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Original Article

A meta-analysis of the association of fracture risk and body mass index in women†

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Cover letter

We have studied the relationship between BMI and future fracture risk at different skeletal sites in 398,610 women aged 20-105 years from 25 prospective cohorts from more than 25 countries. The relationship was studied adjusted and not adjusted for BMD, during a follow-up of 2.2 million person-years. The prevalence of obesity (BMI≥30 kg/m^2) was 22%. A majority of osteoporotic fractures (81%) and hip fractures (87%) arose in non-obese women. Low BMI is a risk factor for osteoporotic fracture and hip fracture, but is a protective factor for tibia and fibula fractures. High BMI is a protective factor for osteoporotic fracture, hip fracture and distal forearm fracture, but is a risk factor for humerus and elbow fracture. When adjusted for BMD low BMI was still a risk factor for hip fracture but a protective factor for osteoporotic fracture, distal forearm fracture, tibia/fibula fracture and humerus and elbow fracture. When adjusted for BMD high BMI remained a risk factor for humerus plus elbow fracture and also for osteoporotic fracture. The interaction between BMI and fracture risk is complex, differs across skeletal sites and is modified by the interaction between BMI and BMD. At a population level, high BMI remains a protective factor for most sites of fragility fracture. The contribution of increasing population rates of obesity to apparent decreases in fracture rates requires exploration.

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Abstract

Several recent studies suggest that obesity may be a risk factor for fracture. The aim of this study was to investigate the association between body mass index (BMI) and future fracture risk at different skeletal sites.

In prospective cohorts from more than 25 countries, baseline data on BMI were available in 398,610 women with an average age of 63 years (range 20-105 years) and follow up of 2.2 million person-years during which 30,280 osteoporotic fractures (6,457 hip fractures) occurred. Femoral neck BMD was measured in 108,267 of these women. Obesity (BMI≥30 kg/m^2) was present in 22%. A majority of osteoporotic fractures (81%) and hip fractures (87%) arose in non-obese women. Compared to a BMI of 25 kg/m^2, the hazard ratio (HR, 95% CI) for osteoporotic fracture at a BMI of 35 kg/m^2 was 0.87 (0.85-0.90). When adjusted for BMD, however, the same comparison showed that the hazard ratio for osteoporotic fracture was increased (HR= 1.16; 95% CI=1.09-1.23). Low BMI is a risk factor for hip and all osteoporotic fracture, but is a protective factor for lower leg fracture, whereas high BMI is a risk factor for upper arm (humerus and elbow) fracture. When adjusted for BMD, low BMI remained a risk factor for hip fracture but was protective for osteoporotic fracture, tibia and fibula fracture, distal forearm fracture and upper arm fracture. When adjusted for BMD, high BMI remained a risk factor for upper arm fracture but was also a risk factor for all osteoporotic fractures.

The association between BMI and fracture risk is complex, differs across skeletal sites and is modified by the interaction between BMI and BMD. At a population level, high BMI remains a protective factor for most sites of fragility fracture. The contribution of increasing population rates of obesity to apparent decreases in fracture rates should be explored.

Key words:

BMI, fracture risk, population studies, Poisson regression model, women, obesity

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Introduction

Fractures are an important cause of morbidity in the population, especially in women. Hip fractures in particular are a major cause of pain, loss of function, increased mortality and are associated with very high costs to society(1-3). Since fracture incidence increases with age, the burden from fracture is predicted to increase in the future due to an increase in the numbers of elderly(3-5).

Apart from low bone mineral density (BMD), many risk factors for fragility fractures have been identified(6,2,7). Strong risk factors include a prior fragility fracture, a family history of fracture, exposure to glucocorticoids and low body mass index (BMI) (8-11). Low BMI has been considered as a risk factor for fracture and obesity as a protective factor for fracture(11-13) but this association has been recently challenged(14,15) . Compston et al reported that obesity was not protective against fracture in postmenopausal women and, indeed, was associated with an increased risk of ankle and upper leg fractures (15). Similarly, Prieto-Alhambra concluded that obesity, though protective against hip and pelvis fracture, was associated with an increase in risk for proximal humerus fractures(16). In a recent review Nielson et al(17) stated that the importance of fractures occurring in the overweight and obese elderly may have been lost in the message that being underweight increases the risk of fracture.

The aim of this study was to investigate the association between BMI and future fracture risk at different skeletal sites in 25 international prospective cohorts comprising almost 400,000 women.

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Methods

Cohorts studied

We used baseline and follow-up data from 25 prospective cohorts, the majority of which were population based (20/25). Details of each of the cohorts are published elsewhere, but are summarized briefly below and in Tables 1, 2 and 3.

