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1   **Association between overweight and obesity and risk of clinically diagnosed knee, hip, and**

2   **hand osteoarthritis: a population-based cohort study.**

3

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

5

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2   All authors, external and internal have full access to all the data (including statistical reports and

3   tables) in the study and can take responsibility for the integrity of the data and the accuracy of

4   the data analysis.

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1 **ABSTRACT**

2 **[248/250 words]**

3 **Objective**: Previous cohorts have reported associations between overweight/obesity and knee

4 and hand osteoarthritis (OA). However, no data on the effect of these on the OA burden are

5 available. We aimed to analyse the effect of overweight and obesity on the incidence of routinely

6 diagnosed knee, hip, and hand OA.

7 **Methods:**

8 Design: population-based cohort

9 Setting: primary care records from the SIDIAP database (>5.5 million subjects) covering >80%

10 of the population of Catalonia, Spain.

11 Participants: ≥40 years old with no OA on 01/01/2006 and with body mass index (BMI) data

12 available. Follow-up: from 01/01/2006 to 12/31/2010, loss to follow-up, or death.

13 Measures: BMI World Health Organization categories (exposure), and incident clinical diagnoses

14 of knee, hip, or hand OA (ICD-10 codes).

15 **Results**

16 1,764,061 subjects were observed for a median (inter-quartile range) of 4.45 (4.19 to 4.98) years.

17 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

18 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

19 (3.9 to 4.2) in the grade II obese respectively.

20 Compared to normal-weight subjects, being overweight or obese increased the risk of OA at all

21 three sites, especially at the knee: overweight and (grade I, II) obesity increased knee OA risk by

22 a factor of 2, 3.1 and 4.7 fold respectively.

23 **Conclusions**

1   Both overweight and obesity increase the risk of hand, hip, and knee OA, especially for the

2   latter, with a dose-response gradient with increasing BMI.

3

4

1   Obesity and osteoarthritis (OA) are two interconnected health care problems affecting a large

2   proportion of the adult population worldwide. The increasing weight of the population will lead

3   to nearly 1.3 billion and 573 million adults overweight and obese respectively by 2030 [1].

4   Moreover, OA increases as the population ages [2] representing a leading cause of chronic pain

5   and disability among older people [3].

6

7   There is extensive evidence supporting obesity as one of the major risk factors for knee OA [4-

8   7,8], independent of the method of assessment used [9]. To a lesser extent there are reports

9   associating obesity with hand OA [10,8] and more conflicting results are found regarding hip OA

10   [6,7,11,8]. The mechanical overload of the weight-bearing joint or the activation of metabolic

11   factors contributing to the joint damage have both been proposed as possible mechanisms to

12   explain how weight increases the risk of knee or hand OA [12].

13

14   Nevertheless the limited treatments for OA make prevention of modifiable risk factors, such as

15   obesity, a key target for public health and medical interventions today. Consequently, the aim of

16   this study is to analyse the effect of obesity on the incidence of symptomatic knee, hip and hand

17   OA, using a large population database.

18

1   **PATIENTS AND METHODS**

2   **Study design and setting:**

3   We conducted a population-based cohort study using routinely collected data from the Sistema

4   d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP) database

5   (http://www.sidiap.org).

6   **Data source:**

7   SIDIAP gathers clinical information as recorded by general practitioners (GP) and primary care

8   nurses including prescriptions, events (ICD-10 codes) and measurements (such as body mass

9   index, blood pressure, or spirometry results amongst others collected using structured

10   spreadsheets) during routine practice. It covers >5.5 million people (a representative >80% of the

11   population of Catalonia, Spain) registered with one of the 3,414 GPs working in any of the 274

12   primary care practices run by the Catalan Institute of Health (ICS for its acronym in Catalan

13   [15].

14   The Spanish (and by extension, the Catalan) healthcare system is of universal coverage, and GPs

15   are, as in the British NHS, gatekeepers to any other medical or allied healthcare professional

16   attention with the exception of Accident and Emergency rooms.

