mass index, other anthropometric measures of obesity and risk of knee or hip osteoarthritis in the GOAL case-control study. Osteoarthritis Cartilage 2011;19:37-43.

21- 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.

22- Wills AK, Black S, Cooper R, Coppack RJ, Hardy R, Martin KR, et al. 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 2012;71:655-60.

23- 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.

24-_Losina E, Weinstein AM, Reichmann WM, Burbine SA, Solomon DH, Daigle ME, et al. Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. Arthritis Care

Res (Hoboken) 2013;65(5):703-11.

25- Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA 2013;310:1263-73.

26- Aaboe J, Bliddal H, Messier SP, Alkjær T, Henriksen M. Effects of an intensive weight loss program on knee joint loading in obese adults with knee osteoarthritis. Osteoarthritis Cartilage 2011;19:822-8.

27- Bay-Jensen AC, Slagboom E, Chen-An P, Alexandersen P, Qvist P, Christiansen C, et al. Role of hormones in cartilage and joint metabolism: understanding an unhealthy metabolic phenotype in osteoarthritis. Menopause 2013;20:578-86.

28- Yusuf E, Ioan-Facsinay A, Bijsterbosch J, Klein-Wieringa I, Kwekkeboom J, Slagboom PE, et al. Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis. Ann Rheum Dis 2011;70:1282-4.

1 **TABLES:**

Table 1 Baseline characteristics of subjects based on their BMI category

		BMI categories, N , %			
		<25	25 to <30	30 to <35	>35
Follow-up (median (inter-quartile range))		5.99 (4.81 - 5.99)	5.99 (3.97-5.99)	5.99 (2.83-5.99)	5.99 (1.84-5.99)
Gender	**Female**	271,175 60.8	350,771 47.3	218,236 53.3	115,151 69.3
	Male	174,859 39.2	391,487 52.7	191,478 46.7	50,904 30.6
Age Mean (SD)		60.7 (15.2)	65.1 (13.9)	66.1 (13.1)	64.4 (12.9)
Ischemic heart disease		2,258 0.5	7,664 1.0	6,168 1.5	2,648 1.6
Cerebrovascular disease		1,735 0.4	4,667 0.6	3,379 0.8	1,339 0.8
COPD*		2,865 0.6	7,812 1.0	6,346 1.5	2,933 1.8
Diabetes mellitus		5,137 1.15	20,798 2.8	19,541 4.8	11,847 7.1

Hypertension	16,804 3.8	63,659 8.6	58,850 14.4	32,645 19.7

* COPD : Chronic obstructive pulmonary disease

Table 2 Incident rates (IR) of knee, hip and hand OA per 1,000 persons/year

			Incident diagnosed site-specific OA (N)	Crude IR per 1,000 persons/year (99% CI)
Knee OA[β]	Overall IR		83,469	9.1 (9.0-9.2)
	BMI*	Normal-weight	8,785	3.7 (3.6-3.8)
		Overweight	31,415	8.0 (7.9-8.2)
		Obesity I	27,777	13.5 (13.2-13.7)
		Obesity II	15,492	19.5 (19.1-19.9)
Hip OA[β]	Overall IR		27,701	2.9 (2.8-2.9)
	BMI*	Normal-weight	4,250	1.7 (1.7-1.8)
		Overweight	11,846	2.9 (2.8-3.0)
		Obesity I	8,141	3.6 (3.5-3.7)
		Obesity II	3,464	3.8 (3.7-4.0)
Hand OA[β]	Overall IR		30,909	3.2 (3.2-3.3)
	BMI*	Normal-weight	6,302	2.6 (2.5-2.7)
		Overweight	12,856	3.2 (3.1-3.3)
		Obesity I	8,141	3.7 (3.6-3.8)
		Obesity II	3,610	4.0 (3.9-4.2)

* BMI based on WHO definitions: Norma-weight (<25kg/m2), overweight (25 to <30 kg/m2), obesity I (30 to <35 kg/m2) and obesity II (35 kg/m2 and over).

[β] Osteoarthritis.

