Original Article

Relationship Between Body Mass Index and Fracture Risk Is Mediated By Bone Mineral Density[†]

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DISCLOSURES

Professor J.A. Eisman has served as consultant on the Scientific Advisory Board for Amgen, Eli Lilly, Merck Sharp & Dohme, Novartis, Sanofi-Aventis, Servier and deCode. He was the editor-in-chief for the Journal of Bone and Mineral Research from 2003 to 2007 and was a committee member of Department of Health and Aging, Australian Government and Royal Australian College of General Practitioners. Dr Jacqueline R. Center has given educational talks for Amgen, Merck Sharp & Dohme, and Sanofi-Aventis. Professor T.V. Nguyen has received honorarium for consulting and speaking in symposia sponsored by Merck Sharp & Dohme, Roche, Servier, Sanofi-Aventis, and Novartis. Other authors have no conflict of interest.

ABSTRACT

Aim The relationship between body mass index (BMI) and fracture risk is controversial. We sought to investigate the effect of collinearity between BMI and BMD on fracture risk, and to estimate the direct and indirect effect of BMI on fracture with BMD being the mediator. **Methods** The study involved 2,199 women and 1,351 men aged 60 years or older. BMI was derived from baseline weight and height. Femoral neck BMD was measured by dual energy X-ray absorptiometry (GE-LUNAR, Madison, WI). The incidence of fragility fracture was ascertained by X-ray reports during 1991-2012. Causal mediation analysis was used to assess the mediated effect of BMD on the BMI-fracture relationship. **Results** Overall, 774 women (35% of total women) and 258 men (19%) had sustained a fracture. Approximately 21% of women and 20% of men were considered obese (BMI $\geq$ 30). In univariate analysis, greater BMI was associated with reduced fracture risk in women (HR 0.92; 95% CI, 0.85-0.99) and in men (HR 0.77; 95% CI, 0.67-0.88). After adjusting for femoral neck BMD, higher BMI was associated with greater risk of fracture in women (HR 1.21; 95% CI, 1.11-1.31) but not in men (HR 0.96; 95% CI, 0.83-1.11). Collinearity had minimal impact on the BMD-adjusted results (VIF=1.2 for men and women). However, in mediation analysis, it was found that the majority of BMI effect on fracture risk was mediated by femoral neck BMD. The overall mediated effect estimates were -0.048 (95% CI, -0.059 to -0.036; $P < 0.001$) in women and -0.030 (95% CI, -0.042 to -0.018; $P < 0.001$) in men. **Conclusion** These analyses suggest that there is no significant direct effect of BMI on fracture, and that the observed association between BMI and fracture risk is mediated by femoral neck BMD in both men and women.

KEY WORDS: BMI; OBESITY; BMD; FRACTURE; MULTICOLLINEARITY; MEDIATION ANALYSIS.

INTRODUCTION

There are currently conflicting views on the relationship between obesity and fragility fracture. Traditionally, obesity is believed to be protective against fragility fracture, this view is supported by many earlier studies [1-3]. For instance, hip fracture risk in women was increased by 7.4% for each unit decrease in body mass index (BMI).[1] In men, lower BMI was also found to be a significant risk factor for hip fracture, with a reduction of 32% in relative risk per unit change in BMI.[3] In contrast, more recent findings suggest that obesity may not be beneficial to bone health. Some studies even showed that higher body mass is a significant risk factor for fragility fracture, particularly for those occurring at sites other than hip.[4-7]

It is notable that most of the findings supporting an adverse effect of body mass on fracture risk were derived from the BMD-adjusted data. In those studies, it was shown that after controlling for BMD, individuals with higher BMI had greater risk of fracture than those with low BMI.[5,8,9] For example, in a prospective study on elderly women, lower BMI was found to be associated with greater risk of hip fracture before adjustment for BMD, but the association was reversed after BMD was included in the statistical model.[8] Since BMI is known to be correlated with BMD,[10,11] a model with both BMI and BMD included could be confounded by the presence of collinearity, a statistical phenomenon in which two independent variables in a regression model are linearly related and provide redundant information about the response. As a consequence, change in one variable affects the estimate of the other, resulting in inaccurate regression estimation, and sometimes incorrect sign for the estimated coefficients.[12,13]

However, a significant change in the estimated coefficient of a predictor with inclusion of a second variable could also be an indication of a mediation effect. Mediation is defined as "the generative mechanism through which the focal independent variable is able to influence the dependent variable of interest".[14] Thus, according to the definition of mediation, [15] BMD is likely a mediator in the relationship between BMI and fracture risk because (i) the variations in BMD significantly accounts for variation in BMI; [16,17] (ii) variations in BMD significantly accounts for fracture risk,[18,19] and (iii) when BMD is controlled for, the effect of BMI on fracture is no longer significant or partially diminished. In case of inconsistent mediation, the sign of the mediated effect of BMI on fracture could be opposite to that of the total effect without controlling for BMD. [20]

The causal structure of the relationship between BMI, BMD and fracture has not been investigated. The present study sought to examine the effect of collinearity between BMI and BMD on fracture risk, and to estimate the direct and indirect effect of BMI on fracture with BMD being the mediator.