17   **Participants:**

18   Eligible participants were all subjects aged at least 40 years old without a history of diagnosed

19   OA in primary care records at index joint on 1st January 2006 and with at least one measurement

20   of BMI coded in the primary care computerized records (SIDIAP database)

21   **Study period:**

22   Participants were observed from study initiation (1st January 2006) or from the date when they

23   registered at any of the primary health care practices covered by the SIDIAP (whatever came

1 last) to the earliest of the following: end of the study (31st December 2010), transfer out of

2 catchment area, or death.

3 **Variables:**

4 Study exposure**:** The BMI coded by health care professionals in kg/m^2 during the study period

5 was the main study exposure. Values of BMI <10 or >60 were assumed as typing errors and not

6 used for the current analyses. When more than one measurement was available, the closest to

7 index date (1st January/2006) was used. Patients were classified according to the World Health

8 Organization definitions in: normal (BMI below 25 kg/m$^{2)}$, overweight (BMI 25 or over and

9 below 30 kg/m^2), obese grade I (BMI 30 or above and below 35 kg/m^2), and obese grade II (BMI

10 35 kg/m^2 or above).

11 Study outcomes**:** Incident clinical diagnoses of OA as registered by general practitioners during

12 the study period (1 January 2006 to 31 December 2010) were identified using a previously

13 validated list of ICD-10 codes: knee OA (M17, M17.0, M17.1, M17.2, M17.3, M17.4, M17.5

14 and M17.9), hip OA (M16, M16.0, M16.1, M16.2, M16.3, M16.4, M16.5, M16.6, M16.7 and

15 M16.9) and hand OA (M15.1, M15.2, M18, M18.0 to M18.5 and M18.9). OA coding within

16 SIDIAP has been validated against self-reported OA in the Global Longitudinal Study of

17 Osteoporosis in Women (GLOW) population-based cohort [13], as well as by reviewing free text

18 and x-ray reports collected in primary care records [14].

19 **Statistical analyses:**

20 Age (in 5-year groups) and gender-specific incidence rates (IRs) and 99% Confidence Intervals

21 (99%CIs) for each of the outcomes identified in the study period were estimated assuming a

22 Poisson distribution.

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

1 99%CIs for an incident clinical diagnosis of knee, hip, and hand OA according to BMI

2 (continuous, per kg/m^2 increase) and BMI category (using normal weight as a reference group).

3 Age-specific adjusted rate ratios (RRs) for overweight, obese grade I and obese grade II

4 compared to normal-weight were calculated using Poisson regression.

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

6

7 **Ethical approval:**

8 Scientific approval was obtained from the SIDIAP Scientific Committee, and ethics approval

9 was granted by the relevant board (CEIC IDIAP Jordi Gol) with certificate number P14/153.

10 Patient consent was not required as only anonymised retrospective data was used for this study,

11 and no patient or GP contact was required.

12

1   **RESULTS**

2

3   **Baseline characteristics**

4   A total of 1,764,061 (54.0%) out of 3,266,826 potentially eligible subjects registered in SIDIAP

5   had data on BMI, and were therefore included in the study. Compared to the source population,

6   the included participants (i.e. with BMI data available) were slightly older (64.1 versus 62.4

7   years) and more likely to be women (54.2% versus 51.8%).

8   Eligible subjects were categorized into the following BMI categories: 446,034 (25.3%) normal-

9   weight, 742,258 (42.1%) overweight, 409,714 (23.2%) grade I obesity, and 166,055 (9.4%)

10   grade II obesity. Baseline characteristics of subjects according to their BMI category are shown

11   in table 1.

