# MODELS FOR ASSESSEING FIRST INCIDENT FRAGILITY FRACTURE RISK

# DEVELOPMENT OF MODELS FOR ASSESSING FIRST INCIDENT FRAGILITY FRACTURE RISK IN POSTMENOPAUSAL WOMEN: DATA FROM THE CLSA

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## Lay Abstract

This thesis developed a simple screening tool to help identify postmenopausal women who may be at higher risk of experiencing first incident fragility fracture. Using data from over 10000 women aged 45 to 85 from the Canadian Longitudinal Study on Aging, a model was built on 11 common factors including age, alcohol consumption, antidepressants, balance, epilepsy, hand grip strength, height, osteoarthritis, parent hip fracture after age 50, fall in the past 12 months, and smoking. The tool was better at identifying women at risk than using BMD T-score alone. It correctly identified most women who sustained a fracture during the follow-up period. Because it relies on information that can be collected easily during regular visits, this model could be used in primary care and similar settings to help decide who might need further examinations or early prevention. Further studies are needed to test how well it works in other populations.

## Abstract

**Objective**: To develop models for assessing first incident fragility fracture risk in postmenopausal women which could be used as a screening tool in primary care and similar settings.

**Design**: Cohort study.

**Methods**: Outcome was defined as first incident fragility fracture reported at either year 3 or year 6. Model development was conducted using logistic regression with multiple imputation as sensitivity analysis. Model performance was assessed through AUC, sensitivity, and specificity.

**Results**: Analysis included 10930 female participants (1048 events) aged 45 to 85 years old without a history of fragility fracture before baseline from the Canadian Longitudinal Study on Aging (CLSA). The final model consisted of 11 factors including age, alcohol consumption, antidepressants, balance, epilepsy, hand grip strength, height, osteoarthritis, parent hip fracture after age 50, fall in the past 12 months, and smoking. The model outperformed BMD T-score total hip alone showing moderate discrimination with an AUC of 0.63 [0.61, 0.65]. With a threshold of a fracture probability at 7.30%, sensitivity was 80.49% and specificity was 34.61%. After adjusting for BMD T-score total hip, antidepressants, balance, epilepsy, hand grip strength, height, osteoarthritis,

parent hip fracture after age 50, and fall in the past 12 months remained statistically significant.

**Conclusion**: This model uses routinely collected factors and shows reasonable ability to distinguish between individuals at higher and lower risk of first incident fragility fracture. It demonstrates good sensitivity capturing the majority of true cases. Although its specificity is relatively limited, the model still has potential as a screening tool to help identify those at high risk who might benefit from further examinations and early intervention. Further studies are needed to validate the model performance in external populations

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## List of Abbreviations

3C: three city study

ALSWH: Australian Longitudinal Study in Women's Health

ARIC: Atherosclerosis Risk in Communities Study

ASPREE: Aspirin in Reducing Events in the Elderly

AUC: area under the curve

AusDiab: Australian Diabetes, Obesity and Lifestyle Study

BMD: bone mineral density

BMI: body mass index

CAIFOS: Calcium Intake Fracture Outcome Study

CaMos: Canadian Multicentre Osteoporosis Study

CCHS: Copenhagen City Heart Study

CEOR: Center of Excellence for Osteoporosis Research study

CHI: community health index

CI: confidence interval

CKB: China Kadoorie Biobank

CLSA: Canadian Longitudinal Study on Aging

CPRD: Clinical Practice Research Datalink

CPS: Cancer Prevention Study

CSHA: Canadian Study of Health and Aging

DOES: Dubbo Osteoporosis Epidemiology Study

DOPS: Danish Osteoporosis Prevention Study

E3N: Etude Epidemiologique de Femmes de la Mutuelle Generale de l'Education Nationale Study

EPESE: Established Populations for Epidemiologic Studies of the Elderly

EPIC: European Prospective Investigation into Cancer

EVOS: European Vertebral Osteoporosis Study

FHS: Framingham Heart Study

FRISBEE: Fracture Risk Brussels Epidemiological Enquiry study

GERICO: Geneva Retirees Cohort study

GLOW: Global Longitudinal Study of Osteoporosis in Women

GOS: Geelong Osteoporosis Study

GPRD: UK based General Practice Research Database

Health ABC: Health, Aging, and Body Composition Study

HR: hazard ratio

IRR: incidence rate ratio.