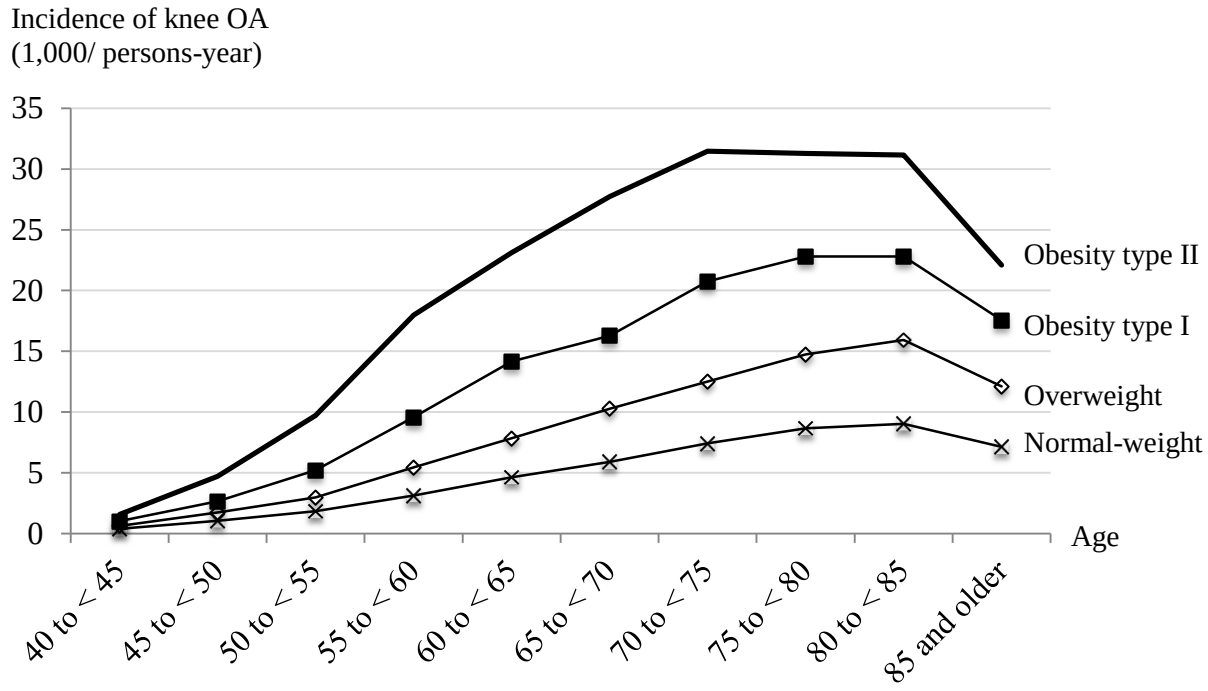
Table 3 Adjusted HR [99%CI] for the effect of BMI on OA.

		Any OA	Knee OA	Hip OA	Hand OA
Age (per year)		1.04 [1.04-1.05]	1.04 [1.04-1.04]	1.05 [1.05-1.05]	1.03 [1.02-1.03]
Sex Female		1.75 [1.75-1.78]	1.53 [1.51-1.56]	1.20 [1.16-1.23]	2.56 [2.5-2.63]
BMI (kg/m^2)	Overall	1.05 [1.05-1.06]	1.09 [1.08-1.09]	1.04 [1.04-1.04]	1.02 [1.01-1.02]
	<25	Ref	Ref	Ref	Ref
	25-30	1.49 [1.46-1.51]	2.00 [1.94-2.06]	1.46 [1.39-1.52]	1.22 [1.17-1.27]
	30-35	1.96 [1.93-2.00]	3.19 [3.09-3.30]	1.75 [1.66-1.83]	1.30 [1.25-1.36]
	≥35	2.51 [2.45-2.56]	4.72 [4.56-4.89]	1.93 [1.82-2.05]	1.31 [1.24-1.38]