12

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

14   Participants were observed for a median (IQR) of 4.45 (4.19 to 4.98) years. Incidence rates are

15   reflected in figures 1, 2 and 3. During this period, 83,469 incident cases with knee OA were

16   identified with crude-incidence rates of 9.1, 99%CI (9.0 to 9.2) per 1,000 person-years at risk

17   respectively, 27,701 incident cases with hip OA were identified with crude-incidence rates of 2.9

18   (2.8 to 2.9) per 1,000 person-years at risk respectively and 30,909 incident cases with hand OA

19   were identified with a crude-incidence rates of 3.2 (3.2 to 3.3) per 1,000 person-years at risk

20   respectively. Incidence rates of knee, hip and hand OA for each BMI category are represented in

21   table 2.

22   The incidence rates for knee and hip OA increased since the age of 40 years old with a special

23   increase at the age of 55-60 and 70 to 75 years old respectively (figures 1 and 2)

1 **Association of BMI and knee, hip and hand OA:**

2 The incidence of knee, hip, and hand OA increased with increasing BMI, with a greater increase

3 for knee OA (figures 1-3). The adjusted HR for the effect of BMI on OA is reported in table 3.

4

5 In the fitted survival model, age increased the risk of OA similarly at all three sites (knee, hand

6 and hip) whereas female gender increased the risk mostly in hand OA.

7 After categorization into WHO-recommended groups, and compared to those with normal

8 weight ($<25kg/m^2$), those with overweight had an excess risk of OA, especially at the knee. This

9 excess risk continued increasing as the BMI increased, being more pronounced for knee OA in

10 subjects with grade 2 obesity ($>35kg/m^2$); these subjects were 4.7 fold more frequently

11 diagnosed with knee OA compared to subjects with BMI $<25kg/m^2$.

12 The observed associations between overweight/obesity and the risk of knee, hip were present

13 throughout all the participant ages (40 years or older) (Figures 1, 2 respectively). However, the

14 excess risk of OA associated with obesity varied at different ages for knee OA while this

15 association was more constant (unmodified by age) for hip OA, (Figure 4).

16

1 **DISCUSSION**

2 **Principal findings:**

3 Our study confirms that the incidence of OA mostly affects the knee in our population, compared

4 to the other joint sites, reaching a maximum incident rate of 19.5 per 1,000 persons-year for

5 subjects with grade II obesity compared to the 3.7 per 1,000 persons-year for normal-weight

6 subjects. Obesity seemed to increase the risk in all three joint sites, including the hip, but the

7 greatest increase was reported for knee. The effect of obesity on knees was more pronounced at

8 younger ages, which could be useful for public health messaging.

9 We found a positive association between overweight and obesity with the risk of developing OA

10 at the knee, hip and hand. The excess risk found was greater for subjects with grade II obesity,

11 who were 4.7 times more likely to develop knee OA compared to subjects with normal-weight.

12

13 **Strengths and weaknesses of the study:**

14 Our main strength is the large population included in this study, which allows us to easily

15 extrapolate our results using a clinically relevant outcome. Moreover, to our knowledge this is

16 the first study to analyse the impact of obesity on osteoarthritis using routinely collected data

17 from primary care. However, this study must be also interpreted in the light of certain

18 limitations; the main outcome was based on symptomatic OA and no information was collected

19 regarding radiographic OA. However, there is strong evidence that obesity is associated with

20 radiographic OA [7], which suggests that our results would remain unchanged. Moreover,

21 SIDIAP does not contain information on the side of the joint affected (joint site (eg, knee) was

22 considered as a whole and nearly 46% of the subjects had missing information on their BMI. The

23 missing BMI could be a source of bias, however the BMI registration in Spain is part of the

1   recommended health check programme called PAPPs required by the government in order to

2   give funding to the primary health cares [16], hence it is not always linked to a more pathological

3   population but maybe to a population that more frequently uses primary health care resources.