JPOS: Japanese Population-Based Osteoporosis Study

KHGS: Korean Health and Genome Study

LASA: Longitudinal Aging Study Amsterdam

LHID: Longitudinal Health Insurance Database

MDCS: Malmö Diet and Cancer Study

MOF: major osteoporotic fracture

MONICA: Monitoring trends and determinants on cardiovascular diseases

NHANES: National Health and Nutrition Examination Survey

NHI: Taiwan's National Health Insurance

NHIS: Korean National Health Insurance Service

NORA: National Osteoporosis Risk Assessment

NORD: Nordic Osteoporosis Research Dataset

NR: not reported

OFELY: Os des Femmes de Lyon cohort

OPRA: Osteoporotic Prospective Risk Assessment

OR: odds ratio

OSTPRE: Kuopio Osteoporosis Risk Factor and Prevention Study

PACE: Pennsylvania's Pharmaceutical Assistance Contract for the Elderly program

PK-VF: Peking Vertebral Fracture Study

PLSA: Perth Longitudinal Study of Aging

PRIMOS: primary health care and osteoporosis

RR: relative risk

SD: standard deviation

SEMOF: Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk study

SMC: Swedish Mammography Cohort

SOF: Study of Osteoporotic Fractures

SPAH: São Paulo Aging and Health

SUPERB: Sahlgrenska University Hospital Prospective Evaluation of Risk of Bone Fractures

SWAN: Study of Women's Health Across the Nation

SWHS: Shanghai Women's Health Study

TLGS: Tehran Lipid and Glucose Study

VIF: variance inflation factor

WHI: Women's Health Initiative

WHILA: Women's Health in the Lund Area Project

## Declaration of Academic Achievement

The work presented in this thesis was primarily carried out by Yi Wu. Yi Wu played a principal role in formulating the research question, designing the study, developing the methodology, collecting and cleaning the data, conducting the analysis, interpreting the results, and drafting and revising the manuscript. Dr. Parminder Raina supervised the study providing methodological guidance and substantial editorial input on the thesis. The committee members, Dr. Alison Shea and Dr. Jinhui Ma, also contributed domain expertise, provided ongoing feedback throughout the research process, and reviewed the draft.

# Chapter 1 Introduction

## 1.1 Background and Rationale

### 1.1.1 Fragility Fractures in Women

Fragility fracture is a major health-related cause of chronic disease morbidity ranking just after ischemic heart disease, dementia and lung cancer, and ahead of chronic obstructive pulmonary disease and ischemic stroke (1). The lifetime risk for hip, forearm and vertebral fractures coming to clinical attention combined altogether is approximately 40%, the same as that of cardiovascular disease (2). Between 1988 and 2012, the incidence rate of fragility fractures among women over 50 years old in the UK was 98.6 per 10,000 person-years, more than 2.5 times higher than the rate in men of the same age group (3). In 2019, approximately 76.4 million new fracture cases were reported among women globally. An upward trend in fracture incidence was observed in older age groups, particularly in older women (4).

Fragility fractures as a common complication of osteoporosis are estimated to occur to one in two women aged 50 years or older during their remaining lifetime (5). The consequences of osteoporosis especially fragility fractures profoundly

influence postmenopausal women by causing pain and impaired functionality thereby reducing both life quality and quantity (6). Previous studies suggested that women frequently faced challenges in daily activities due to pain and changes in routines to deal with health problems. The overall health related quality of life is remarkably worse in postmenopausal women who have sustained fragility fractures (7).

In Canada, osteoporosis is a prevalent condition that predisposes up to 16% of women over 50 to fractures. From 2000 to 2005, there were approximately 150,000 cases of hospitalized hip fractures across the ten Canadian provinces with an annual age-standardized rate of 86.4 per 100,000 among women (8). Of these fractures, 71.8% were in women and 96% occurred in those aged 50 or older. The immediate first-year health costs for treating a hip fracture were about 48,468 dollars per case as of 2025 highlighting the significant financial burden these injuries impose on the healthcare system (9).

