**Body mass index and subsequent fracture risk: A meta-analysis to update FRAX®**

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**Abstract**

The aim of this international meta-analysis was to quantify the predictive value of body mass index (BMI) for incident fracture and relationship of this risk with age, sex, follow-up time and bone mineral density (BMD). 1,667,922 men and women from 32 countries(63 cohorts), followed for a total of 16.0 million person-years were studied. 293,325 had femoral neck BMD measured (2.2 million person-years follow-up). An extended Poisson model in each cohort was used to investigate relationships between WHO-defined BMI categories (Underweight:<18.5kg/m2; Normal:18.5-24.9kg/m2; Overweight:25.0-29.9kg/m2; Obese I:30.0-34.9kg/m2; Obese II:≥35.0kg/m2) and risk of incident osteoporotic, major osteoporotic and hip fracture (HF). Inverse-variance weighted β-coefficients were used to merge the cohort-specific results. For the subset with BMD available, in models adjusted for age and follow-up time, the hazard ratio (95%CI) for HF comparing underweight with normal weight was 2.35 (2.10-2.60) in women and for men was 2.45 (1.90-3.17). HF risk was lower in overweight and obese categories compared to normal weight [obese II vs normal: women 0.66 (0.55-0.80); men 0.91 (0.66-1.26). Further adjustment for femoral neck BMD T-score attenuated the increased risk associated with underweight [underweight vs normal: women 1.69 (1.47-1.96); men 1.46 (1.00-2.13)]. In these models, the protective effects of overweight and obesity were attenuated, and in both sexes the direction of association reversed to higher fracture risk in Obese II category [Obese II vs Normal: women 1.24 (0.97-1.58); men 1.70 (1.06-2.75)]. Results were similar for other fracture outcomes. Underweight is a risk factor for fracture in both men and women regardless of adjustment for BMD. However, whilst overweight/obesity appeared protective base models, they became risk factors after additional adjustment for femoral neck BMD, particularly in the Obese II category. This effect in the highest BMI categories was of greater magnitude in men than women. These results will inform the second iteration of FRAX®.

**Key words:** Body mass index; Meta-analysis; Hip fracture; Osteoporosis; Epidemiology; Major osteoporotic fracture; FRAX

**Introduction**

Body mass index (BMI), calculated as weight divided by height squared, is an accepted surrogate for adiposity for population studies and as a clinical risk factor in assessment for outcomes such as myocardial infarction and fracture.(1,2) Multiple studies have documented the complex relationships between fat mass, lean mass and bone mineral density in the determination of fracture risk.(3,4) Obesity is associated with an increased risk of falling;(5) Both low and high BMI have been associated with greater risk of fracture, but importantly, with different fracture sites at either end of the BMI spectrum.(3) (5,6) Findings from the Global Longitudinal study of Osteoporosis in Women (GLOW) suggested high risk of ankle and upper leg fractures with obesity,(7) with similar results in the Spanish SIDIAP dataset.(8) More recently, a Mendelian Randomisation study demonstrated causal associations between low BMI and risk of forearm fracture.(9) Consistent with these observations, in our previous meta-analysis of 398,610 women, mean age 63 years, low BMI was a risk factor for hip and all osteoporotic fractures, but appeared to be protective for lower leg /ankle fracture.(2) In contrast, high BMI was associated with increased risk for humerus and elbow fractures. This relationship was dependent partly on bone mineral density (BMD). Thus, after adjustment for femoral neck BMD, high BMI remained a risk factor for upper arm fracture but also predicted increased risk of all osteoporotic fractures. BMI therefore conveys risk information for incident fracture, but with important considerations regarding the relationships with BMD and fracture site. However, the evidence base thus far principally focuses on women, with relationships in men, and indeed across ethnicities in either sex, still requiring detailed elucidation.

FRAX®, currently available in 86 territories, is the most widely used fracture risk assessment tool and is incorporated into a large number of assessment guidelines,(10) recommended by the Committee for Medicinal Products for Human Use (CHMP),(11) and approved by the National Institute for Health and Care Excellence (NICE).(12) The incorporation of BMI as an input variable for risk prediction was based on an earlier meta-analysis.(13) Since then, many more prospectively studied cohorts have become available that have the potential to improve the accuracy of FRAX and understand better the potential influences of BMD, sex and ethnicity in these relationships.(14)

The aim of the present study was to quantify magnitude of the risk relationship between BMI and incident fracture in an international setting, and to explore the dependence of this risk on age, sex, ethnicity, time since baseline assessment and BMD.

**Methods**

Details of our initial systematic review undertaken to identify appropriate cohorts, and of the cohorts included, have been documented previously(14) and are summarized in Appendix Table 1. This was registered in the PROSPERO international prospective register of systematic reviews (CRD42021227266), and followed the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. In brief, we studied 1,667,922 men and women from 63 prospectively studied cohorts. 57 cohorts included women (n=1,127,206) and 40 cohorts included men (n=540,716). Of these 293,325 men and women had BMD measured, from 53 cohorts in 20 countries, with a total follow-up time of 2.2 million person-years.