4   Moreover, we compared the BMI distribution of the population in our study with another large

5   national study carried out in Spain, where the trends of the BMI were analysed on over 11,000

6   subjects and found similar percentages of obesity between 2008-2010 [17], witch reinforces the

7   representativeness of our population. Conversely, we analysed the IR of knee, hip and hand OA

8   in those subjects with missing BMI and found a lower IR of OA in this population (Unadjusted

9   IR 2.98 per 1000persons-year for knee, IR 1.03 per 1000 persons-year for hip and IR 1.33 per

10   1000 persons-year for hand OA), although we do not think that this invalidates the association

11   between BMI and OA at the different sites found in this study, this may limit its

12   representativeness. Another limitation to be considered is the lack of information on incident

13   overweight subjects during the study period; the information on BMI relied on the available data

14   on the SIDIAP database and given that periodic BMI registering is quite uncommon we were not

15   able to account for this.

16   Despite previous validation of the data collected in the SIDAP database, [13] and due to the

17   retrospective nature of this study, the possibility of misclassification and registration biases

18   should be considered. Finally, we did not collect information on occupation, physical activity or

19   previous injuries, which could have influenced our results. Previous studies have shown an

20   increased risk with manual labour occupations and OA [18], while physical activity has been

21   found to have an unclear association with OA [6]

22   **Strength and weaknesses in relation with other studies**

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

1   association has been especially reported for knee [4-8] and hand OA [10], with more inconsistent

2   results for hip OA [6,7,8,11]. Our results confirm these previous findings for knee and hand OA

3   and extend what has been previously published regarding hip OA [11]; compared to those

4   subjects with normal-weight, our overweight and grade II obese population had a 46 and a 93%

5   excess risk of hip OA respectively. Some previous studies [6-8] did not find an association

6   between BMI and hip OA which could be due to the low number of subjects with hip OA

7   included (compared to the 27,701 cases found in our population), the self-reported OA [6-7]

8   (compared to our routinely collected data by primary health care professionals) or the selection

9   of a rather healthy and younger population [6-8], leading to an underestimation of this

10   association. Among the studies that did analyze the association between obesity and OA through

11   a life-course approach [19-23], early and middle adulthood [19, 20, 22, 23] and up to the age of

12   60 years old [20, 22, 23] were identified as periods in life where there was an excess risk of OA

13   for obese and overweight subjects. Furthermore, another previous study based on data from the

14   National Health Interview Survey in the US [24] found that the incidence of knee OA peaked in

15   those subjects aged 55 to 64 years old and was higher among obese subjects. Our results are

16   consistent with these findings; compared to the normal-weight subjects those with obesity (grade

17   I and II) had an excess risk of OA that varied with age, especially at the knee.

18

19   **Meaning of the study and implications of current findings:**

20   Obesity is a modifiable risk factor and correctly identifying the population with a higher risk of

21   OA, such as the one identified by our study, could help prevention strategies to reduce the

22   symptomatology or even the future progression of OA. Despite that interventions aiming to

23   reduce the clinical outcomes of OA have proven to be effective [25,26], changes in peoples

1   lifestyles and habits are not easy to implement. By identifying the age at which obesity would

2   more seriously influence the risk of OA, healthcare providers could focus prevention strategies

3   on a narrower target population (i.e. middle adulthood).

4

5   **Unanswered questions and future research**

6   The mechanism through which obesity increases the risk of OA has not yet been fully elucidated

7   and falls outside the scope of this study. Whether the peak excess risk observed in middle

8   adulthood for knee and hand OA reflects the pathogenic pathways involved in the appearance of

9   OA at the different sites (eg due to the increase in metabolic disorders such as diabetes or due to

10   menopause [27,28]) should be investigated in future research.

11

12   **Conclusions:**

13   Both overweight and obesity increase the risk of hand, hip, and knee OA, especially for the

14   latter, with a dose-response gradient with increasing BMI. Health care providers should

15   implement prevention tools, especially focused on these ages, in order to reduce the risk of

16   developing OA at these sites.

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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

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

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2   * COPD : Chronic obstructive pulmonary disease

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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.