All p-vals<0.001

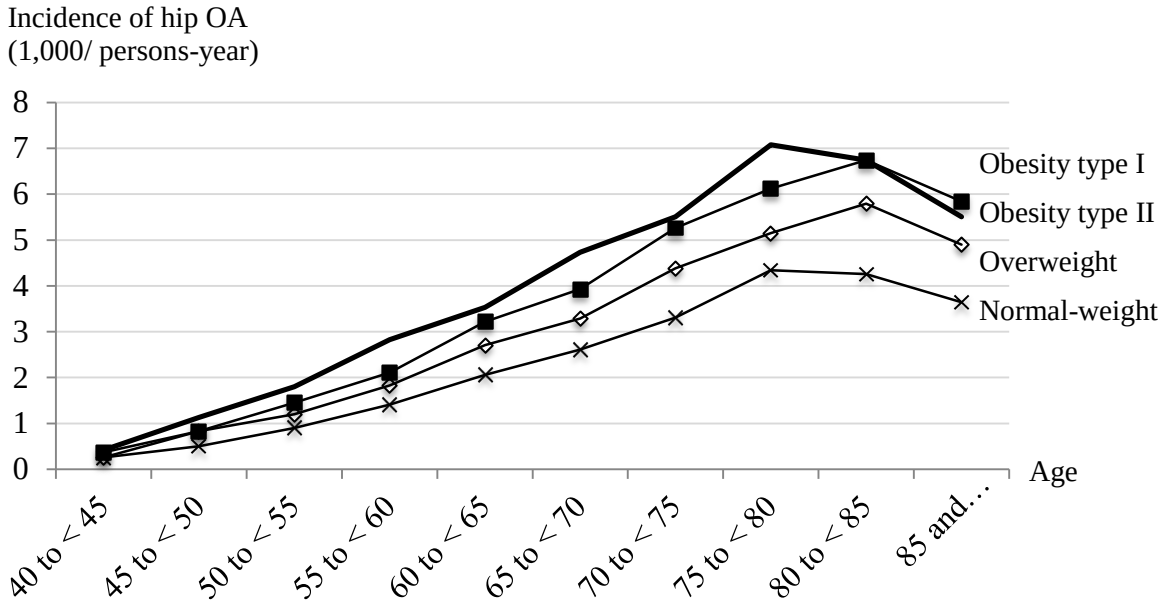
FIGURES

Figure 1 Incidence of knee OA for each range of BMI* per 1,000/persons-year.



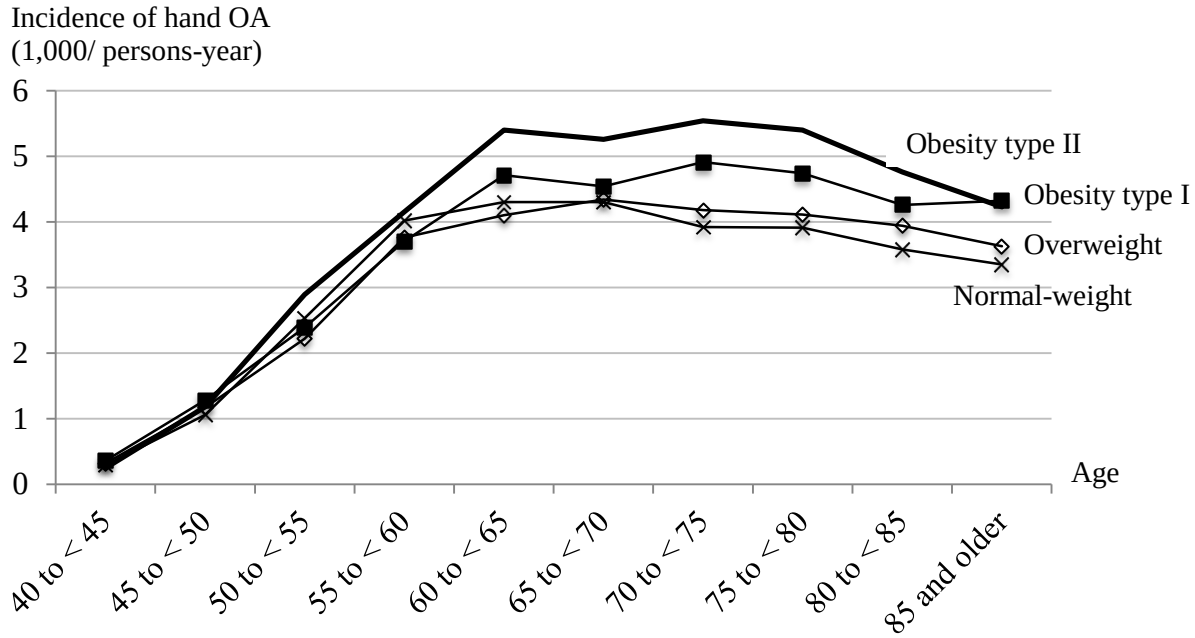
* BMI based on WHO definitions: Normal-weight (<25kg/m^2), overweight (25 to <30 kg/m^2), obesity I (30 to <35 kg/m^2) and obesity II (35 kg/m^2 and over).

Figure 2 Incidence of hip OA for each range of BMI* per 1,000/persons-year.



* BMI based on WHO definitions: Normal-weight (<25kg/m^2), overweight (25 to <30 kg/m^2), obesity I (30 to <35 kg/m^2) and obesity II (35 kg/m^2 and over).

Figure 3 Incidence of hand OA for each range of BMI per 1,000/persons-year.



* BMI based on WHO definitions: Normal-weight (<25kg/m^2), overweight (25 to <30 kg/m^2), obesity I (30 to <35 kg/m^2) and obesity II (35 kg/m^2 and over).

Figure 4 Multivariate Hazard Ratio of the effect of BMI >35 kg/m^2 on the knee, hip and hand compared to BMI <25 kg/m^2.