STUDY DESIGN AND METHODS

Participants

Participants in this study were drawn from the Dubbo Osteoporosis Epidemiology Study (DOES), which was commenced in 1989 and has been on-going since. The setting is the city of Dubbo, with a population of ~32,000, situated 400 km northwest of Sydney Australia. DOES is an ongoing community-based prospective study on risk factors for fracture and chronic diseases. Details of the study design and population have been described elsewhere.[21] Briefly, the initial study population included 1,581 men and 2,095 women aged 60 years or above, of whom 98.6% was Caucasian and 1.4% was indigenous Aboriginal. Recruitment has since been extended to the younger community and the DOES study population has expanded to ~20,000 people by December 2012. The present study consisted of 3,550 participants (2,199 women and 1,351 men) aged ≥ 60 years, who were recruited between 1989 and 2011. The median follow-up period was 6 years (range between 0.1 - 22 years). This study was approved by the St Vincent's Hospital Ethics committee and written informed consent was obtained from all participants.

Measurements

Anthropometric and clinical history data were ascertained by a structured questionnaire at baseline and subsequent visits. The interview was conducted by registered nurses to collect information on clinical risk factors such as smoking, history of falls in the last 12 months, prior fracture after age 50, use of hormonal replacement therapy (HRT) and glucocorticoid.

At baseline, body weight (with heavy clothing and shoes removed) was obtained on an electronic scale, which was calibrated prior each measurement. Height was measured without shoes with a wall-mounted stadiometer. BMI was calculated as weight in kilogram divided by square of height in meter (kg/m²). Based on the WHO definition, individuals with a BMI <25kg/m² were classified as 'normal-weight', BMI between 25–29kg/m² were 'overweight', and individuals with BMI ≥ 30 kg/m² were identified as 'obese'.[22]

Bone mineral density (BMD) was measured at the femoral neck by dual-energy X-ray absorptiometry (DXA), using GE Lunar DPX-L densitometer (GE-Lunar, Madison, Wisconsin, USA). The radiation dose is less than 0.1 μGy and the coefficient of variation for femoral neck BMD was 1.5% in our institution.[23]

Fracture Ascertainment

Fractures were the primary outcome of this study and referred to those occurring with minimal trauma e.g. falls from standing height or less. All fracture cases were ascertained through X-ray reports from two to three radiology centers within the Dubbo region as previously described.[21] High trauma (e.g. motor vehicle accident, sport injury or falls from above standing height) and pathological fractures (e.g. malignant disease and Paget's disease of bone) were excluded from the analysis. No systemic X-ray screening for asymptomatic vertebral fractures was conducted and vertebral fractures were clinically diagnosed. Fractures were analyzed as any fracture, or as subgroup of hip, upper limb, lower limb and symptomatic vertebral fracture.

Data analysis

The primary statistical model for the analysis of association between BMI and fracture risk was the Cox's proportional hazards model, with time to fracture being the outcome. Because BMI is correlated with BMD and other clinical risk factors, we considered 4 models as follows: (1) an univariate model with BMI alone; (2) a multivariate model with BMI and femoral neck BMD; (3) a multivariate model with BMI and clinical risk factors, i.e. falls, prior fracture, history of smoking, use of glucocorticoid and hormonal replacement therapy (HRT; in women); and (4) the full model with BMI, femoral neck BMD and clinical risk factors as predictors. In each model, the strength of association between BMI and fracture risk was measured by the hazard ratio and 95% confidence interval per standard deviation (SD). The proportional hazards assumption was tested by using Schoenfeld's residuals, in which the residual of individual covariate was plotted against time to determine if the effect of the covariate was constant over time. Chi-squared test was then used to evaluate the linear association between the Schoenfeld residuals and time as proposed by Grambsch & Therneau,[24,25] and no significant relationship was found in any of the covariates involved.