The Adult Health Study (AHS) at the Radiation Effects Research Foundation was established in 1958 to document the late health effects of radiation exposure among atomic bomb survivors in Hiroshima and Nagasaki, Japan. The original AHS cohort consisted of about 15,000 atomic bomb survivors and 5,000 controls selected from residents in Hiroshima and Nagasaki using the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. AHS subjects have been followed through biennial medical examinations since 1958(18,19). In the Aberdeen Prospective Osteoporosis Screening Study from the UK (APOSS)(20) women were randomly selected from a community-based register and invited to participate in a population-based screening program for osteoporotic fracture risk. The Canadian Multicentre Osteoporosis study (CaMos) is an ongoing prospective age-stratified cohort cohort of men and women ages 25 to 80+ randomly selected from regional residential telephone listings. The sampling frame was a 50 km radius around nine study centres in seven provinces and participants are representative of 41% of the Canadian population (21). The Dubbo Osteoporosis Epidemiology Study (DOES) is a population-based study from Dubbo, Australia(22). The Ecografía Osea en Atención Primaria (ECOSAP) study was a referral population recruited in 58 primary care centres throughout Spain, regardless of the reason for consultation(23). The Norfolk cohort of the European Prospective Investigation into Cancer (EPIC-Norfolk) comprise men and women aged 40-79 years who were resident in Norfolk, UK, at the time of recruitment and were recruited from general practice listings(24). The Epidemiologie de l'osteoporose (EPIDOS) study comprises a population-based cohort from five French centres (Amiens, Lyon, Montpellier, Paris and Toulouse)(25): women were recruited through mailings using large population based listings such as voter registration rolls. The European Vertebral Osteoporosis Study (EVOS) comprised age- and sex-stratified random samples from 36 centres in 19 European countries(26). Equal numbers of men and women were drawn in each centre within six 5-year age bands (50–74 and 75+ years). BMD was measured in 13 centres. This sample provided the framework for the European Prospective Osteoporosis Study (EPOS), where repeated assessment was undertaken in 29 of

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the centres (27,28). The Gothenburg I subjects were drawn randomly from the population register in Gothenburg, Sweden by the date of birth to provide cohorts aged 70, 76, 79 and 85 years at the time of investigation(29). The Gothenburg II study comprised a randomly drawn population that attended for mammography screening(30). The Geelong Osteoporosis Study (GOS) is an age-stratified sample of women drawn randomly from electoral roll of Geelong and surrounding districts in south eastern Australia(31). The Manitoba cohort is a referral population of all women attending for BMD measurements in the Province of Manitoba, Canada, where health services are provided to residents through a single public health care system(32). The Miyama study is a population-based cohort drawn from inhabitants born in Miyama, Japan between 1910 and 1949(33). Of 1543 inhabitants, an age-stratified sample of 400 men and women was drawn by birth decade. The MsOS study is a cohort study on osteoporosis in a convenience sample of ambulant Asian women recruited from the community in Hong Kong(34). The Os des Femmes de Lyon (OFELY) cohort comprised an age-stratified female cohort randomly selected from the regional section of a large health insurance company (Mutuelle Generale d'Education Nationale, Lyon, France)(35). The Osteoporosis and Ultrasound Study (OPUS) comprises five age-stratified population-based female cohorts drawn from different European centres (Sheffield and Aberdeen (UK), Berlin and Kiel (Germany), and Paris (France))(36). The Kuopio osteoporosis risk factor and prevention (OSTPRE) study in Finland comprised a postal inquiry sent to all 14220 women who were residents of Kuopio province(37). The Prospective Epidemiological Risk Factors (PERF) study was a population based cohort in Copenhagen, Denmark(38). The survey invited women to participate in screening for various placebo controlled clinical trials and epidemiological studies at Copenhagen. The Rochester cohort was recruited from two random population samples of women from Minnesota, USA women stratified by decade of age (39) (40). The Rotterdam Study is an ongoing prospective cohort study that aimed to examine and follow up all residents aged 55 years and older living in Ommoord, a district of Rotterdam, Netherlands (41) (42,43). The Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk (SEMOF) study is a prospective multicentre study (10 centres in Switzerland)(44). Women were randomly selected from an address register. The Sheffield cohort comprised women aged 75 years or more selected randomly from the population of Sheffield, UK and surrounding districts identified from general practitioner listings. The women willing to participate and meeting inclusion criteria were randomly allocated to treatment with placebo or the bisphosphonate, clodronate, to study its effects on fracture risk. The material for this study comprised 2,171 women allocated to treatment with placebo

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only(45,46). The Study of Osteoporotic Fractures (SOF) is a multicentre cohort study of risk factors for osteoporosis and fracture(47). Participants were ambulatory Caucasian women selected by convenience and recruited at four clinical centres from the USA (Baltimore, Minneapolis, Pittsburgh and Portland). The Health Improvement Network (THIN) research database was derived from computerized records of a sample of general practitioners in the UK, similar to the General Practice Research Database (48). The study population comprised all women aged 50 years or more. The Women's Health Initiative (WHI) study comprises three overlapping randomised controlled studies and an observational study in a convenience sample of postmenopausal women (49,50). The trials comprised dietary modification with low fat (n=48,836), hormone replacement therapy (HRT) in women with or without a uterus (n=27,347), and supplementation with calcium and vitamin D (n=36,282). The total sample size was 161,808. For this analysis women taking bone active medication (HRT, bisphosphonates, and calcitonin) were excluded, leaving a sample size of 81,377.

Measurements

Height and weight were measured using standard techniques in all cohorts. BMI was calculated as weight in kilograms divided by height squared in metres and used as a continuous variable or categorised according to the WHO criteria(51): underweight (BMI <18.5 kg/m^2); normal (18.5-24.9 kg/m^2); overweight (25.0-29.9 kg/m^2); obese I (30.0-34.9 kg/m^2) and obese II (≥35.0 kg/m^2). BMD was assessed in 27% of the women using several different techniques summarised in Table 1 and converted to standardised cohort specific Z-scores. The proportion of women with BMD measurement varied by cohorts from 0 to 100% (Table 2).

For fracture outcomes, we used information on fractures only at sites considered to be associated with osteoporosis(52), i.e. fractures of the spine, coccyx, ribs, pelvis, humerus, forearm, elbow, hip, other femoral, tibia and fibula, clavicle, scapula, sternum. Fractures of the skull, face, hands and fingers, feet and toes, ankle and patella were excluded. In addition to 'osteoporotic fractures', incident hip, distal forearm, lower leg (tibia and/or fibula) and upper arm (humerus and/or elbow) were considered separately.