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

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4 All p-vals<0.001
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1   **FIGURES**

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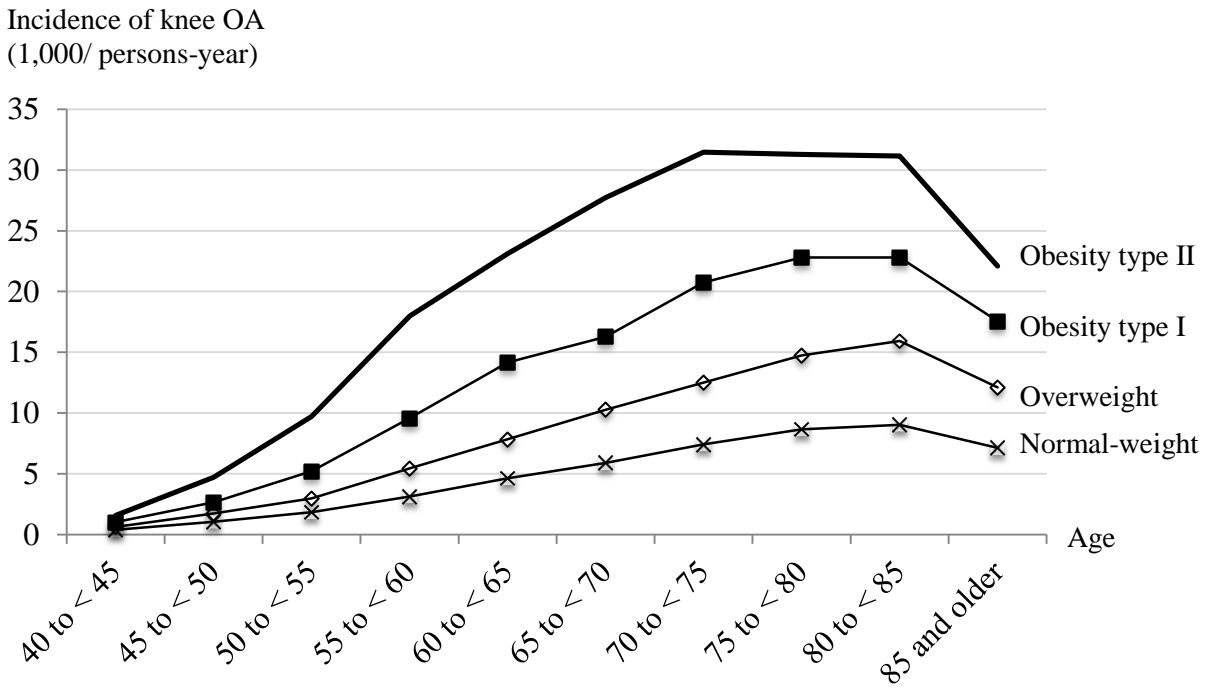
Incidence of knee OA
(1,000/ persons-year)
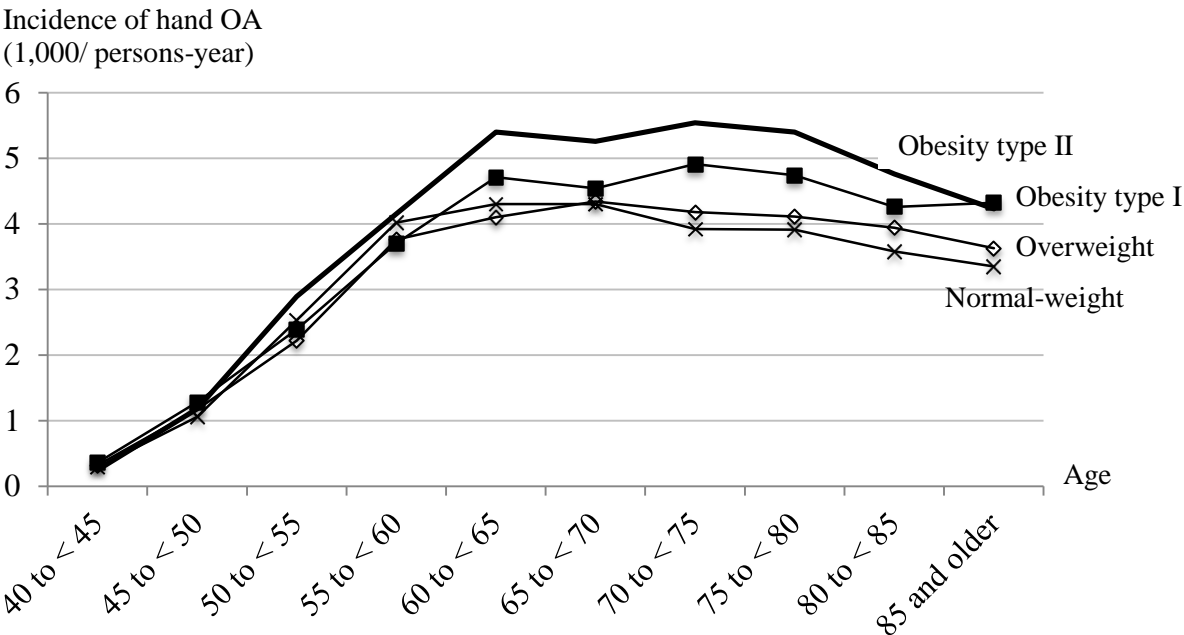