In order to detect the existence and severity of collinearity between BMI and BMD in the fracture risk predictive model, we calculated the linear dependence between BMI and femoral neck BMD using Pearson's product-moment correlation coefficients (r). In addition, variance inflation factor (VIF) was used to assess the

extent to which the variances of the estimated coefficients were inflated (i.e. VIF = 1/[1-R^2] , where R^2 is the coefficients of determination for regression of *i*th independent variable against the remaining variables).[26] A predictor with VIF > 10 is considered as an indicative of serious collinearity. We also used the ridge regression [27] to detect collinearity in the data. Ridge regression is a statistical technique which is often used as an alternative to overcome collinearity by introducing a small amount of bias into the estimate so as to minimize the variance and control the instability of the estimators.[28] However, the technique can also be used to assess the existence of collinearity by examining the ridge coefficients with incremental bias or constant (*k*). If the regression coefficients remained stable with additional bias (*k*), then collinearity, even if it did exist, would not pose significant impact on the parameter estimates.[29] In the present study, we examined the variation in the regression coefficients of BMI and femoral neck BMD for $0 < k < 1$, using the Cox's ridge method proposed by Xue and colleagues [27].

To determine whether the relation between BMI and fracture risk was mediated by BMD, causal mediation analysis was carried out based on the following statistical models:

$$Model\ I: Fracture\ risk = \alpha_1 + \beta_1 (BMI) + \varepsilon_1$$

$$Model\ II: BMD = \alpha_2 + \beta_2 (BMI) + \varepsilon_2$$

$$Model\ III: Fracture\ risk = \alpha_3 + \beta_3 (BMI) + \beta_4 (BMD) + \varepsilon_3$$

where α, β and ε represent the intercepts, regression coefficients and residuals, respectively.[15,20] The indirect or mediated effect was estimated as the product of the regression of femoral neck BMD on BMI (β_2) and fracture risk on femoral neck BMD (β_4). The direct effect is the net association of BMI and fracture risk without the mediation effect (β_1). All models were adjusted for covariates which included age, falls, prior fracture, smoking, physical activity level, glucocorticoid use and HRT (in women). Because the outcome variable is dichotomous, logit regression with weighted least squares estimation method was used to calculate the estimated coefficients and the mediation effects were estimated from the standardized regression coefficients.[20] One of the key criteria to define a variable as mediator is that the mediator must precede the outcome. Given the prospective design of the study, the temporal precedence between the femoral neck BMD and fracture risk was readily established.[30] The statistical significance of the mediated effect was assessed by

using Sobel test.[31] Bias-corrected bootstrapping technique [32] with 1000 replications was used to determine the confidence intervals and confirmed the statistical significance of the proposed mediational pathway.

To assess whether prediction of fracture risk from BMI differs across levels of femoral neck BMD (i.e. femoral BMD as a moderator), an interaction term of BMI and femoral neck BMD was included in the model as follows:

$$Fracture\ risk = \alpha_4 + \beta_5(BMI) + \beta_6(BMD) + \beta_7(BMI * BMD) + \varepsilon_4$$

where β_7 is the regression coefficient for the interaction term. Moderation effect is indicated if regression estimate of the interaction term is statistically different from zero.[33]

In order to quantify the percentage of variance that can be explained by an individual predictor and the degree of improvement in fit of the models with different variables, we used Nagelkerke's method to calculate the pseudo-R^2 for each factor [34] . Furthermore, net reclassification analysis was performed to quantify the level of improvement in discrimination between fracture and non-fracture cases when BMI was added to the base model with femoral neck BMD. In this analysis, the study population was divided into lower, middle and upper risk groups based on their 10-year absolute risk of fracture for the model with and without BMI included. To ensure a comparable sample size for each risk group, the cut-off values were chosen according to the distribution of fracture incidence in the study population (i.e. lower tertile, middle tertile and upper tertile). The difference in proportion of those with and those without fracture moving up or down a risk category was calculated as proposed by Pencina et.al.[35] All statistical analyses were performed using the R statistical environment Version 3.0.2 for Windows.[36]

RESULTS

Baseline characteristics

During the 22-year follow-up period, 774 women (35%) and 258 men (19%) had sustained at least one low-trauma fracture. Compared with those without fracture, individuals with fracture were older, lighter and had lower femoral neck BMD. They were more likely to be glucocorticoid users, had prior fracture after age 50 with higher incidence of falls in the preceding 12 months. Women with fracture also tended to be current or past smokers and were less likely to have received HRT compared to their non-fracture counterparts **(Table 1)**.

The prevalence of obesity (i.e. BMI ≥ 30) was 21% in women and 20% in men. Women and men with greater BMI had lower risk of fracture (**Figure 1**). In the unadjusted bivariate analysis **(Table 2)**, greater BMI was associated with reduced risk of fragility fracture in women (HR 0.92; 95% CI 0.85 – 0.99) and men (HR 0.77; 95% CI 0.67 – 0.88). This association was also observed for hip fracture and vertebral fracture. After adjusting for femoral neck BMD, greater BMI was associated with greater risk of fracture in women (HR 1.21; 95% CI 1.11 – 1.31), but not in men (HR 0.96; 95% CI 0.83 – 1.11). Further adjustment for other covariates including age, falls, prior fracture, smoking, glucocorticoid and HRT use (in women) did not significantly alter the results.