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Statistical methods

Correlation tests between BMI and other variables used nonparametric Pitman's permutation test and Pearson correlation coefficient were calculated.

The association between BMI and the risk of fracture was examined using an extension of the Poisson regression model(53) in each cohort. The observation period of each participant was divided in intervals of one month. The first fracture per person was counted for each relevant outcome. Covariates included current age and time since start of follow-up, and analyses were performed with and without adjustment for BMD. Interactions between BMD and BMI were also studied. The β-coefficients from each cohort were weighted according to the variance, and then merged to determine the weighted mean of the coefficient and its standard deviation. The associations between BMI and risk of fracture were described as the hazard ratio (HR) for fracture per 1 unit change in BMI together with 95% confidence intervals (CI).

Heterogeneity between cohorts was tested by means of the I^2 statistic (54). Heterogeneity was found for the osteoporotic fracture outcome (I^2=75%; 95% CI: 63-83) and the hip fracture outcome (I^2=86%; 95% CI: 81-90). When the interaction between BMI and current age was included, there was no significant heterogeneity between cohorts for BMI (I^2=14%; 95% CI: 0-48) for the outcome of osteoporotic fracture. For the outcome of hip fracture there was a moderate heterogeneity between cohorts for BMI (I^2=61%; 95% CI: 39-75). Since we had a moderate heterogeneity for the outcome of hip fracture even when including an interaction with age we performed both a fixed and a random effect model when merging the result from the different cohorts. Overall the weighted β-coefficient describing the association between BMI and the outcome of osteoporotic fracture was -0.0215 when using fixed effect model and -0.0210 when using random effect model (with a SD describing the variance between cohorts 0.013) resulting in the same HR per 1 unit 0.98. When describing the association between BMI and the outcome of hip fracture the β-coefficient was -0.0740 when using fixed effect model and -0.0719 when using random effect model (with a SD of 0.014) resulting in the same HR per 1 unit 0.93. Since the estimates were so similar, we use the fixed effect model to present the results.

In order to study the association between BMI and fracture risk in more detail, a spline Poisson regression model was fitted using cohort specific knots at the 10^{th}, 50^{th} and 90^{th} percentiles of BMI, as recommended by Harrell (55). The splines were second order functions between the breakpoints and linear functions at the tails resulting in a smooth curve. When the

comparisons between two points at the curve was done, a piecewise linear model with knot at BMI 25 kg/m^2 were used to study the relationship between BMI and the risk of fracture.

In sensitivity analyses, we repeated the calculations (a) in those cohorts that were population based (see Table 1), (b) in cohorts without excluding women that received treatments for osteoporosis and (c) using a random effect rather than a fixed effect model.

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Results

The cohorts comprised 398,610 women aged 20-105 years with an average age of 63 years, who were followed for approximately 2.26 million person-years (Table 2 and 3). During an average follow up of 5.7 years 30,280 osteoporotic fractures were documented of which 6,457 were at the hip (Table 3). The mean BMI was 26.6 kg/m^2 and approximately half of the women were overweight or obese (56%), with 22.1% being obese (Table 4). Approximately 7,700 women (1.9%) were underweight. There was a weak but significant negative correlation between age and BMI ($p<0.001$; r= -0.01; 95% CI= -0.01 to -0.01). For example, in women aged 55-59 years, 1.3% of women were underweight and the proportion increased progressively with age so that 5.8% of women aged 85-89 years were underweight. Conversely, the prevalence of obesity decreased with age from 25.3% in the age group 55-59 years to 10.9% between the ages of 85 and 89 years. There was a significant positive correlation between BMI and BMD ($p<0.001$; r=0.33; 95% CI=0.32-0.33). In underweight women, the mean BMD femoral neck z-score was -0.89 and for the obese II category it was 0.67 (Table 4).

BMI and risk of fracture

A total of 30,280 osteoporotic fractures were reported during follow up (Table 3). A minority (19%) of all osteoporotic fractures occurred in obese women (Table 5) and the observed number was lower than expected (5,798 vs. 6,691 respectively) if BMI was assumed to exert no influence on fracture risk. Thus obesity was a protective factor for osteoporotic fractures as a whole. Similar results were found when hip fracture or distal forearm fractures were considered individually (Table 5). In contrast, the observed incidence of lower leg fractures was not reduced, and the risk of upper arm fractures was higher than expected in obese women.

When BMI was used as a continuous variable, there was a significant association between BMI and fracture risk ($p<0.001$). In the case of all osteoporotic fractures, the HR per unit increase of BMI was 0.98 (95% CI= 0.98-0.98) and for hip fracture was 0.93 (95% CI=0.92-0.94). The HR was not, however, uniform across BMI in that low BMI was associated with a greater risk than would be predicted from a uniform HR and, conversely, a high BMI contributed less to fracture prevention than expected. Thus, when studying the relationship in more detail with spline functions, the function was steeper below a BMI of 25 kg/m^2 than

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above this value (Figure 1). When a woman with a BMI of 15 kg/m^2 was compared with a woman with a BMI of 25 kg/m^2 using piecewise linear functions, the HR was 1.5 (95% CI= 1.4-1.6) for osteoporotic fracture and 2.9 (95% CI= 2.6-3.3) for hip fracture (Table 6). By contrast, if a woman with a BMI of 25 kg/m^2 was compared to one with a BMI of 35 kg/m^2, the HR was 0.9 (95% CI: 0.9-0.9) for osteoporotic fracture and 0.7 (95% CI= 0.6-0.8) for hip fracture.