*Baseline and outcome variables*

Body mass index (BMI, kg/m2) was calculated from height and weight assessed at baseline. We considered incident fractures in the following categories: all, osteoporotic, major osteoporotic (MOF: clinical spine, distal forearm, hip or humerus) and hip fracture. For the purpose of this analysis, and related meta-analyses informing the next iteration of FRAX,(15-17) we defined “osteoporotic fractures" on the basis of previously identified sites at which fractures were more common with increasing age and decreasing BMD, thus excluding fractures of the skull, face, hands, feet, ankle and patella, as well as tibia and fibula fractures in men.(18,19) This should not be taken to mean that anyone experiencing such a fracture has osteoporosis, merely that they appear more frequent in those with low BMD and/or higher age. No distinction was made according to trauma since both high- and low-trauma fractures show similar relationships with low BMD and future fracture risk.(20,21) Details of fracture ascertainment and validation have been published previously.(14)

*Statistical methods*

The risk of incident fracture, expressed as hazard ratio per 1 kg/m2 greater baseline BMI, was estimated using an extended Poisson model applied separately to each cohort (and also separately by sex for those cohorts with both men and women).(22) Because of an embargo on data transfer, Cox regression was used on the Manitoba cohort. Covariates included current time since start of follow-up, current age, prior history of fracture, and BMD T-score at the femoral neck. Femoral neck BMD was adjusted for manufacturer and T-scores were calculated from the NHANES III White female reference values.(14) We categorised BMI according to WHO recommendations (Underweight<18.5; Normal 18.5-24.9 (referent); Overweight 25.0-29.9; Obese I 30.0-34.9; Obese II ≥ 35.0 kg/m2)(23) for analyses by category. We illustrated non-linear associations using spline models with nodes at 21, 25 and 33 kg/m2. Results of each cohort and the two sexes were weighted according to the variance and merged to determine the weighted means and standard deviations. The HR was equal to eweighted mean of β. A priori, a random effects model was used in the meta-analysis. Assessment of the effects of ethnicity was confined to those cohorts recording more than one ethnic group [Asian, Black, Hispanic, White and the Black, Asian and Minority Ethnic category (BAME)], comprising Health ABC, CAMOS, MrOS USA, LASA, WHI, SOF, Manitoba and UK Biobank. Ascertainment of these data was via self-report. On the basis of these 8 cohorts there was sufficient data to undertake pairwise comparisons. Finally, we investigated associations between BMI and risk of death during follow-up.

**Results**

Of 1,667,922 men and women studied in 32 countries, the average BMI was 27.2 kg/m2. At follow up, 151,473 men and women were identified as having a subsequent fracture of any kind; 125,135 were characterized as osteoporotic in men and women, 95,748 men and women sustained a MOF; 31,383 were hip fractures. The total follow-up time was 16.0 million-person years in men and women. BMD measurements were available in 17.6% (293,325) of individuals. Appendix Table 1 summarises key characteristics of the cohorts.

*Association between BMI and risk of incident fracture*

In continuous models, summarised in Table 1, after adjustment for age and time since baseline, greater BMI was associated with lower risk of incident fracture in both men and women, for example hazard ratio (HR) (95% CI) for major osteoporotic fracture per unit greater BMI in women was 0.98 (0.97, 0.98); in men 0.98 (0.97, 0.98). Figure 1 documents these associations for hip fracture and major osteoporotic fracture in men and women combined as Forest plots. Associations appeared similar by sex and were not materially different in the subset of cohorts in which BMD was measured. In this subset, after further adjustment for BMD there was a reversal in the relationships such that greater BMI was weakly associated with higher fracture risk. For example, amongst women HR for major osteoporotic fracture per unit greater BMI was 1.01 (1.00, 1.02) and for men 1.02 (1.01, 1.03) (Table 1). Overall, associations were similar between men and women (Appendix Table 2).

*Categorical and non-linear associations between BMI and risk of incident fracture*

On average, those who were underweight tended to be somewhat older than those in other categories and had lower femoral neck BMD T-score (Appendix Table 3). Indeed, there was modest but positive gradient of mean femoral neck BMD T-score going from underweight to normal to overweight to obese categories. Table 2a-b and Figure 2 document the associations between BMI category relative to the normal BMI for men and women, in the subset with BMD measurements, unadjusted and adjusted for femoral neck BMD. As with the initial models, associations were not materially different in the subset with BMD, without BMD adjustment, but the increased risk associated with low BMI and the more modest protective effect of higher BMI category was attenuated by adjustment for femoral neck BMD. Indeed, after BMD adjustment obesity became a risk factor for fracture in both sexes, with evidence of a greater effect size in men than women (Tables 2 a-b, and Appendix Table 4). Appendix Figure 1 presents the continuous relationships between BMI (HR for fracture for a given BMI versus a BMI of 25 kg/m²) and risk of hip fracture in men and women separately, in the subset with BMD, without and then with adjustment for femoral neck BMD.