Collinearity analysis

BMI was positively and significantly correlated with femoral neck BMD. The coefficient of correlation was 0.41 (95% CI, 0.37-0.44; $P < 0.001$) for women and 0.37 (95% CI, 0.32-0.41; $P < 0.001$) for men. In women, the variance inflation factors (VIFs) were 1.26 for BMI, 1.50 for femoral neck BMD and 1.37 for age. Similar results were observed in men (VIF for BMI = 1.20, femoral neck BMD = 1.23 and age =1.17). In both men and women, the ridge regression coefficients of BMI and femoral neck BMD were relatively stable with incrementing bias being introduced into the models (**Table 3)**, suggesting that collinearity did not contribute to the sudden change in the regression estimate of BMI on fracture risk.

Mediation and moderation analysis

Figure 2 presents the path coefficients for the proposed mediation models, and the resulting total and mediated effects are summarized in **Table 4**. BMI was significantly associated with femoral neck BMD, which

in turn, was significantly associated with fracture risk. This inter-relationship was observed for hip, vertebral, upper limbs and lower limbs fracture. In all fracture sites examined, there was no significant direct effect of BMI on fracture risk. In contrast, the indirect effects (i.e. effect that was mediated by femoral neck BMD) were all statistically significant. The magnitudes of indirect effect of BMI on fracture risk were greater in women than in men, with their respective estimates being -0.048 (95% CI, -0.059 to -0.036) and -0.030 (95% CI, -0.042 to -0.018) for any fracture. The statistical significance of the mediated effects was further confirmed by the Sobel test (**Table 4)**.

Moderation analysis showed that there was no significant moderation effect between femoral neck BMD and BMI. The estimated coefficients for the interaction terms of femoral neck BMD and BMI were -0.05 (P = 0.52) for women and 0.07 (P = 0.58) for men, and hence, were not included in the final models.

Contribution of BMI to fracture prediction

The proportion of variance in fracture liability that could be explained by BMI was estimated by Nagelkerke's method in the Cox's regression model. In the unadjusted bivariate model, BMI alone accounted for 1.2% and 3% of fracture liability variance in women and men, respectively. Reclassification analysis **(Table 5)** shows that compared to model with femoral neck BMD alone, a model with BMI and femoral neck BMD reclassified ~16% of women and ~4% of men into different risk categories. However, the net reclassification attributable to BMI was less than 0.5%. In fact, the inclusion of BMI worsened the predictive value with net reclassification being -0.2% in both men and women.

DISCUSSION

Many studies have reported a significant change in the BMI-fracture association after BMD adjustment.[5,8,9] Some studies showed that greater BMI had adverse effect on fracture risk after "adjusting" for BMD.[5,6,8,37] Given the significant correlation between BMI and BMD, such change could either be a sign of collinearity and/or result of mediation effect of BMD. In the present study, we tested both hypotheses and found little evidence for the effect of collinearity; instead, our results suggest that the effect of BMI on fracture risk is largely mediated by BMD. Thus, we propose that lower BMI is an independent risk factor for fracture through lower femoral neck BMD (mediator).

Our findings are in line with that previously suggested, but not yet proven, by other authors[8,9] The significance of the mediational effect is, perhaps, not surprising as low BMD is a well-known risk factor for fracture [18,19] and there is a biological link between fat and BMD. In fact, adipose tissue is one of the major sources of estrogen production, particularly in postmenopausal women. Its main function on bone is to suppress osteoclasts activity, and thus, increases bone formation.[38] Leptin is another adipocyte-derived hormone involved in bone turnover regulation.[39] In vitro studies have shown that leptin can act directly on osteoblasts to enhance their proliferation and differentiation.[40] Also, in mice with leptin-deficiency, they were found to have greater weight but significantly lower BMD compared to their wild-type counterparts.[41]

The form of mediational effect of femoral neck BMD on the BMI-fracture path appeared to be site-specific. In men, apart from upper limb fracture, the mediated effects found in all fracture sites being examined were of "consistent mediation", as they had the same sign as the direct effects.[20] Similar mediational effects were also observed in women for hip and lower limb fracture, in which, the mediated effect from femoral neck BMD had accounted for ~96% and ~71% of the total effect of BMI on hip and lower limb fracture risk respectively. These findings are in agreement with many previous reports on BMI and hip fracture risk.[1,8,42] For example, in a meta-analysis of 12 prospective studies, hip fracture risk was found to be lower with higher BMI before BMD-adjustment, however, the protective effect of higher BMI on osteoporotic and any fracture was diminished when BMD was taken into account.[9]