The use of BMI as a continuous variable also confirmed the different patterns between fracture sites. In the case of upper arm fractures, a BMI of 35 kg/m^2 conferred a significantly higher risk than a BMI of 25 kg/m^2, whereas a BMI of 15 kg/m^2 had a similar risk to that at 25 kg/m^2 (Table 6). The lower BMI was associated with a significant reduction in lower leg fractures, whilst the risk was similar at 25 and 35 kg/m^2 (Table 6)

Adjustment for BMD

When the association between BMI and hip fracture risk was adjusted for BMD, the association was weaker than in the absence of BMD but was still significantly negative. The HR was 0.99 per 1 kg/m^2 increase (95% CI= 0.98-0.99; p=0.0014). When the relationship was examined with spline functions, the relationship was much flatter with BMD adjustment (Fig. 2) than without (Fig. 1). Not withstanding, the risk of hip fracture with low BMI was greater than the protective effect of a high BMI. Thus, a BMI of 15 kg/m^2 had a hazard ratio of 1.4 (95% CI 1.2-1.7) compared to a BMI of 25 kg/m^2 (Table 6) but a BMI of 35 kg/m^2 conferred no greater hip protection than a BMI of 25 kg/m^2 (HR 1.0, 95% CI 0.9-1.2).

Interestingly, the association between BMI and osteoporotic fracture risk was weaker but inverted when adjusted for BMD, so that a higher BMI was now associated with a small but significant increase in fracture risk (HR per unit increase in BMI = 1.01; 95% CI 1.01-1.02; p<0.001). For example, the HR for all osteoporotic fracture was 1.16 (95% CI 1.09=1.23) when comparing a BMI of 35 kg/m^2 with a BMI of 25 kg/m^2; at a BMI of 15 kg/m^2, the risk was reduced. Thus, for all osteoporotic fractures a higher BMI was, if anything, a modest albeit significant risk factor following adjustment for BMD. A similar pattern was observed for distal forearm fractures. The association of high BMI with increased fracture risk following adjustment for BMD was most marked for upper arm fractures (Table 6). For lower

leg fractures, fracture risk was increased and decreased at high and low BMIs respectively compared to 25 kg/m^2 (Table 6).

Interactions with BMI

There was a significant interaction between age and BMI for osteoporotic fracture ($p<0.001$). This age interaction was significant both below and above a BMI of 25kg/m^2 ($p=0.042$ and $p<0.001$, respectively). Thus, when BMI was set at 15 kg/m^2 and compared with a BMI of 25 kg/m^2 using piecewise linear functions the HR was 1.4 at the age of 50 years and 1.7 at the age of 80 years, suggesting that low BMI was a stronger risk factor for osteoporotic fractures in elderly women. The same age-BMI interaction was true for BMI greater than 25 kg/m^2, in that high BMI was a stronger protective factor for elderly women. A significant interaction between age and BMI was seen for hip fracture below a BMI of 25 kg/m^2 ($p<0.001$) but not for BMI above 25 kg/m^2 ($p=0.058$). Thus, when BMI, set at 15 kg/m^2, was compared with a BMI of 25 kg/m^2 using piecewise linear functions, the HR was 9.2 at the age of 50 and 3.1 at the age of 80 years, indicating that low BMI was a stronger risk factor for hip fracture in younger women than in elderly women.

Since there was a significant correlation between BMD and BMI, and BMD affected the relationship between BMI and the risk of fracture, the interaction between BMI and BMD was investigated with both linear and cubic models. No such interactions were found, indicating that the correlation between BMI and fracture risk did not change for different values of BMD. There were also no significant interactions between age and time since baseline, i.e. the predictive value of BMI did not change with time ($p>0.20$ for both osteoporotic and hip fracture outcomes).

When women allocated to treatments for osteoporosis in the WHI cohort were included, the results were similar. So too were the results when the analysis was confined to population-based cohorts.

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Discussion

The principal finding of the present meta-analysis of prospective population-based cohorts of women is the significant association between BMI at baseline and future osteoporotic fracture, in that a low BMI was a significant risk factor for all osteoporotic fractures, including hip and forearm fractures. These finding are very consistent with an earlier but smaller meta-analysis(11), though it should be acknowledged that 11% of the women over a shorter time appeared in both meta-analyses. As previously reported in that study, a high BMI was a protective risk factor for osteoporotic fracture, including hip fracture, but a high BMI was weaker as a protective factor than low BMI was as a risk factor. An important conclusion is that obesity itself is not a risk factor for osteoporotic fracture, hip or forearm fracture. As also seen in the earlier analysis(11), the association between BMI and fracture risk was dependent on BMD. In the subset of women in whom femoral neck BMD was measured, the association of BMI with hip fracture risk was attenuated and was not evident for all osteoporotic fractures combined. It should be noted that the HRs with and without adjustment for BMD are not strictly comparable in that a minority of women (27%) had a BMD test and there was a significant cohort bias in the proportion of women with a BMD test. With this caveat, the results are consistent with the earlier meta-analysis.