*Ethnicity*

Appendix Table 5 documents the fracture outcome models with continuous BMI as the exposure, by ethnicity (hazard ratio and 95%CI fracture risk for each one-unit greater BMI for White, Asian, Black and Hispanic ethnicities, together with p value for a BMI•ethnicity interaction). There was no statistical evidence for a difference in the association between BMI and hip fracture by ethnicity. In contrast to White ethnicity, for Asian and Hispanic ethnicities, higher BMI was associated with a greater risk of any fracture [Asian: HR (95% CI) 1.02 (1.00, 1.04); Hispanic 1.02 (1.00, 1.05).

*Interaction with age and follow-up time*

For all, osteoporotic and MOF fracture outcomes, the hazard ratio for fracture per one-unit greater BMI tended to decrease with increasing age. Conversely, for the outcome of hip fracture, there was no obvious relationship with age. (Appendix Table 6). There was a modest increase in hazard ratio with greater follow-up time for the hip fracture and MOF in the whole cohort after adjusting for age (Appendix Table 7).

*Association between BMI and mortality*

Compared to normal weight, both underweight [HR (95%CI): 1.60 (1.44,1.78) in women and 1.71 (1.50, 1.94) in men] and obese I and II categories [e.g. obese II: 1.31 (1.21, 1.43) in women and 1.27 (1.07, 1.51) in men] were associated with greater risk of death during follow-up, in both sexes. Overweight was not associated with increased mortality risk and indeed was protective in women [0.92 (0.88, 0.95)] and men [0.96 (0.92, 1.00)]. Overall associations were similar after adjustment for femoral neck BMD T-score. Appendix Table 8a-b summarises these associations.

**Discussion**

*Summary of findings*

The present study represents the largest meta-analysis to date on the association between body mass index and subsequent fracture risk. It confirms our previous observation in women that low BMI is associated with increased fracture risk, persisting after adjustment for femoral neck BMD.(2) Furthermore, it confirms in women that overall higher BMI becomes a risk factor for fracture after adjustment for BMD, despite being protective when used unadjusted. In addition to these confirmatory findings, our new analysis documents important novel associations in men: although we observed a similar pattern overall to that in women, the increased risk of fracture associated with obesity after adjustment for BMD was of greater magnitude in men compared with women.

*Comparison with previous studies*

This analysis provides an updated comparison with our previous meta-analysis, which examined relationships between BMI and fracture risk only in women, based on a much smaller cohort database with substantially less time at risk available.(2) There, we observed that low BMI was a risk factor for hip and all osteoporotic fractures; when adjusted for BMD, it remained a risk factor for hip fracture but was weakly protective for osteoporotic fracture. In contrast, high BMI, when adjusted for BMD, was a risk factor for osteoporotic fractures. Our initial 2005 meta-analysis focused on both men and women but with a smaller number of participants and, whilst the results were broadly comparable, was not able to elucidate any differences by sex.(13) Similar adverse effect of high BMI on fracture risk, after adjustment for BMD, were observed in the US MrOS cohort.(24) Compston et al. examined the relationship between BMI and fracture outcomes in the Global Longitudinal Study of Osteoporosis in Women observing, in 52,939 postmenopausal women, a protective association between greater BMI and risk of hip, clinical spine and wrist fractures.(25) In contrast higher BMI was associated weakly with greater risk of ankle fracture. Whilst this study has sometimes been interpreted by others as demonstrating that obesity is not protective for osteoporotic fracture, there is clearly a question of whether ankle fractures are a consequence of osteoporosis per se, given that the age and sex relationship differs from that with classical osteoporotic fractures.(18,19,26-28) Thus rather than being protective for ankle fractures, obesity appears to be a risk factor for these events. The findings are overall consistent with our current meta-analysis in suggesting that associations between BMI and fracture risk are site specific, with potential further mechanistic implications.

Whilst factors such as chronic inflammation, type 2 diabetes and propensity to falls may contribute to fracture risk in obesity,(5,29) other considerations may underpin apparent sex differences observed. For example, in the present analysis, the greater risk of hip fracture in men compared with women at high BMI after consideration of femoral neck BMD may reflect sex dependent distribution of adipose tissue, with the female distribution more classically subcutaneous around the hips than abdomen, compared with the visceral abdominal deposition in men.(30,31) Biomechanically, the additional adipose tissue overlying the proximal femur would favour a protective effect for hip fracture in women compared with men. Additionally, or alternatively, a further mechanism might relate to sex-dependent differential hormonal patterns in obesity. Excess adipose tissue is associated with increased oestrogen activity, with likely positive effects on bone and muscle.(32) However, in men obesity may lead to a concomitant reduction in male sex steroids and thus potentially effective hypogonadism,(6,33) with increased fracture risk possibly additionally mediated via impaired muscle health in addition to reduced BMD.(34)