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5   * BMI based on WHO definitions: Normal-weight (<25kg/m²),
     overweight (25 to <30 kg/m²), obesity I (30 to <35 kg/m²) and obesity
     II (35 kg/m² and over).

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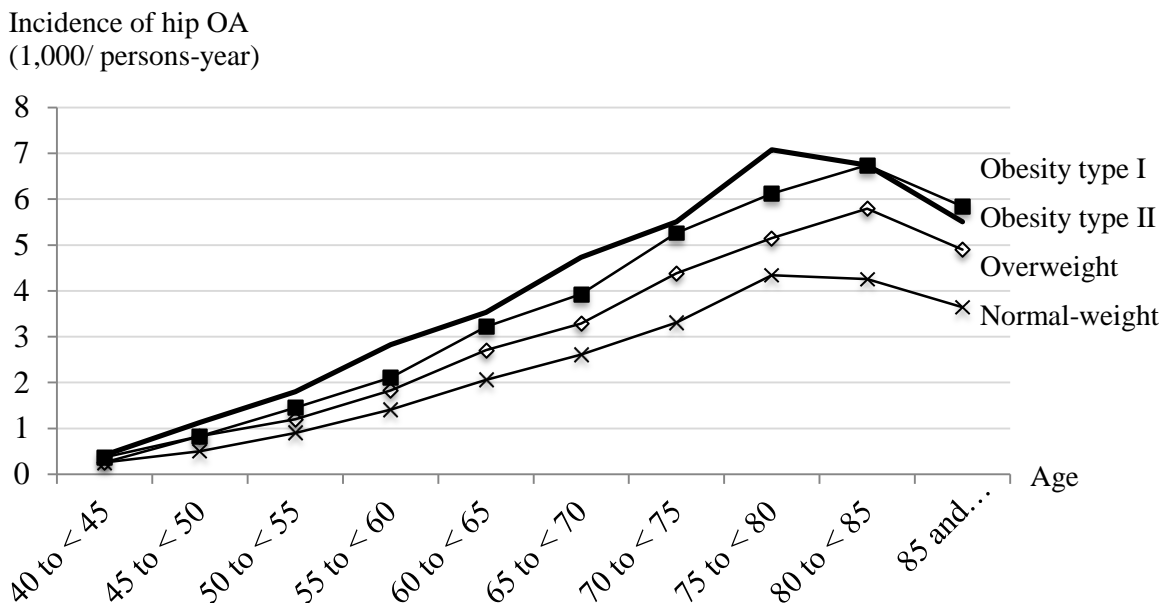
Incidence of hip OA
(1,000/ persons-year)

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* 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).

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

Incidence of hand OA
(1,000/ persons-year)

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

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1   **Figure 4 Multivariate Hazard Ratio of the effect of BMI >35 kg/m² on the knee, hip and**

2   **hand compared to BMI <25 kg/m².**

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