Our results also suggest that the association between BMI and risk of future fracture is site-specific. Whereas low BMI was a risk factor for all osteoporotic fractures, a low BMI was a protective factor for lower leg fracture. In this regard, several of the cohorts did not adequately distinguish fractures of the lower leg that are associated with low BMD (e.g. proximal tibial fractures) from ankle fractures which are not regarded as being associated with osteoporosis(52). Exclusion of these cohorts from the analysis still showed a similar pattern of association of lower leg fractures with BMI (data not shown). In the present study, a high BMI was a significant risk factor for humerus fractures and this persisted after adjustment for BMD. The finding is consistent with a recent short term (1 year) prospective analysis in 832,775 Spanish women aged 50 years or more visiting general practitioners (SIDIAP)(16), in which a protective effect of obesity was found on future hip fracture and forearm fracture (relative risk (RR) = 0.49 (95% CI=0.44-0.55) and 0.83 (95% CI=0.75-0.91) respectively) but obese women were at significantly higher risk of future proximal humeral fracture than the rest of the study population (RR = 1.28; 95% CI=1.04-1.58). These findings are also consistent with an earlier report that obese women had a higher prevalence of a prior humeral fracture (odds ratio (OR) = 3.48; 95% CI= 0.18–6.68)(56). The reasons for the site specific

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association between high BMI and humeral fracture risk are not known, though conceivably may reflect a different pattern of falling or a greater load upon bones in the upper extremity in falls amongst the obese population. Moreover, a different padding effect of the soft tissues in different skeletal regions may produce diverse energy dissipation after trauma and, therefore, a different protection of the underlying bone.

Our results are at first sight at variance with the conclusions of Compston et al who state that that obesity is not protective against fracture in postmenopausal women (15). That study, however, included a large number of non-adjudicated ankle and tibial fractures. Ankle fractures are not generally regarded as being associated with osteoporosis (51, 56) and, as implied above, the accuracy of a self-reported distinction between ankle and other lower leg fractures is questionable. In their report, ankle fractures were significantly more frequent in obese compared with non-obese women. Given that the incidence of forearm, hip, pelvic, upper leg and spine fractures was higher in underweight women than in obese women, their report is not inconsistent with our findings. Moreover the present study also found a protective effect of low BMI for future lower leg fracture.

The question arises whether our findings have implications for FRAX which predicts the probability of a hip and a major fracture based on clinical risk factors such as sex, age, BMI, previous fracture, family history, glucocorticoid use, smoking, alcohol use and secondary osteoporosis (57). BMI is used as a continuous variable in FRAX and BMD can be optionally entered into the model. Data from the meta-analysis of DeLaet et al (11) were used in the construct of FRAX. The association between BMI and the risk of hip fracture and other osteoporotic fractures in the present study is nearly identical to that described by De Laet et al in the absence of BMD. After adjustment for BMD, the risk of hip fracture associated with low BMI was attenuated in the same way as that described previously(11). In the case of osteoporotic fractures, we have shown a slight though significant increase in risk with increasing BMI (see table 6). This finding is consistent with the earlier meta-analysis, though the increase in risk was not statistically significant due to the smaller sample size. These considerations indicate that modifications of the FRAX algorithm are not warranted based on the present analysis a view consistent with a recent report from the SOF study that FRAX is of value predicting fractures in obese women, particularly when used with BMD(58).

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The present study has several limitations some of which have been discussed above. These include the limited sampling frame for BMD measurements, inaccuracies in the estimate of BMD in the presence of a high fat mass as well as uncertainties in the coding of some fractures. With regard to the former, our results were similar when HRs not adjusted for BMD were calculated in those 27% of women in whom BMD was measured. The different settings of the cohorts are also a limitation but that would rather weaken not strengthen an association between BMI and fracture. Conversely, the different settings increase the generalisability of our findings. The greatest limitation is that the present analysis is confined to women. Several lines of evidence suggest that the relationship between BMI and fracture risk may differ in men (11,59).

A limitation in the understanding of possible mechanisms is that we have not been able to examine all potential confounding factors (e.g. smoking, previous fracture, alcohol, comorbidities). Of possible relevance is the association of type 2 diabetes with high BMI. In a recent large clinical database in Manitoba, Canada, individuals with diabetes had a BMI approximately 3 kg/m^2 higher than those without diabetes(60). Of particular interest, diabetes was associated with a 60% increased risk for major osteoporotic fracture when adjusted for clinical risk factors for fracture including BMI and BMD (HR 1.61 (95% CI=1.42-1.83)). Thus, the higher risk for osteoporotic fracture for obese women (BMI 35 kg/m^2 versus 25 kg/m^2) in this report could be related in part to diabetes. Diabetic status was recorded in the present analysis for only 9% of women. In the women that had information on diabetes, the prevalence of diabetes was 3.4% in women with a normal BMI and 6.7% in obese women (data not shown). The small size of the available sample meant that we were unable to examine the impact of diabetes on the relationship between BMI and future fracture risk in more detail. The age interactions, the result with and without BMD and some of the fracture specific findings might suggest an important role for low physical function and frailty in explaining these associations but, as was the case for diabetes, we were unable to examine this further.

With these caveats, we conclude that low BMI remains an important clinical risk factor for hip and all osteoporotic fractures combined and that obesity in women is associated with a significant, albeit modest, reduction in fracture risk. In contrast, obese postmenopausal women appear to be at higher risk for humeral fractures than those with normal BMI. Moreover, after adjustment for BMD there is a slight increase in osteoporotic fracture risk with increasing BMI.

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Figure 1. Relationship between BMI and risk of fracture (HR versus BMI 25 kg/m^2) for osteoporotic fracture (solid line) and hip fracture (dashed line), adjusted for age and time since baseline.