*Strengths and limitations*

We undertook the largest meta-analysis to date of mostly population-based cohorts to investigate and quantify associations between BMI and risk of incident fractures. We were able to investigate BMI as a continuous exponential, nonlinear and categorical exposure, and investigate possible interactions by age, sex, ethnicity and follow-up time. The use of primary data decreases the risk of publication bias and the general consistency of the BMI-fracture association between cohorts provides strong support for the international validity of this risk variable. However, there are limitations which need to be considered in the interpretation of our findings. Firstly, as with nearly all population-based studies, non-response biases may have occurred, which we were unable to document for all cohorts. This is likely to result in a cohort which is healthier than the background population and may thus lead to underestimation of the absolute risk of fracture. In particular, there may have been reduced responses from those at the lowest and highest BMI values. It is therefore likely, if anything, to have had a conservative effect on our risk estimates. Secondly, it is possible that there were differences in protocols and, for example, execution of height and weight measures between cohorts. This is unavoidable in such a study, and importantly, exposure-outcome analyses were undertaken within each cohort and then the beta coefficients merged through random effects meta-analysis. Thirdly, we were not able to elucidate whether the association between BMI and incident fracture was causal. However, this was not the purpose of the study and for the purpose of risk assessment, a causal relationship is not required. Fourthly, BMI is affected by both fat and lean mass and does not account for distribution of fat between subcutaneous and visceral compartments. This is irrelevant in terms risk assessment, but of course limits mechanistic influence. Finally, we were not able to account for levels of physical activity, which might be related to both BMI and fracture risk. Although this might be mechanistically interesting, it would not reflect the way in which BMI is considered in the FRAX algorithm.

*Clinical and risk assessment implications*

The role of BMI in the FRAX model was informed by an earlier meta-analysis by De Laet et al.,(13) which was broadly consistent with the Johansson et al., 2014 study,(2) the conclusion at that time being that the new findings did not necessitate modification of the FRAX engine itself. Here we present novel associations relating to men as well as women, with interactions by sex, follow-up time, ethnicity and age, which will directly inform the revised FRAX engine, as a continuous exposure, in the second version of this globally established tool. Importantly our current findings also confirm the non-linear association between BMI and fracture. The variably modifying effects of age, ethnicity and follow-up time, together with differences by sex, support the accommodation of such nuances in the FRAX risk engine, but conversely mitigate against using BMI thresholds in risk assessment, since these would not necessarily convey consistent risk information across these parameters or fracture outcomes. The associations between increased risk of death during follow-up and underweight, and to a lesser extent obesity, are consistent with a large recent analyses,(35) and will also be important to consider in the derivation of the revised FRAX tool.

Whilst there are likely to be causal implications, underpinned by our understanding of biology and biomechanics, for the purposes of risk assessment, the principal requirement is quantification of the exposure-outcome association and of interactions between this relationship and with other potential input variables. Notwithstanding, our findings directly inform clinical practice, indicating that greater BMI is not necessarily protective for all fracture types. Whilst this may play into strategies to tackle obesity, there is evidence that weight loss usually leads to concomitant loss of muscle and bone and so approaches addressing obesity in the context of fracture risk must be carefully thought out.(36) Adequate calcium and protein nutrition, together with a mix of weight-bearing and resistance exercise training, alongside dietary interventions to reduce calorie intake are likely to be important,(37) given the clear demonstration of increasing risk of hip fracture with lower BMI, even after adjustment for BMD.

*Conclusion*

In the largest meta-analysis to date of prospective cohorts worldwide, we have confirmed inverse associations between fracture risk and BMI, with the apparent protective effect of higher BMI reversed after adjustment for femoral neck BMD. The magnitude of this effect appeared greater in men than women. The increased accuracy of the elucidated effect sizes, and their specificity by age, sex, follow-up time and ethnicity will inform improved risk assessment in the second iteration of the FRAX tool.

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**Compliance with ethical standards**

*Conflict of interest*

NC Harvey has received consultancy/lecture fees/honoraria/grant funding from Alliance for Better Bone Health, Amgen, MSD, Eli Lilly, Radius Health, Servier, Shire, UCB, Consilient Healthcare, Kyowa Kirin, Theramex and Internis Pharma.

JA Kanis led the team that developed FRAX as director of the WHO Collaborating Centre for Metabolic Bone Diseases. EV McCloskey, WD Leslie, M Lorentzon, NC Harvey, E Liu, L Vandenput and H Johansson are members of the FRAX team. JA Kanis, NC Harvey, and EV McCloskey are members of the advisory body to the National Osteoporosis Guideline Group. JA Kanis reports no additional competing interests.

KE Åkesson has no financial interest related to FRAX; chaired the National SALAR Group for Person-Centered Care Pathway Osteoporosis.

FA Anderson led the team that developed GLOW, while director of the Center for Outcomes Research at the University of Massachusetts Medical School; he has no financial interest in FRAX.

R Azagra has received funding for research from Instituto Carlos III of Spanish Ministry of Health, IDIAP Jordi Gol of Catalan Government and from Scientific Societies SEMFYC and SEIOMM

CL Bager is employed at Nordic Bioscience and owns stock in Nordic Bioscience. She declares no competing interests in relation to this work.

