Sex-specific dose-response relationships between obesity and incidence of fractures

Anne-Frédérique Turcotte (1,2), Sonia Jean (3,4), Suzanne Morin (5), Fabrice Mac-Way (1,3), Claudia Gagnon (1,2,3)

(1) Endocrinology and Nephrology Unit, CHU de Quebec Research Centre, Quebec City, Canada; (2) Quebec Heart and Lung Institute Research Centre, Quebec City, Canada; (3) Department of Medicine, Laval University, Quebec City, Canada; (4) Bureau d'information et études en santé des populations, Institut national de santé publique du Québec, Québec (QC), Canada; (5) Department of Medicine, Faculty of Medicine, McGill University, Montreal (QC), Canada.

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INTRODUCTION

Obesity has long been thought to be a protective factor against fractures. However, contradicting results have emerged in recent years on the relationship between obesity and the risk of fracture. This may be explained by the fact that the association between obesity and fracture risk appears to vary depending on sex, the skeletal site studied and definition of obesity used (body mass index vs. waist circumference) (1–3).

OBJECTIVE

This study aimed to evaluate the sex-specific dose-response relationships between obesity, defined using body mass index (BMI) or waist circumference (WC), and fracture incidence at any site and by skeletal site (major osteoporotic fractures (MOF), distal lower limbs and distal upper limbs).

METHODOLOGY

We used CARTaGENE, a large prospective population-based cohort of individuals aged 40–70 years from the province of Quebec, Canada.

- Random selection in 2009–2010 and followed through healthcare administrative databases until March 31st 2016.
- Incident fractures were identified using a previously validated algorithm (4).
- BMI and WC were measured at recruitment and used as continuous variables.
- Cox proportional hazard models were used to evaluate the dose-response relationships.
- Analyses were adjusted for potential confounders identified using a directed acyclic graph: age, menopausal status, ethnicity, marital status, education, income, area of residence, smoking status, alcohol consumption, physical activity level, supplemental calcium and vitamin D intake, history of fracture, and comorbidities and medications known to influence fracture risk.

RESULTS

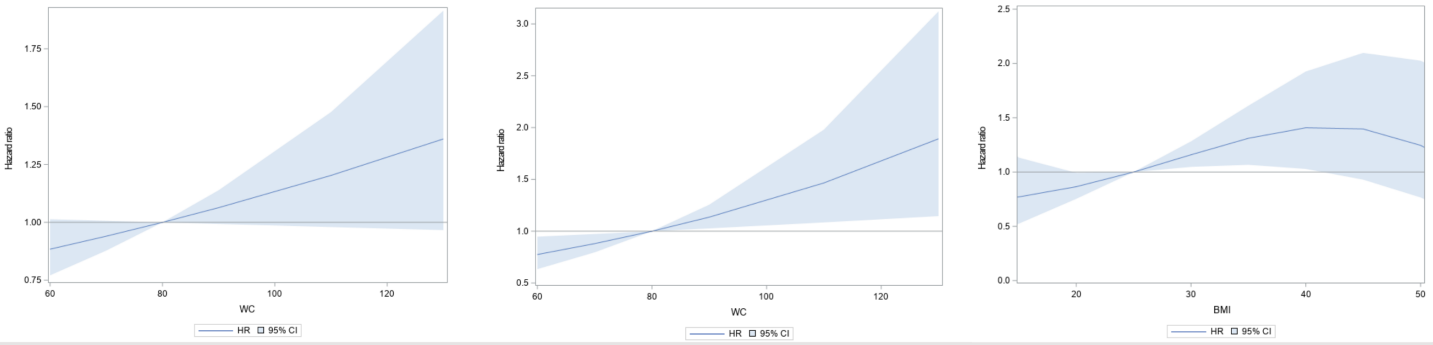
- Median follow-up of 5.8 years
- Fractures by sites were as follows:
  - 415 MOFs (260 in women and 155 in men)
  - 353 fractures at the distal lower limbs (219 in women and 134 in men)
  - 203 at the distal upper limbs (141 in women and 62 in men)
- WC was treated linearly and BMI was treated using cubic splines (best model fit based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).
- In men, WC and increased BMI were not significantly associated with any fracture outcome. However, men with a BMI of 17.5 kg/m2 and lower had a 2-fold increased risk of distal upper limb fractures compared to men with a BMI of 25 kg/m2.

Table 1. Baseline characteristics of the CARTaGENE population (selected characteristics).