Figure 2. Relationship between BMI and risk of fracture (HR versus BMI 25 kg/m^2) for osteoporotic fracture (solid line) and hip fracture (dashed line), adjusted for age, time since baseline and BMD.

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Table 1 Cohorts studied

Cohort	Year for baseline	Bone densitometry	Fracture report
AHS	1958 (BMD:1994)	DXA FN, Hologic QDR 2000	Spinal radiographs and self-report
APOSS	1990-1994	DXA left FN, Norland (Cooper Surgical)	Self-report, computer reports from radiologists, hospital record, primary care physicians' record
CaMos	1996-1997	DXA FN, Hologic QDR and Lunar DPX Alpha phantom-calibrated across centres and machines	Self-report. Radiographic or medical report verification of incident fractures was obtained when information was available.
DOES	1989	DXA FN, GE-Lunar, DPX and Prodigy	Radiologists' report
ECOSAP*	2000-2001	QUS right calcaneus, Sahara^{TM} (Hologic)	Self-report, confirmed by investigator by X-ray or radiological or surgical reports
EPIC-Norfolk	1997-2000	-	Hospital record linkage
EPIDOS	1992-1993	DXA FN, Lunar DPX.	Self-report, family or physician.
EVOS/EPOS	1989	DXA FN, cross-calibrated using European Spine Phantom	Self-reported fractures were confirmed where possible by radiograph, attending physicians or subject interview
GBG I	1985-1993	Dual photon absorptiometry right heel	Radiology departments servicing the region
GBG II*	1992-1997	Distal forearm, Osteometer DTX-200	Radiology departments servicing the region
GOS	1994-1997	DXA FN, Lunar DPX-L	Radiographically confirmed from hospital records
Manitoba*	1990-2007	DXA FN, Lunar DPX or Lunar prodigy	Ascertained using ICD codes, where two or more hospitals or physicians ICD fracture codes had to be present to confirm a fracture. Site-specific orthopaedic intervention codes for hip

			and forearm fractures.
Miyama	1989-1990	DXA FN, Lunar DPX	Self-report, confirmed by X-ray
MsOs HK*	2001	DXA FN, Hologic QDR-4, 500-W	Self-report, confirmed by X-ray or medical record
OFELY	1992-1993	DXA FN, Hologic QDR 2000	Radiography, X-rays, surgical reports
OPUS	1999-2001	DXA FN, Hologic QDR 4500 or Lunar Expert	Spinal radiograph; verification of non-vertebral incident fractures when information was available.
OSTPRE	1989	DXA FN, Lunar DPX	Self-report
PERF	1977-1997	DXA FN, Hologic QDR-2000	Spinal radiographs and self-report
Rochester	1980	DXA FN, Hologic QDR 2000 and dual photon absorptiometry cross calibrated to DXA	Self-report combined with review of the in-patient and outpatient medical records of all local care providers
Rotterdam	1990-1993	DXA FN, Lunar DPX-L	Automatic link with general practitioner computer systems and hospital admission data. Validated by two independent research physicians.
SEMOF	1997-1999	DXA FN, Hologic QDR 4500	Questionnaire and confirmed from medical records
Sheffield	1993-1999	DXA FN, Hologic QDR 4500	Self-report at home visits
SOF*	1986-1988 (BMD:1990-1991)	DXA FN, Hologic QDR 1000	Telephone or correspondence and confirmed from X-ray reports
THIN	1995-2004	-	General practitioners records
WHI*	1990	DXA FN, Hologic 2000	Hip fractures by medical records and adjudicated at a central facility. Other fractures were adjudicated locally (clinical trials) and by self report (observational study for patients without BMD).

* Denotes that the cohort was not population-based

DXA – Dual Energy X-ray Absorptiometry

FN – femoral neck

ICD - International Classification of Diseases

QDR - quantitative digital radiography

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QUS - Quantitative Ultrasound

*EPIC Norfolk collected QUS data on approximately 15,000 men and women between 1997-2000; fractures were ascertained by hospital record linkage

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Table 2. Details of cohorts studied

Cohort	n	Length of follow up (years) mean (max)	Age (years) Mean (range)	BMI (kg/m^2) mean (SD)	BMD n
AHS	1 810	3.8 (6.8)	66 (47- 95)	23.1 (3.6)	1 797
APOSS	5 110	7.0 (12.3)	48 (44- 56)	25.5 (4.6)	5 102
CaMos	6 315	6.0 (8.6)	63 (25-103)	26.9 (5.2)	5 719
DOES	1 270	7.8 (13.6)	71 (57- 94)	25.4 (4.6)	1 259
ECOSAP	5 128	2.9 (4.5)	72 (65-100)	29.2 (4.7)	-
EPIC-Norfolk	8 856	5.4 (6.9)	62 (42- 81)	26.6 (4.4)	-
EPIDOS	7 593	3.4 (5.0)	80 (70-100)	25.4 (4.2)	7 560
EVOS/EPOS	9 013	3.0 (5.9)	64 (41- 93)	27.2 (4.6)	2 761
GBG I	1 158	7.9 (16.3)	79 (69- 85)	25.3 (4.2)	947
GBG II	7 065	12.4 (16.2)	59 (21- 89)	24.6 (3.6)	7 056
GOS	1 863	6.3 (10.9)	63 (35- 95)	26.8 (5.3)	1 805
Manitoba	43 860	5.3 (18.4)	62 (40- 102)	26.6 (5.4)	43 186
Miyama	400	8.6 (13.0)	59 (40- 79)	22.1 (2.8)	400
MsOs HK	2 000	3.5 (5.3)	73 (65- 98)	23.9 (3.5)	2 000
OFELY	668	10.9 (14.2)	62 (50- 89)	24.0 (3.5)	663
OPUS	2 881	6.0 (8.2)	61 (20- 81)	26.3 (4.6)	2 836
OSTPRE	3 058	10.0 (10.0)	52 (47- 57)	26.1 (4.3)	1 743
PERF	5 433	7.2 (24.0)	63 (44- 81)	25.5 (3.9)	2 305
Rochester	655	8.1 (19.0)	58 (21- 94)	25.5 (4.9)	650
Rotterdam	4 068	5.9 (9.4)	70 (55- 99)	26.7 (4.1)	3 325
SEMOF	7 062	2.8 (4.9)	75 (70- 91)	25.9 (4.3)	908
Sheffield	2 170	3.8 (5.8)	80 (74- 96)	26.7 (4.5)	2 150
SOF	9 704	11.9 (20.6)	72 (65- 99)	26.4 (4.6)	7 963
THIN	180 093	4.7 (13.9)	60 (50-105)	26.0 (5.1)	-
WHI	81 377	7.4 (11.2)	64 (49- 79)	28.6 (6.2)	6 132
Totals	**398 610**	**5.7 (24.0)**	**63 (20-105)**	**26.6 (5.4)**	**108 267**