HA Bischoff-Ferrari has no financial interest in FRAX. For the DO-HEALTH trial cohort, Prof. Bischoff-Ferrari reports independent and investigator-initiated grants from European Commission Framework 7 Research Program, from the University of Zurich, from NESTEC, from Pfizer Consumer Healthcare, from Streuli Pharma, plus non-financial support from DNP. For the study cohort extension, she reports independent and investigator-initiated grants from Pfizer and from Vifor. Further, Prof. Bischoff-Ferrari reports non-financial support from Roche Diagnostics and personal fees from Wild, Sandoz, Pfizer, Vifor, Mylan, Roche, Meda Pharma, outside the submitted work with regard to speaker fees and travel fees.

JR Center has received honoraria for speaking at educational meetings and for advisory boards from Amgen and honoraria for an advisory board from Bayer, all unrelated to this work.R Chapurlat has no financial interest in FRAX. He has received grant funding from Amgen, UCB, Chugai, MSD, Mylan and Medac. He has received honoraria from Amgen, UCB, Chugai, Galapagos, Biocon, Abbvie, Haoma Medica, Pfizer, Amolyt, MSD, Lilly, BMS, Novartis, Arrow, PKMed, Kyowa-Kirin, and Sanofi.

C Christiansen owns stock in Nordic Bioscience. He declares no competing interests in relation to this work.

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MA Kotowicz has received funding from the National Health and Medical Research Council (NHMRC) Australia, and the Medical Research Future Fund (MRFF) Australia. He has served on advisory boards for Amgen Australia, Novartic and Eli Lilly – all unrelated to this work and was the Director of the Geelong Bone Densitometry Service until 2022.

A Langhammer is PI of the HUNT Lung and Osteoporosis project, the project got some funding from AstraZeneca for data collection. He has received lecture or consultant fees from AstraZeneca, GSK, Boehringer Ingelheim, and Diagnostica. No funding related to this study.

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C Ohlsson is listed as a coinventor on two patent applications regarding probiotics in osteoporosis treatment.

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NC Wright sits on the Board of Trustee of the US Bone Health and Osteoporosis Foundation, and has received consulting fees from Radius and ArgenX

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*Human and animal rights*   
This review does not contain any original studies with human participants or animals performed by any of the authors.

*Ethics*All individual cohorts with candidate risk factors available have been approved by their local ethics committees and informed consent has been obtained from all study participants. General ethics approval for the use of these cohorts is also given by the University of Sheffield. Participant data are stored in coded, de-identified form. Only summary statistics and aggregate data are published, not allowing for identification of individual study participants.

*Data Availability Statement*

Data availability is cohort specific and individual cohort Principal Investigators should be contacted for enquiries about data access.

**References**

1. Wolk R, Berger P, Lennon RJ, Brilakis ES, Somers VK. Body mass index: a risk factor for unstable angina and myocardial infarction in patients with angiographically confirmed coronary artery disease. Circulation. Nov 4 2003;108(18):2206-11. Epub 2003/10/15.

2. Johansson H, Kanis JA, Oden A, McCloskey E, Chapurlat RD, Christiansen C, et al. A meta-analysis of the association of fracture risk and body mass index in women. J Bone Miner Res. Jan 2014;29(1):223-33. Epub 2013/06/19.

3. Nielson CM, Srikanth P, Orwoll ES. Obesity and fracture in men and women: an epidemiologic perspective. J Bone Miner Res. Jan 2012;27(1):1-10. Epub 2013/01/26.

4. Harvey NC, Kanis JA, Liu E, Johansson H, Lorentzon M, McCloskey E. Appendicular lean mass and fracture risk assessment: implications for FRAX(R) and sarcopenia. Osteoporos Int. Mar 2019;30(3):537-9. Epub 2019/03/01.

5. S GRN, J SO, A BD, R ML, Tiedemann A. Does Obesity Increase the Risk and Severity of Falls in People Aged 60 Years and Older? A Systematic Review and Meta-analysis of Observational Studies. J Gerontol A Biol Sci Med Sci. Apr 17 2020;75(5):952-60.

6. Ahmed F, Hetty S, Laterveer R, Surucu EB, Mathioudaki A, Hornbrinck E, et al. Altered expression of aromatase and estrogen receptors in adipose tissue from men with obesity or type 2 diabetes. J Clin Endocrinol Metab. Jan 21 2025. Epub 20250121.

7. Compston JE, Watts NB, Chapurlat R, Cooper C, Boonen S, Greenspan S, et al. Obesity is not protective against fracture in postmenopausal women: GLOW. Am J Med. Nov 2011;124(11):1043-50. Epub 2011/10/25.

8. Prieto-Alhambra D, Premaor MO, Fina Aviles F, Hermosilla E, Martinez-Laguna D, Carbonell-Abella C, et al. The association between fracture and obesity is site-dependent: a population-based study in postmenopausal women. J Bone Miner Res. Feb 2012;27(2):294-300. Epub 2011/11/19.

9. Nethander M, Movérare-Skrtic S, Kämpe A, Coward E, Reimann E, Grahnemo L, et al. An atlas of genetic determinants of forearm fracture. Nat Genet. Nov 2023;55(11):1820-30. Epub 2023/11/03.

10. Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. Sep 2012;23(9):2239-56. Epub 2012/03/16.

11. CHMP. Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis. Ref CPMP/EWP/552/95Rev.2, London, UK2006.

12. NICE. CG146: Osteoporosis: Fragility fracture risk. Short clinical guideline- evidence and recommendation. London: National Clinical Guideline Centre; 2012.

13. De Laet C, Kanis JA, Odén A, Johanson H, Johnell O, Delmas P, et al. Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporos Int. Nov 2005;16(11):1330-8. Epub 2005/06/02.

14. Vandenput L, Johansson H, McCloskey EV, Liu E, Åkesson KE, Anderson FA, et al. Update of the fracture risk prediction tool FRAX: a systematic review of potential cohorts and analysis plan. Osteoporos Int. Oct 2022;33(10):2103-36. Epub 2022/06/01.

15. Kanis JA, Johansson H, McCloskey EV, Liu E, Åkesson KE, Anderson FA, et al. Previous fracture and subsequent fracture risk: a meta-analysis to update FRAX. Osteoporos Int. Aug 11 2023. Epub 2023/08/11.

16. Vandenput L, Johansson H, McCloskey EV, Liu E, Schini M, Åkesson KE, et al. A meta-analysis of previous falls and subsequent fracture risk in cohort studies. Osteoporos Int. Mar 2024;35(3):469-94. Epub 20240117.

17. Kanis JA, Johansson H, McCloskey EV, Liu E, Schini M, Vandenput L, et al. Rheumatoid arthritis and subsequent fracture risk: an individual person meta-analysis to update FRAX. Osteoporos Int. Apr 2025;36(4):653-71. Epub 20250216.

18. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int. Dec 2001;12(12):989-95. Epub 2002/02/16.

19. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int. 2001;12(5):417-27. Epub 2001/07/11.

20. Leslie WD, Schousboe JT, Morin SN, Martineau P, Lix LM, Johansson H, et al. Fracture risk following high-trauma versus low-trauma fracture: a registry-based cohort study. Osteoporos Int. Jun 2020;31(6):1059-67. Epub 2020/03/17.

21. Crandall CJ, Larson JC, LaCroix AZ, Robbins JA, Wactawski-Wende J, Johnson KC, et al. Risk of Subsequent Fractures in Postmenopausal Women After Nontraumatic vs Traumatic Fractures. JAMA internal medicine. Aug 1 2021;181(8):1055-63.

22. Breslow NE, Day NE. Statistical Methods in Cancer Research. IARC Scientific Publications No 32. 1987;Volume II:p 131-5.

23. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253. Epub 2001/03/10.

24. Nielson CM, Marshall LM, Adams AL, LeBlanc ES, Cawthon PM, Ensrud K, et al. BMI and fracture risk in older men: the osteoporotic fractures in men study (MrOS). J Bone Miner Res. Mar 2011;26(3):496-502. Epub 2010/09/04.

25. Compston JE, Flahive J, Hosmer DW, Watts NB, Siris ES, Silverman S, et al. Relationship of weight, height, and body mass index with fracture risk at different sites in postmenopausal women: the Global Longitudinal study of Osteoporosis in Women (GLOW). J Bone Miner Res. Feb 2014;29(2):487-93. Epub 2013/07/23.

26. Stone KL, Seeley DG, Lui LY, Cauley JA, Ensrud K, Browner WS, et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. J Bone Miner Res. Nov 2003;18(11):1947-54.

27. Chalhoub D, Orwoll ES, Cawthon PM, Ensrud KE, Boudreau R, Greenspan S, et al. Areal and volumetric bone mineral density and risk of multiple types of fracture in older men. Bone. Nov 2016;92:100-6. Epub 20160820.

28. Charles A, Mugisha A, Iconaru L, Baleanu F, Benoit F, Surquin M, et al. Distribution of Fracture Sites in Postmenopausal Overweight and Obese Women: The FRISBEE Study. Calcif Tissue Int. Jul 2022;111(1):29-34. Epub 20220322.

29. Khosla S, Samakkarnthai P, Monroe DG, Farr JN. Update on the pathogenesis and treatment of skeletal fragility in type 2 diabetes mellitus. Nature reviews Endocrinology. Nov 2021;17(11):685-97. Epub 2021/09/15.

30. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues - the biology of pear shape. Biol Sex Differ. May 31 2012;3(1):13. Epub 2012/06/02.

31. Gavin KM, Bessesen DH. Sex Differences in Adipose Tissue Function. Endocrinol Metab Clin North Am. Jun 2020;49(2):215-28. Epub 2020/05/19.

32. Kopelman PG, Pilkington TR, White N, Jeffcoate SL. Abnormal sex steroid secretion and binding in massively obese women. Clin Endocrinol (Oxf). Apr 1980;12(4):363-9. Epub 1980/04/01.