The world's population is aging faster than ever before (10). Even countries with growing populations are expected to experience demographic shifts in the coming decades (11). By 2030, one in six people globally will be aged 60 or over and by 2050, the total number of people in this age group is estimated to be 2.1 billion. In 2024, life expectancy at birth reached 73.3 years and as mortality continues to decline, people are expected to live even longer. While this reflects progress in health and living conditions, it also highlights the need

for greater efforts to address the healthcare needs of the aging population.

As a first step in fracture prevention, it is recommended to address modifiable risk factors and adopt lifestyle changes such as engaging in regular physical activity, maintaining a healthy BMI, ensuring an adequate dietary intake of protein, and considering nutritional supplements like calcium and vitamin D when needed (12, 13). When indicated, pharmacological treatment can also be considered. The positive effect of menopause hormone therapy, oral bisphosphonate and clodronate in reducing fracture risk in postmenopausal women has been confirmed to be independent of their baseline BMD (14). However, postmenopausal women at increased risk often remain undiagnosed until a fracture occurs due to low perceived personal risk, and restricted access to resources (15). The elevated fracture risk in this population is not solely a result of aging. For example, an earlier age at menopause contributes additional risk independent of chronological age (16, 17). The gradual decline in ovarian estrogen production during menopausal transition could accelerate bone loss (18). The significant underdiagnosis of individuals at high risk remains the primary obstacle of lowering fracture rates leading to a low treatment rate globally (14).

Although low BMD is a well-established risk factor for fractures, most fractures occur in postmenopausal women who do not meet the densitometric criteria for osteoporosis (19-21). Evidence indicated that many women who experienced a

fragility fracture were not appropriately diagnosed and untreated for probable underlying osteoporosis (22-24). Notably, having a history of fracture is associated with an 86% higher risk of a subsequent fracture (25). Following an osteoporotic fracture at any site, around one in four patients will experience a subsequent hip fracture (26). Effective strategies aimed at preventing the first fracture are critical not only for avoiding initial injury but also for reducing the risk of future fractures. The International Osteoporosis Foundation Epidemiology/ Quality of Life Working Group recently recommended population screening in primary care to reduce the burden of fractures in healthcare systems (27). This recommendation stems from an increasing consensus that osteoporosis treatments should be strategically directed based on individual fracture risk necessitating the use of accessible and user-friendly assessment tools in clinical settings.

### 1.1.2 Current Screening Strategy

Currently, the bone mineral density (BMD), usually obtained by dual-energy x-ray absorptiometry (DXA) scan, is a recognized tool for screening in some countries but its low sensitivity (28) has limited its widespread use. The fact that fractures occur more frequently in individuals who do not meet the BMD threshold for osteoporosis as reported in previous studies also undermines its

value as a screening test. On top of that, using the DXA scan alone for screening the general population is not always practical due to its resource-intensive nature (29). WHO projected that by 2050, two-thirds of the global population aged 60 and older will live in low- and middle- income countries (10).

Over the past two decades, abundant evidence on risk factors beyond BMD became available and has contributed to the development of tools for assessing fracture risk such as FRAX (30), Garvan (31), QFracture (32), FORE, and CAROC (33). While the number of risk factors included in each tool varies, age, gender, and prior fracture are consistently recognized across all five tools (34). Additionally, four of them incorporated hip BMD and current glucocorticoid use as evaluation factors. A meta-analysis of three randomized controlled studies conducted in Europe demonstrated that FRAX-based screening methods led to significant reduction in major osteoporotic fractures and hip fractures by 9-10% and 20% respectively, clearly supporting the efficacy of population screening (27, 35).

Multiple professional organizations including International Osteoporosis Foundation, National Osteoporosis Foundation, Osteoporosis Canada, Academia Nacional de Medicina de Mexico, and Bone Health and Osteoporosis Foundation recommended an assessment-first approach suggesting performing clinical evaluation in all postmenopausal women to identify risk factors, determining the necessity of a BMD test based on age and the number

of risk factors present, and initiating pharmacotherapy in women with a BMD T-score less than -2.5 or a high 10-year fracture risk estimated by FRAX (36-38). The list of important risk factors provided by Osteoporosis Canada consists of previous fracture after age 40, glucocorticoids use of more than three months in the last year, more than two falls in the last year, parent fractured hip, BMI<20 kg/m2, secondary osteoporosis, current smoking, more than three alcohol drinks per day. Routine clinical assessment for new or active risk factors such as falls is also a part of the good practice of monitoring and pharmacologic treatment follow-up.