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Table 3 Details of incident fractures by cohort

Cohort	Person-years	Incident fracture				
		Osteo-porotic	Hip	Distal forearm	Tibia/ fibula	Humerus /elbow
AHS	6 928	78	25	32	-	14
APOSS	34 588	236	7	113	-	47
CaMos	38 016	618	90	220	18	109
DOES	9 892	339	94	100	25	48
ECOSAP	14 811	282	52	108	-	49
EPIC-Norfolk	47 973	172	82	73	-	-
EPIDOS	25 714	1 056	311	312	-	237
EVOS/EPOS	20 945	520	30	153	36	43
GBG I	9 191	255	198	-	-	-
GBG II	87 577	887	116	443	31	98
GOS	7 315	143	32	34	9	15
Manitoba	232 076	2 855	536	1 070	-	770
Miyama	3 423	51	7	11	1	5
MsOs HK	6 975	96	21	43	-	8
OFELY	7 290	132	20	50	1	17
OPUS	12 019	113	13	68	-	28
OSTPRE	30 568	259	8	192	-	24
PERF	38 991	561	58	353	-	78
Rochester	5 318	219	42	39	16	20
Rotterdam	23 977	550	156	221	37	84
SEMOF	19 639	534	80	184	20	104
Sheffield	8 235	292	91	106	14	37
SOF	115 810	3 211	1 269	967	159	735
THIN	852 566	8 343	1 953	-	-	-
WHI	596 434	8 478	1 166	3 318	1 553	1 385
Totals	**2 256 271**	**30 280**	**6 457**	**8 210**	**1 920**	**3 955**
Age at fracture (mean)		72.7	79.5	71.0	69.6	73.6
SD		10.4	8.8	9.6	8.5	9.7

-, site of fracture not given

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Table 4. Baseline characteristics by body mass index (BMI, kg/m^2) category, mean (SD)

	Underweight (<18.5) (n=7 699)	Normal (18.5-24.9) (n=166 087)	Overweight (25.0-29.9) (n=136 873)	Obese I (30.0-34.9) (n=58 919)	Obese II (≥35.0) (n=29 032)
Age (years)	65.7 (14.0)	62.2 (11.6)	63.6 (10.7)	63.2 (10.1)	61.2 (9.3)
Body Mass index (kg/m^2)	17.2 (1.3)	22.5 (1.6)	27.2 (1.4)	32.0 (1.4)	39.3 (4.5)
Femoral neck BMD (z-score)	-0.89 (0.97) n=2 309	-0.25 (0.93) n=46 796	0.12 (0.94) n=37 741	0.41 (0.96) n=15 051	0.67 (1.0) n=6 370

Table 5. Number of fractures according to fracture outcome and category of baseline BMI. In brackets, the expected number of fractures according to the proportion of women in each category of BMI.

Fracture outcome	Under-weight (1.9%)	Normal (41.7%)	Over-weight (34.3%)	Obese I (14.8%)	Obese II (7.3%)	Obese vs. non-obese HR	95% CI	p
Osteoporotic	806 (575)	13,293 (12,627)	10,383 (10,386)	4119 (4481)	1679 (2210)	0.85	0.82-0.88	<0.001
Hip	320 (123)	3257 (2693)	2062 (2215)	628 (956)	190 (471)	0.63	0.59-0.68	<0.001
Distal forearm	126 (150)	3424 (3424)	2990 (2816)	1202 (1215)	468 (599)	0.81	0.76-0.86	<0.001
Tibia/fibula	10 (36)	608 (801)	704 (659)	361 (284)	237 (140)	1.04	0.94-1.14	>0.30
Humerus/ elbow	76 (75)	1452 (1649)	1399 (1357)	694 (585)	334 (289)	1.21	1.11-1.31	<0.001

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Table 6 Hazard ratios (HR)* for fracture and 95% confidence intervals (CI) comparing a BMI of 25kg/m^2 with BMIs of 15 and 35kg/m^2, respectively, according to different fracture outcomes.