33. Trabert B, Graubard BI, Nyante SJ, Rifai N, Bradwin G, Platz EA, et al. Relationship of sex steroid hormones with body size and with body composition measured by dual-energy X-ray absorptiometry in US men. Cancer Causes Control. Dec 2012;23(12):1881-91. Epub 2012/10/12.

34. Mouser JG, Loprinzi PD, Loenneke JP. The association between physiologic testosterone levels, lean mass, and fat mass in a nationally representative sample of men in the United States. Steroids. Nov 2016;115:62-6. Epub 2016/08/21.

35. Xia X, Chen S, Tian X, Xu Q, Zhang Y, Zhang X, et al. Association of body mass index with risk of cardiometabolic disease, multimorbidity and mortality: a multi-state analysis based on the Kailuan cohort. Endocrine. May 2024;84(2):355-64. Epub 2023/10/25.

36. Weiss EP, Jordan RC, Frese EM, Albert SG, Villareal DT. Effects of Weight Loss on Lean Mass, Strength, Bone, and Aerobic Capacity. Med Sci Sports Exerc. Jan 2017;49(1):206-17. Epub 2016/09/01.

37. Clinical guideline [CG189]: Obesity: identification, assessment and management. National Institute for Health and Care Excellence; 2014.

**Table 1:** Hazard ratio (HR) and 95% confidence interval (CI) for fracture at the sites indicated per unit greater BMI (linear models). HRs are adjusted for age and time since baseline.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Adjusted for age and time since baseline | | | Adjusted for age and time since baseline – for **those with BMD** | | | Adjusted for age, time since baseline **and BMD** | | |
| **Outcome**  **fracture** | **Number**  **of cohorts** | **I2** | **HR (95% CI)** | **Number**  **of**  **cohorts** | **I2** | **HR (95% CI)** | **Number**  **of**  **cohorts** | **I2** | **HR (95% CI)** |
| ***Female*** |  |  |  |  |  |  |  |  |  |
| Any | 55 | 73 | 0.99 (0.98, 0.99) | 46 | 65 | 0.98 (0.98, 0.99) | 46 | 42 | 1.01 (1.01, 1.01) |
| Hip | 57 | 57 | 0.95 (0.94, 0.95) | 46 | 41 | 0.95 (0.94, 0.96) | 46 | 33 | 0.99 (0.98, 1.00)0.060 |
| MOF | 52 | 83 | 0.98 (0,97, 0,98) | 45 | 77 | 0.98 (0.97, 0.98) | 45 | 57 | 1.01 (1.00, 1.02)0.0018 |
| Ost | 51 | 83 | 0.98 (0.97, 0.98) | 44 | 73 | 0.98 (0.97, 0.98) | 44 | 55 | 1.01 (1.00, 1.01)0.0051 |
| ***Male*** |  |  |  |  |  |  |  |  |  |
| Any | 38 | 25 | 0.99 (0.98, 0.99) | 32 | 0 | 0.99 (0.98, 0.99) | 32 | 0 | 1.02 (1.01, 1.02) |
| Hip | 36 | 48 | 0.95 (0.93, 0.96) | 29 | 32 | 0.95 (0.93, 0.97) | 28 | 0 | 1.03 (1.01, 1.04) |
| MOF | 35 | 60 | 0.98 (0.97, 0.98) | 30 | 0 | 0.98 (0.97, 0.98) | 30 | 1 | 1.02 (1.01, 1.03) |
| Ost | 34 | 56 | 0.98 (0.97, 0.99) | 30 | 18 | 0.98 (0.97, 0.99) | 30 | 0 | 1.02 (1.01, 1.03) |