### 1.1.3 Fracture Risk Assessment in Women

The inclusion of gender in abovementioned fracture risk assessment approaches and tools reflects the consensus that the fracture risk differs by gender. However, the clinical risk factors used, which is an essential component in all stages of fracture prevention, are largely the same for women and men. As a result, the performance of these tools in postmenopausal women has been suboptimal.

In a study comparing three fracture risk assessment tools, OST, SCORE, and FRAX without BMD, for predicting incident MOF in 10 years in postmenopausal women aged 50-64 years (39), thresholds corresponding to approximately 90%

sensitivities yielded specificities of 9.6%, 10.2%, and 16.1%, respectively. When the thresholds were adjusted to achieve sensitivities at least 80%, none of the tools reached a specificity of 30% or higher. For thresholds corresponding to sensitivities above 80%, their AUC values ranged from 0.50 to 0.54 indicating performance only slightly better than pure guessing. Another study evaluated the performance of Garvan and FRAX without BMD using the same cohort and concluded that no useful threshold for 10-year incident MOF probability could be identified for either tool (40). Sensitivities of both were low across all age groups ranging from 26.7% to 46.8%. Only Garvan, in the 60 to 64 age group, achieved a specificity above 80%. The AUC were approximately 0.56 regardless of age group or tool used. One study compared FRISK, FRAX, and Garvan without BMD (41) reporting sensitivities from 55.8% to 66.7% and specificities between 59.7% and 63.7% for predicting 10-year absolute risk of fracture. The AUC values ranged from 0.62 to 0.66 showing moderate discriminative ability.

There is clearly potential for further refinement in fracture risk assessment tools particularly for this high-risk group as an increasing number of women specific risk factors have been identified such as menopause history, reproductive factors, dietary patterns, etc. Even commonly used risk factors may have different effects by gender considering the remarkably increased fracture risk in postmenopausal women. Given women generally live longer, the duration

during which they are at higher risk of fracture is also longer. This extended period of vulnerability highlights the need for more tailored tools to predict and prevent fractures.

## 1.2 Research Objectives

This thesis aimed at developing models for assessing first incident fragility fracture in postmenopausal women which could be used in primary care and similar settings to screen high-risk individuals who would benefit from further examinations and preventive treatments. The research objectives of this thesis are as follows:

1. To identify candidate predictors for inclusion in the prediction model through literature review of observational studies;
2. To examine the associations between identified factors and fracture outcome using data from the CLSA, and then to construct optimal logistic regression models accordingly;
3. To compare the performance of the newly developed models with the conventional BMD-based diagnostic criterion for osteoporosis.

## 1.3 Thesis Chapter Overview

This thesis consists of five chapters. This first chapter of Introduction depicts the background, rationale and objectives of the study and highlights the need for fracture risk assessment tools for postmenopausal women. The second chapter Literature Review outlines the methods used and results of the literature review. This review aimed at examining observational studies that explore risk factors for incident fragility fractures which have the potential to predict fractures in postmenopausal women and at summarizing the relationships between these factors and the fracture outcome.

The third chapter Methods outlines the methodology and statistical techniques used to investigate the associations between risk factors identified through literature review and first incident fragility fractures using data from the CLSA study. This chapter begins with an overview of the CLSA, followed by a description of how relevant variables were selected from the CLSA dataset, the definitions of exposures and the fracture outcome, and the statistical methods applied at each stage of the data analysis.

The fourth chapter Results begins by presenting the sample characteristics for each selected variable and the fracture outcome. It then details the results of univariate analysis, multivariate analysis using complete cases, and multiple imputation. Model performance metrics including AUC, sensitivity, and

specificity are also reported. Finally, a comparison is made between these newly developed models and the BMD test.

The last chapter five discussion and conclusions explores the key findings of the analysis with a focus on comparisons within the models and with existing studies. This chapter also outlines the clinical implications, strengths and limitations of the thesis. As a final point, it presents suggestions for future research informed by the insights gained from this study.