For vertebral, upper limb and any fracture in women, a different form of mediation seems to be operating in the causal pathway between BMI and fracture risk. The divergent direction of the mediated and direct effect estimates is an indication of "inconsistent mediation", which is defined as mediation in which the sign of the indirect effect is different from that of the direct effect [20]. Hence, BMD behaves like a suppressor that counteracts the direct effect of the independent variable on the outcome. As in our study, the positive effect of BMI on fracture risk was suppressed by the negative mediated effect of femoral neck BMD, and this resulted in a negative total effect of BMI on these fracture when femoral neck BMD was not accounted for. Such findings may explain why some studies, particularly those of vertebral fracture, were observed to have sudden change in the direction of association between BMI and fracture risk when BMD was taken into consideration.[5,43]

It is not fully understood why association of BMI with fracture risk might differ between skeletal sites in women. One possible explanation is that obese women tend to have more fat accumulation at hip and abdomen

than on the back and limbs, and therefore, are more likely to be protected from hip fracture.[44] The direction of falls and impaired motor response during falls could also contribute to greater possibility of sustaining upper limb fracture in obese than non-obese individuals.[45]

We observed that the mediated effects of femoral neck BMD on the BMI-fracture associations were higher in women than in men. Overall, femoral neck BMD accounted for approximately 50% of the total effect of BMI on fracture risk in men. In women, the effects were greater than 70% for all fracture types being examined. This suggests that high BMI may have some protective effect against fracture risk in men, but not in women. Although the underlying reason for the gender difference is unknown, it could be hypothesized that the gender-related difference in body composition is a possible factor. While obese men have higher content of fat-free mass than fat mass, obese women have more fat mass than fat-free mass.[46-48] Since muscle strength or power output, an important protective factors against fracture, is positively correlated with fat-free mass, it may help to explain why obese men are less prone to fracture than women.[46,47] In any case, our results showed that the contribution of BMI to fracture risk prediction is minimal, with less than 0.5% of fracture reclassification being observed, suggesting that a knowledge of BMI (in the presence of BMD) minimally alter fracture prognosis.

Our results have important public health implications. First, since the BMI-fracture relationship is largely driven by BMD, the primary goal in the anti-fracture management should remain on improving an individual's BMD status. Second, the lifestyle modifications and preventive interventions for obesity and osteoporosis should not be contradicting each other. Finally, the site-specific relation of BMI with fracture indicates that a single risk-factor profile may not be suitable for all fracture cases, and thus, preventive measures should be tailored to address individual type of fracture.

However, these findings should be interpreted within the context of strength and limitations. A notable strength of this study is its long duration of follow-up, population-based and prospective design, which helps minimize potential biases inherent in volunteer-based and cross-sectional studies. In the mediation analysis, we did not taken into account the competing risk of mortality, which is a potential weakness in this study. The results of upper limb and lower limb fractures should be interpreted with caution due to the lower number of fracture cases. Since the study population was mainly of Caucasian background aged above 60, our findings may not be readily applicable to other populations, particularly those in the younger age groups and different ethnic backgrounds.

In conclusion, the present study demonstrated that the effect of BMI on fracture risk is largely mediated by femoral neck BMD. However, the magnitude and mode of mediation are both site- and gender-dependent. In the presence of BMD, BMI minimally contributes to fracture prediction.

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FIGURE LEGENDS

Figure 1. Cumulative fracture incidence for different BMI categories by fracture type in women and men.

Figure 2. Mediation models with standardized path coefficients for (a) women and (b) men.

BMI=Body mass index; FNBMD=Femoral neck BMD; a = path coefficients of BMI on FNBMD; b = path coefficients of FNBMD on fracture risk; c' = direct effect estimates of BMI on fracture risk after controlling for FNBMD; Bold-faced values signified non-zero ordered confidence intervals and $p < 0.05$

Table 1. Baseline characteristics of 2199 women and 1351 men.

	Non Fracture	Fracture	P-value
Women	n = 1425	n = 774	
Age (years)	68.5 (6.4)	71 (7.3)	< 0.001
Weight (kg)	69.0 (13.5)	65 (13.1)	< 0.001
Height (cm)	160 (5.9)	159 (6.7)	< 0.001
BMI (kg/m²)	27.8 (5.1)	26 (4.9)	< 0.001
FNBMD (g/cm²)	0.83 (0.13)	0.76 (0.12)	< 0.001
Falls (%)	32.40%	42.90%	< 0.001
Prior fracture (%)	9.70%	10.90%	0.048
Glucocorticoid use (%)	6.80%	10.10%	0.008
History of Smoking (%)	28.60%	34.60%	0.003
HRT (%)	10.70%	7.60%	0.024
Men	n = 1093	n = 258	
Age (years)	68.9 (5.7)	71.9 (6.8)	<0.001
Weight (kg)	81.9 (13.8)	76.7 (13.1)	<0.001
Height (cm)	173 (6.7)	172 (6.9)	0.009
BMI (kg/m²)	27.1 (4.0)	25.8 (3.9)	<0.001
FNBMD (g/cm²)	0.94 (0.14)	0.86 (0.16)	<0.001
Falls (%)	21.60%	37.90%	<0.001
Prior fracture (%)	7.50%	12.00%	0.025
Glucocorticoid use (%)	6.40%	10.90%	0.019
History of Smoking (%)	61.80%	63.60%	0.64