MOF = major osteoporotic fracture; Ost = osteoporotic fracture

Except where indicated, p<0.001

**Table 2a:** Hazard ratio for fracture by BMI category (reference normal) in women and men, adjusted for age and time since baseline, in subset with femoral neck BMD measure available (but not adjusted for BMD). (BMI Categories: Underweight BMI<18.5, Normal BMI 18.5-24.9, Overweight BMI 25.0-29.9, Obese I BMI 30.0-34.9, Obese II BMI ≥ 35.0 kg/m2). HR in bold are <0.001.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **1** | **3** | **4** | **5** |
|  |  | **Underweight vs Normal** | **Overweight vs Normal** | **Obese I vs Normal** | **Obese II vs Normal** |
| Outcome  fracture | *N, cohorts* | *HR (95% CI)* | *HR (95% CI)* | *HR (95% CI)* | *HR (95% CI)* |
| ***Women*** |  |  |  |  |  |
| Any | 38, 47, 45, 40 | **1.31 [1.20-1.43]** | **0.94 [0.90-0.98]** | **0.88 [0.83-0.93]** | **0.84 [0.77-0.91]** |
| Hip | 27, 41, 33, 22 | **2.35 [2.13-2.60]** | **0.75 [0.72-0.78]** | **0.64 [0.59-0.69]** | **0.66 [0.55-0.80]** |
| MOF | 33, 45, 42, 36 | **1.43 [1.30-1.59]** | **0.90 [0.85-0.95]** | **0.82 [0.76-0.89]** | **0.78 [0.70-0.88]** |
| Ost | 34, 44, 42, 36 | **1.38 [1.27-1.50]** | **0.90 [0.86-0.94]** | **0.84 [0.79-0.90]** | **0.77 [0.70-0.85]** |
| ***Men*** |  |  |  |  |  |
| Any | 21, 30, 27, 23 | **1.77 [1.54-2.04]** | **0.87 [0.84-0.90]** | **0.88 [0.82-0.94]** | 1.04 [1.04-1.05] |
| Hip | 14, 23, 16, 11 | **2.45 [1.90-3.17]** | **0.69 [0.65-0.74]** | **0.63 [0.53-0.74]** | 0.91 [0.66-1.26] |
| MOF | 16, 28, 23, 17 | **1.87 [1.60-2.20]** | **0.85 [0.80-0.90]** | **0.80 [0.72-0.89]** | **0.96 [0.96-0.97]** |
| Ost | 19, 28, 25, 21 | **1.83 [1.58-2.12]** | **0.85 [0.82-0.89]** | **0.82 [0.76-0.89]** | **0.96 [0.96-0.97]** |
|  |  |  |  |  |  |
| p  women vs men | |  |  |  |  |
| Any |  | **<0.001** | **0.0067** | >0.30 | **<0.001** |
| Hip |  | >0.30 | **0.024** | >0.30 | 0.088 |
| MOF |  | **0.0040** | 0.18 | >0.30 | **<0.001** |
| Ost |  | **0.0011** | 0.053 | >0.30 | **<0.001** |

MOF = major osteoporotic fracture; Ost = osteoporotic fracture

**Table 2b:** Hazard ratio for fracture by BMI category (reference normal) in women and men, adjusted for age and time since baseline, in subset with femoral neck BMD measure available, additionally adjusted for BMD. (BMI Categories: Underweight BMI<18.5, Normal BMI 18.5-24.9, Overweight BMI 25.0-29.9, Obese I BMI 30.0-34.9, Obese II BMI ≥ 35.0 kg/m2). HR in bold are <0.001.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **1** | **3** | **4** | **5** |
|  |  | **Underweight vs Normal** | **Overweight vs Normal** | **Obese I vs Normal** | **Obese II vs Normal** |
| Outcome  fracture | *N, cohorts* | *HR (95% CI)* | *HR (95% CI)* | *HR (95% CI)* | *HR (95% CI)* |
| ***Women*** |  |  |  |  |  |
| Any | 38, 47, 45, 40 | **1.09 [1.03-1.17]** | **1.08 [1.04-1.12]** | **1.13 [1.07-1.20]** | **1.19 [1.10-1.29]** |
| Hip | 27, 41, 33, 22 | **1.69 [1.47-1.96]** | 0.99 [0.93-1.05] | 0.97 [0.89-1.06] | 1.24 [0.97-1.58] |
| MOF | 33, 45, 42, 36 | **1.16 [1.08-1.25]** | **1.07 [1.01-1.13]** | **1.12 [1.04-1.21]** | **1.21 [1.09-1.35]** |
| Ost | 34, 44, 42, 36 | **1.13 [1.06-1.21]** | **1.06 [1.01-1.11]** | **1.13 [1.05-1.21]** | **1.17 [1.05-1.29]** |
| ***Men*** |  |  |  |  |  |
| Any | 21, 30, 27, 23 | **1.23 [1.00-1.51]** | 1.03 [0.97-1.09] | **1.14 [1.05-1.24]** | **1.43 [1.24-1.65]** |
| Hip | 14, 23, 16, 11 | 1.46 [1.00-2.13] | 1.06 [0.95-1.18] | 1.10 [0.87-1.38] | **1.70 [1.06-2.75]** |
| MOF | 16, 28, 23, 17 | 1.25 [0.98-1.60] | 1.06 [0.98-1.15] | **1.14 [1.01-1.29]** | **1.54 [1.26-1.88]** |
| Ost | 19, 28, 25, 21 | **1.23 [1.00-1.52]** | 1.03 [0.96-1.09] | **1.11 [1.02-1.22]** | **1.53 [1.27-1.83]** |
|  |  |  |  |  |  |
| p women vs men | | |  |  |  |
| Any |  | 0.27 | 0.19 | >0.30 | **0.027** |
| Hip |  | >0.30 | 0.29 | >0.30 | 0.25 |
| MOF |  | >0.30 | >0.30 | >0.30 | **0.037** |
| Ost |  | >0.30 | >0.30 | >0.30 | **0.045** |

MOF = major osteoporotic fracture; Ost = osteoporotic fracture

**Figure 1.** Forest plot showing effect size on hip fracture risk (left panel, A) and major osteoporotic fracture (right panel, B) per one unit greater BMI in men and women combined adjusted for age and time since baseline.

**Figure 2:** Hazard ratio (95% CI for fracture according to categories of BMI (referent: normal BMI) for men and women. 2A: hip fracture; 2B: major osteoporotic fracture (MOF). Associations are adjusted for age and follow-up time +/- femoral neck BMD T-score, in subset with femoral neck BMD measure available.