Fracture	Not adjusted for BMD		Adjusted for BMD	
outcome	BMI 15 vs. 25	BMI 35 vs. 25	BMI 15 vs. 25	BMI 35 vs. 25
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Osteoporotic	1.54 (1.44, 1.64)	0.87 (0.85, 0.90)	0.89 (0.80, 0.99)	1.16 (1.09, 1.23)
Hip	2.88 (2.56, 3.25)	0.68 (0.62, 0.75)	1.41 (1.16, 1.72)	0.99 (0.86, 1.15)
Distal forearm	1.05 (0.91, 1.20)	0.76 (0.71, 0.81)	0.72 (0.60, 0.86)	0.97 (0.87, 1.07)
Tibia/fibula	0.64 (0.45, 0.89)	1.03 (0.94, 1.14)	0.34 (0.16, 0.74)	1.14 (0.87, 1.49)
Humerus/elbow	1.13 (0.92, 1.37)	1.18 (1.04, 1.27)	0.70 (0.54, 0.90)	1.60 (1.42, 1.80)

* HR are adjusted for age and time since baseline

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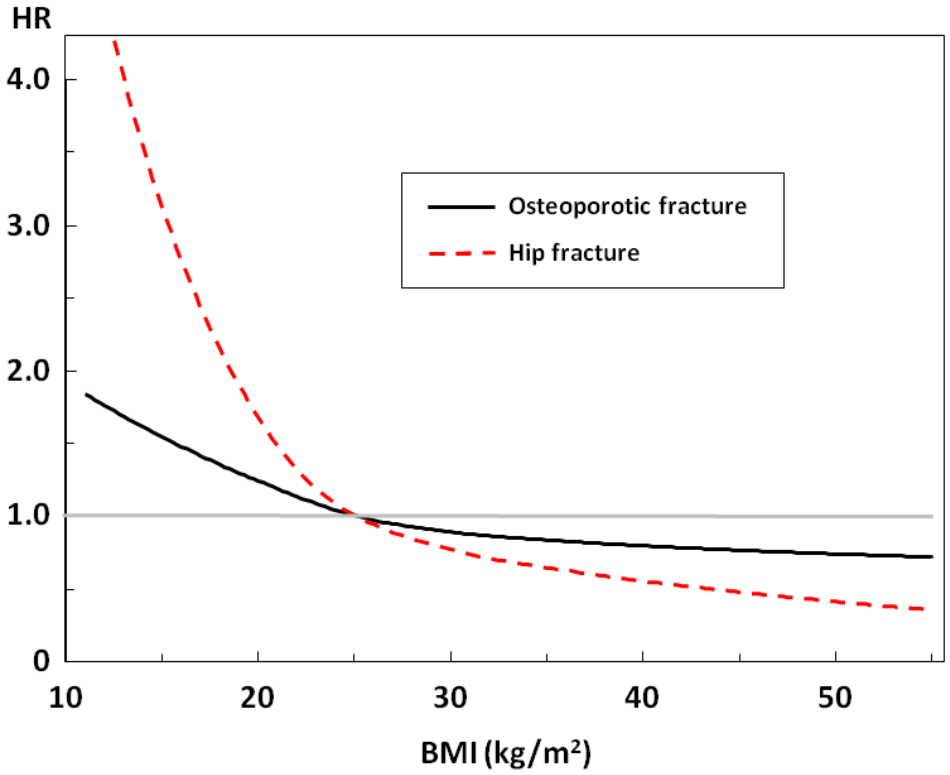

Figure 1

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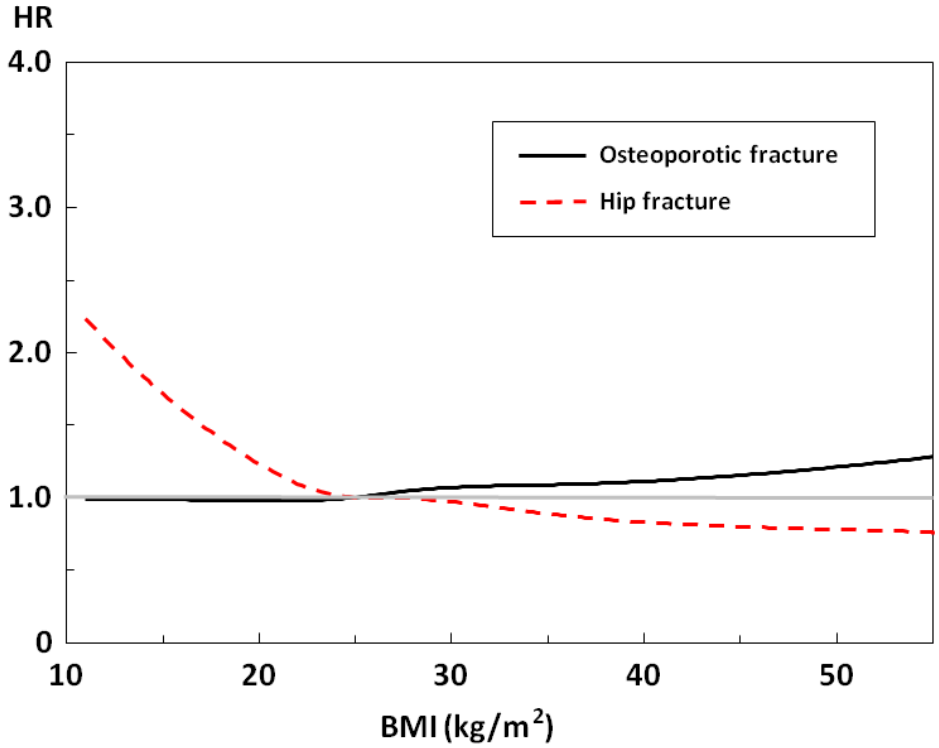

Figure 2