Values are means (SD) unless specified otherwise; Level of significance at p-value < 0.05; FNBMD=femoral neck BMD; Falls in the preceding 12 months; Prior fracture after age 50; HRT=hormone replacement therapy

Table 2. Relative risk of fracture for each standard deviation increase in BMI in men and women

	Hazard ratios of BMI (95% Confidence Interval)							
Women	Unadjusted		Adjusted (clinical factors)		Adjusted (BMD)		Adjusted (BMD + clinical factors)	
Any fracture	**0.92**	**(0.85-0.99)**	0.96	(0.88-1.04)	**1.21**	**(1.11-1.31)**	**1.18**	**(1.08-1.30)**
Hip fracture	**0.65**	**(0.55-0.78)**	**0.76**	**(0.64-0.91)**	1.16	(0.97-1.40)	1.11	(0.92-1.34)
Vertebral fracture	0.93	(0.82-1.06)	1.02	(0.89-1.16)	**1.21**	**(1.05-1.39)**	**1.21**	**(1.05-1.40)**
Upper limb fracture	0.97	(0.84-1.13)	0.98	(0.85-1.14)	**1.25**	**(1.07-1.46)**	**1.22**	**(1.05-1.43)**
Lower limb fracture	0.85	(0.63-1.16)	0.86	(0.64-1.18)	1.12	(0.81-1.55)	1.04	(0.75-1.44)
Men								
Any fracture	**0.77**	**(0.67-0.88)**	**0.81**	**(0.70-0.94)**	0.96	(0.83-1.11)	0.96	(0.82-1.13)
Hip fracture	**0.59**	**(0.44-0.79)**	**0.69**	**(0.51-0.95)**	0.84	(0.61-1.16)	0.93	(0.67-1.29)
Vertebral fracture	**0.68**	**(0.54-0.85)**	**0.75**	**(0.60-0.94)**	0.88	(0.69-1.11)	0.93	(0.73-1.18)
Upper limb fracture	1.01	(0.70-1.48)	1.07	(0.73-1.55)	1.29	(0.87-1.89)	1.33	(0.90-1.97)
Lower limb fracture	0.99	(0.61-1.60)	0.98	(0.61-1.58)	1.09	(0.66-1.81)	1.06	(0.65-1.76)

Clinical factors = age, falls, prior fracture, glucocorticoid use, history of smoking and HRT (in women); BMD = femoral neck BMD; Bold-faced letters = statistically significant; HR was based on one SD increase in BMI

Table 3. Stability of regression coefficients of BMI and femoral neck BMD with incremental biases added to the Cox's ridge regression models in women and men

	Women		Men	
k	BMI (β coefficients)	FNBMD (β coefficients)	BMI (β coefficients)	FNBMD (β coefficients)
0.0	0.1693	-0.5380	-0.0257	-0.4518
0.1	0.1692	-0.5378	-0.0258	-0.4515
0.2	0.1691	-0.5376	-0.0259	-0.4513
0.3	0.1690	-0.5374	-0.0260	-0.4510
0.4	0.1689	-0.5373	-0.0261	-0.4507
0.5	0.1688	-0.5371	-0.0262	-0.4504
0.6	0.1687	-0.5369	-0.0263	-0.4502
0.7	0.1686	-0.5367	-0.0263	-0.4499
0.8	0.1685	-0.5365	-0.0264	-0.4496
0.9	0.1684	-0.5364	-0.0265	-0.4493
1.0	0.1683	-0.5362	-0.0266	-0.4491

All models were adjusted for age, falls, prior fracture, smoking, physical activity level, use of Glucocorticoid and HRT (in women); BMI=Body mass index; FNBMD=Femoral neck BMD; β coefficients= regression coefficients; *k* = non-negative biasing constant;

Table 4. Effect estimates for indirect and total effect of BMI on different fracture risk in women and men.