# Chapter 2 Literature Review of Observational Studies

This chapter presents the methods, and findings of a literature review which aimed to summarize published observational studies that explore risk factors for incident fractures in postmenopausal women. The associations between exposure and fracture events as outcome reported in the literature were examined to identify candidate predictors to be considered for inclusion in the prediction model.

## 2.1 Methods

The search strategy was generated with assistance from a senior library assistant at McMaster University Health Sciences Library. This search strategy was applied to the Ovid MEDLINE and EMBASE electronic databases on September 22nd, 2024. These two databases were chosen because they offer the most comprehensive and up-to-date biomedical and health sciences coverage. Results were limited to human studies published in English. No publication year restriction was applied; therefore, Ovid MEDLINE was searched from 1946 onward and EMBASE from 1974 onward. The details of the search strategy are provided in Appendix 1. In addition to database

searches, citation searching was performed during the title and abstract screening phase in the presence of systematic reviews and/ or meta-analyses. Studies were included if they met the following criteria: studies were cohort or case-control studies conducted in general population; outcome was a composite of real fracture events at multiple sites (e.g. fragility fracture, any fracture, major osteoporotic fracture, nonvertebral fracture, etc.); associations were investigated between a single risk factor and incident fracture events in women only or mixed-gender sample; effect sizes were reported using relative risk (RR), odds ratio (OR), hazard ratio (HR), or incidence rate ratio (IRR). Studies were excluded if the lower limit of the inclusion age range was below 55 years old and no information on menopause status was provided in order to ensure the results were applicable to postmenopausal women. When more than one type of fracture outcome was analyzed in one study, the outcome selected for inclusion followed a predefined hierarchy: fragility/ osteoporotic/ nontraumatic/ low energy, followed by any fracture, non hip/ nonvertebral fracture, major osteoporotic fracture, and lastly other combinations in the order listed. Similarly, when stratified results were available, the effects reported in women only subgroup or in subgroups of participants without a fracture history were selected. When analyses were conducted at multiple endpoints, results with the longest follow-up duration were extracted.

The web-based review platform Covidence and the citation management

software EndNote were used to conduct the literature review. Screening was initially performed at the title and abstract level, and then at the full-text level. Data from eligible studies were extracted subsequently. Information regarding the associations between risk factors and fracture including fracture sites, grouping of risk factors, effect sizes, and adjusted variables as well as study characteristics such as author's name, year of publication, country of study, origin of participants, study design (cohort or case-control), sample size, percentage of female participants, menopause status, mean age, and follow-up duration were extracted.

### 2.2 Results

The electronic database searches yielded 5594 records in Ovid MEDLINE and 1116 in EMBASE to which another 910 publications were added through citation searching resulting in a total of 7620 articles. Upon automatic duplicate removal, 6567 publications were screened for abstract and title of which full texts of 831 articles were reviewed for eligibility. During the full-text review, 648 publications were excluded for the following reasons: being duplicates, failing to retrieve the full-text, including women under 55 years old without providing information on menopause status, focusing on specific population not relevant to the review (e.g. participants on medications, suffering from a chronic disease or with

particular measurements below a specified threshold), risk factors studied being a composite of multiple individual factors, outcome studied being fracture at only one site, not reporting effects in the population or outcome of interest, outcome studied not being real fracture events (e.g. estimates using fracture risk assessment tools), or lacking clarity regarding the time sequence between exposure and outcome. At last, 183 studies remained for data extraction and were included in this review (Figure 2.1).

The characteristics of the included studies are provided in detail in Appendix 2. Geographically, most studies were carried out in Europe (84, 45.9%), North America (51, 27.9%), or Asia (28, 15.3%). All studies were cohort studies except nine (4.9%) were case-control studies. Among them, sample size ranged from 157 to 1,272,115 at baseline while follow-up duration spanned from 0.72 to 25.9 years. Of the included studies, 148 (80.9%) were conducted in a women-only population among which 118 focused on postmenopausal women. In terms of outcome, 131 (71.6%) out of the 183 studies used fragility, osteoporotic, nontraumatic, low energy, or any fracture, 31 (16.9%) investigated non hip or nonvertebral fractures, 10 (5.5%) studied major osteoporotic fractures (MOF) while the remaining 11 (6.0%) examined other combinations of fracture sites. A full list of risk factors by category identified through this literature review is presented in Table 2.1.