Variables	Women				Men			
	All women (n=9 985)	No fracture (n=9 488)	Incident fracture (n=497)	P value	All men (n=9 372)	No fracture (n=9 049)	Incident fracture (n=323)	P value
Sociodemographic characteristics								
Age (years)	54±8	54±8	57±7	<0.001	54±8	54±8	54±8	0.557
≥ 65, n (%)	1186 (11.5)	1095 (11.2)	91 (17.4)		1329 (13.7)	1291 (13.8)	38 (11.3)	
Menopause	4788 (48.0)	4484 (47.3)	304 (61.2)	<0.001				
Ethnicity								
Caucasian	9082 (91.0)	8609 (90.7)	473 (95.2)	0.023	8249 (88.0)	7946 (87.8)	303 (93.8)	0.019
Other	903 (9.0)	879 (9.3)	24 (4.8)		1123 (12.0)	1103 (12.2)	20 (6.2)	
Education								
≤ High school	2659 (27.2)	2530 (27.2)	129 (27.2)	0.136	2329 (25.5)	2229 (25.2)	100 (31.9)	0.023
> High school	7270 (72.8)	6908 (72.8)	362 (72.8)		6988 (74.5)	6768 (74.8)	220 (68.1)	
Lifestyle habits								
Smoking	1348 (13.5)	1276 (13.5)	72 (14.5)	0.509	1449 (15.5)	1384 (15.3)	65 (20.1)	0.012
Alcohol consumption (serving/week)	4±7	4±7	4±7	0.444	6±10	6±10	7±12	0.019
Supplemental calcium intake	3531 (35.4)	3332 (35.1)	199 (40.0)	0.025	486 (5.2)	462 (5.1)	24 (7.4)	0.064
Supplemental vitamin D intake	3178 (31.8)	2987 (31.5)	191 (38.4)	0.001	702 (7.5)	678 (7.5)	24 (7.4)	0.967
Medical history and medications								
History of fracture	81 (0.8)	69 (0.7)	12 (2.4)	<0.001	49 (0.5)	41 (0.5)	8 (2.5)	<0.001
Type 2 diabetes	739 (7.4)	692 (7.3)	47 (9.4)	<0.001	1147 (12.3)	1106 (12.2)	41 (12.7)	0.031
Type 1 diabetes	38 (0.4)	29 (0.3)	9 (1.8)	<0.001	82 (0.9)	77 (0.9)	5 (1.6)	0.186
Osteoporosis	1244 (12.5)	1138 (12.0)	106 (21.0)	<0.001	274 (2.9)	260 (2.9)	14 (4.3)	0.126
Arthritis	542 (5.4)	498 (5.3)	44 (8.9)	<0.001	375 (4.0)	355 (3.9)	20 (6.2)	0.041
Antiresorptive drugs	622 (6.2)	562 (5.9)	60 (12.1)	<0.001	80 (0.9)	74 (0.8)	6 (1.9)	0.046
Glucocorticoids	80 (0.8)	79 (0.8)	1 (0.2)	0.124	74 (0.8)	69 (0.8)	5 (1.6)	0.117

- In women, greater WC was linearly associated with an increased risk of distal lower limb fractures and tended to be associated to any fracture site. For each 5cm increase in WC, the HRs were 1.07 (95%CI: 1.01, 1.12) and 1.03 (95%CI: 1.00, 1.07), respectively. Greater BMI was also associated with a greater risk of distal lower limb fractures. Compared with women with a BMI of 25 kg/m2, those with a BMI of 27.5-40 kg/m2 showed a risk increasing linearly from 5% to 40%, while women with a BMI of 22.5 kg/m2 displayed a 5% lower risk of fracture at this site. There was no association between WC or BMI and either MOFs or distal upper limb fractures.

Figure 1. Dose-response relationships between waist circumference and the risk of fracture at A) any site and B) distal lower limbs, and C) between body mass index and distal lower limb fractures in women.



CONCLUSION

Our findings showed that the relationship between obesity and fractures is complex and varies by sex. In women, there was a linear relationship between waist circumference and the incidence of fracture at any site and at the distal lower limbs. Similar results were observed for women with a BMI between 27 and 40 kg/m2. In men however, there was no relationship between the risk of fracture and obesity (defined by either BMI or WC). Understanding the mechanisms by which women with obesity are more susceptible to fractures is necessary to develop prevention strategies.

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