	Total effect (95% confidence intervals)		Indirect effect (95% confidence intervals)		Sobel test (*p*-value)*
Women					
Any fracture	**-0.033**	**(-0.055, -0.009)**	**-0.048**	**(-0.059, -0.036)**	< 0.001
Hip fracture	**-0.062**	**(-0.107, -0.022)**	**-0.060**	**(-0.082, -0.040)**	< 0.001
Vertebral fracture	-0.019	(-0.052, 0.004)	**-0.030**	**(-0.044, -0.016)**	< 0.001
Upper limb fracture	-0.012	(-0.039, 0.001)	**-0.028**	**(-0.043, -0.015)**	< 0.001
Lower limb fracture	-0.017	(-0.057, 0.001)	**-0.012**	**(-0.028, -0.002)**	0.001
Men					
Any fracture	**-0.061**	**(-0.081, -0.031)**	**-0.030**	**(-0.042, -0.018)**	< 0.001
Hip fracture	**-0.084**	**(-0.127, -0.024)**	**-0.037**	**(-0.056, -0.018)**	< 0.001
Vertebral fracture	**-0.062**	**(-0.105, -0.017)**	**-0.025**	**(-0.043, -0.010)**	< 0.001
Upper limb fracture	-0.005	(-0.013, 0.002)	**-0.006**	**(-0.022, -0.0004)**	0.002
Lower limb fracture	-0.010	(-0.071, 0.001)	**-0.002**	**(-0.014, -0.0003)**	0.003

*significance test of indirect effect; Bold-faced values are statistically significant with non-zero confidence intervals and $p < 0.05$

Table 5. Reclassification analysis of femoral neck model with and without BMI included in women and men

	Model II			
Model I	Lower tertile	Middle tertile	Uppler tertile	NRI
Women				
Fracture				
Lower tertile	116	21	0	
Middle tertile	27	185	40	0.13%
Upper tertile	0	33	352	
Non fracture				
Lower tertile	489	57	3	
Middle tertile	74	377	59	-0.35%
Upper tertile	0	40	325	
Total				-0.22%
Men				
Fracture				
Lower tertile	47	4	0	
Middle tertile	1	67	3	-0.39%
Upper tertile	0	7	129	
Non fracture				
Lower tertile	387	9	0	
Middle tertile	7	352	9	0.18%
Upper tertile	0	13	316	
Total				-0.21%

Model I= femoral neck BMD; Model II= femoral neck BMD and BMI; NRI=Net reclassification index

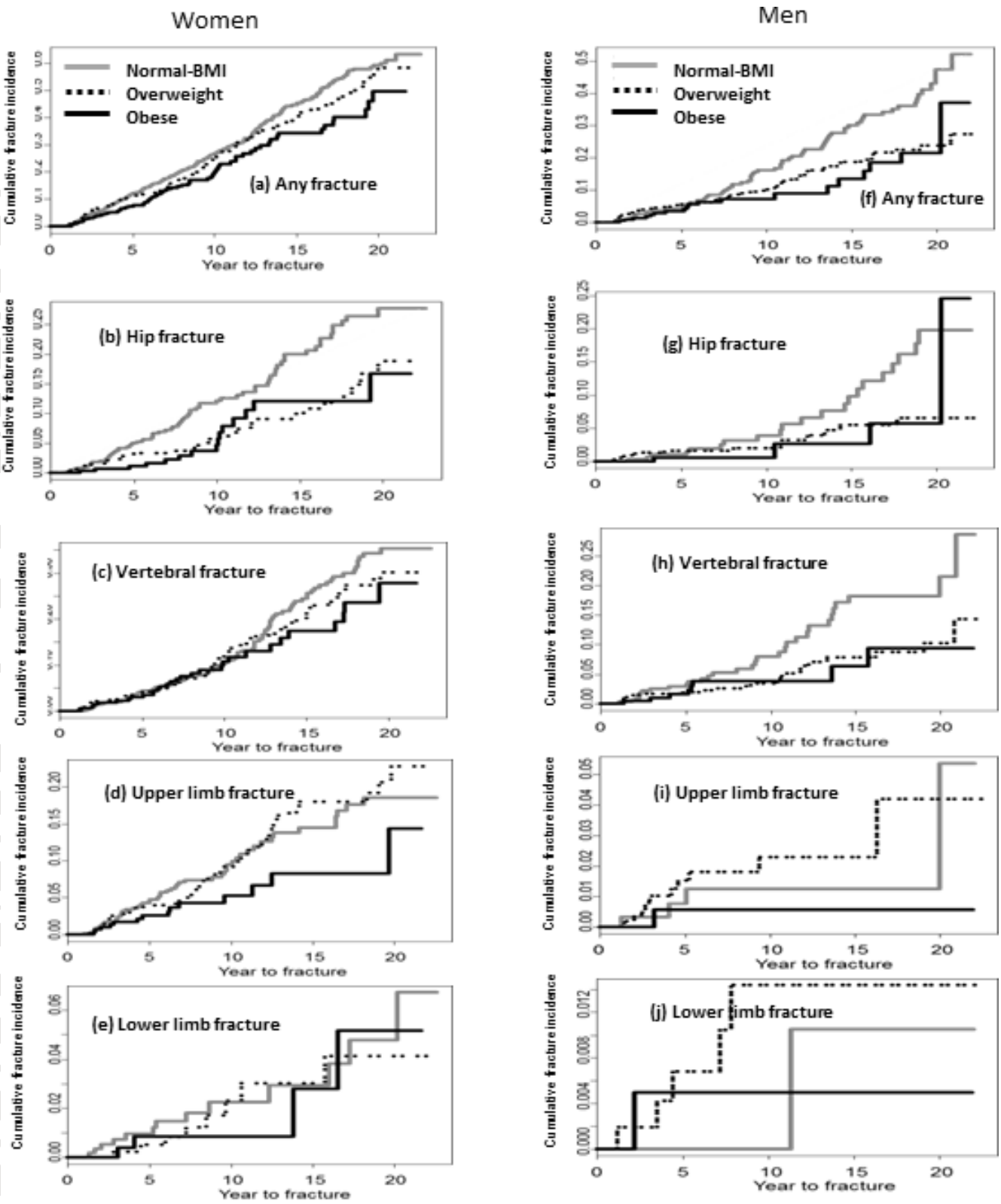

Figure 1

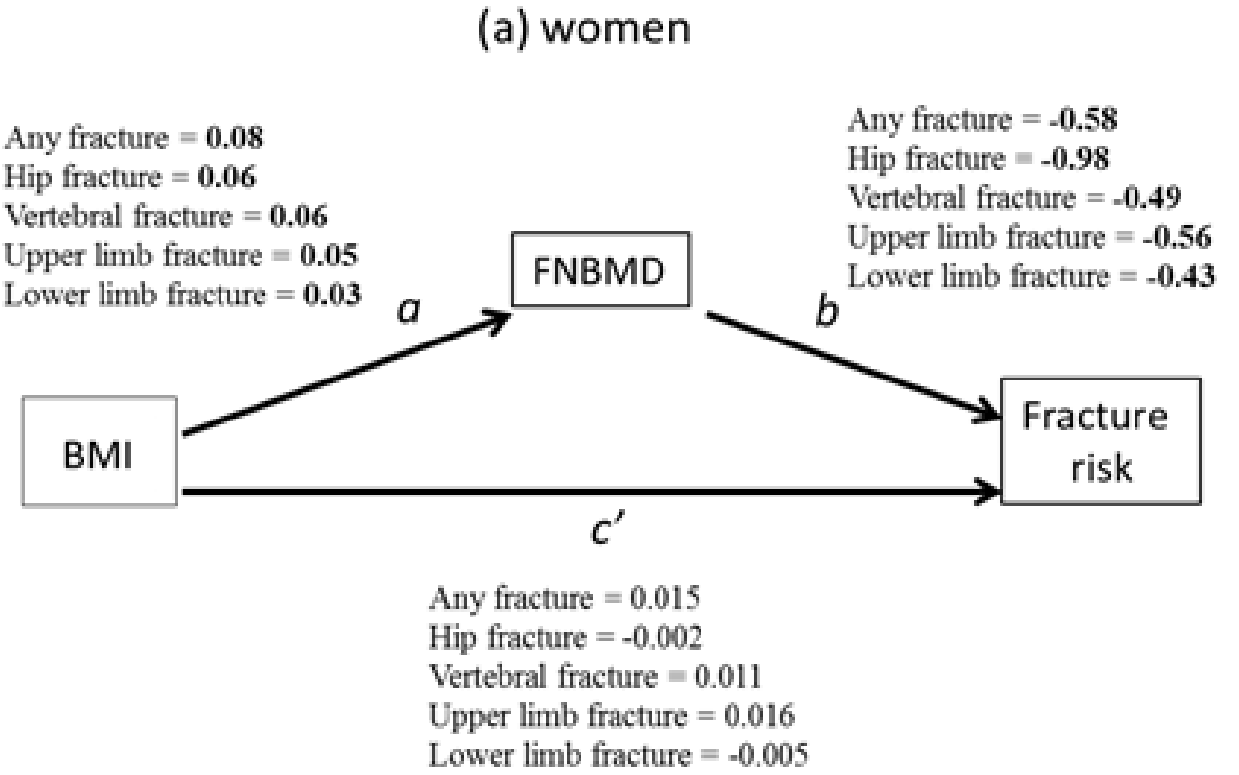

Figure 2