### 2.2.1 Anthropometric Factors

Anthropometric factors including age, BMI, height, hip circumference, ethnic group, waist circumference, and weight were reported in 21 studies as risk factors for fractures. A detailed summary of the associations between these seven risk factors and fractures are presented in Appendix 3.

**Age** was investigated in 11 studies all of which demonstrated that the risk of fracture increases with older age (42-49) or age groups (50-52). Among them, four studies examined the association of age with each 1-year increase. Three (42, 45, 48) reported an OR/ RR of 1.03 while the forth one (49) showed a similar risk with an HR of 1.02 [1.01,1.03]. Three other studies (43, 44, 46) investigated the effect of every 10-year increase in age reporting a RR of 2.07 [1.13,3.82], and HR values of 1.5 and 1.42 [1.14,1.75], respectively.

**BMI** was the second most reported risk factor within this category investigated in seven studies. Among them, five (45, 53-56) examined BMI as a categorical variable while the remaining two focused on change in BMI from baseline to follow-up (57) or from age 35 to 64 (58). Although the BMI groups used varied across the five studies, all of them supported the finding that a lower BMI is associated with a higher risk. Within these studies, two compared participants with a BMI lower than 18.5 kg/m2 to those with a BMI higher than 18.5 or between 18.5 and 22.9 reporting similar effects with an HR of 2.66 [1.13,6.24]

(53) and a RR of 2.61 [1.06,6.45] (55), respectively. Two additional factors related to adiposity were reported. **Hip circumference** (55) and **waist circumference** (59) were found to be associated with increased risk at higher values with cutoffs at 89.8 cm (RR 3.59 [1.06,12.19]) and 95 cm (HR 2.43 [1.53,3.86]), respectively.

The next most frequently examined factor was **height** reported in three studies (45, 49, 60). Despite the use of different scales for comparison, all indicated that the risk of fracture increases with height. **Weight** was investigated by three studies with only one (44) testing weight at baseline and reporting an HR of 0.9 per each 10-kg increase. The same study as well as another study (61) also attempted to demonstrate the association between unintentional weight loss in the past 12 months and fracture with both showing a harmful effect of weight loss greater than 10 pounds compared to participants without weight loss (HR 1.3 and 1.49, respectively). The final study (62) which investigated weight change since age 20 reached a similar conclusion that the risk of fracture is higher in participants with a gradually decreasing weight pattern compared to those whose weight remained stable (HR 1.39 [1.17,1.65]).

In terms of **ethnic groups**, one study (54) compared White participants with the others (HR 2.20 [1.74,2.51]) while another study (45) compared Black participants to Caucasians (RR 0.45 [0.32,0.63]) with both indicating that White/ Caucasian are more vulnerable to fractures.

### 2.2.2 Biomarkers

Biomarkers including 25(OH)D, androstenedione, androstenedione/ sex hormone-binding globulin (SHBG) ratio, bioavailable estradiol (BioE2), bioavailable testosterone (BioT), bone material strength index, C-reactive protein (CRP), C-terminal cross-linking telopeptide of type I collagen ratio, collagen type I N-telopeptide, cross-linked N-telopeptide of type I collagen, cystatin C, estimated glomerular filtration rate (eGFR), fluoride, free estradiol index, HbA1c, hemoglobin, high-density lipoprotein cholesterol (HDL-C), homocysteine, insulin-like growth factor-binding protein 1 (IGFBP-1), parathyroid hormone (PTH), pentosidine, periostin, sphingosine 1-phosphate (S1P), triglycerides, uric acid, vitamin B12, vitamin D metabolite ratio were reported in 36 studies as risk factors for fractures. A detailed summary of the associations between these 27 risk factors and fractures are presented in Appendix 4.

Serum **25(OH)D** is the most frequently explored factor within this category investigated by seven studies. Despite using different thresholds to categorize participants according to one single measurement of 25(OH)D at baseline, all of the four studies (51, 63-65) that tested 25(OH)D as a categorical variable concluded that higher values are protective against fracture. However, the

methods used to group participants varied across studies including comparisons by quintiles, greater or equal to 71 nmol/L versus lower levels, a cutoff at 17.9 nmol/L, and a threshold of 25 ng/ml (approximately 62.4 nmol/L). In addition, one of them (63) speculated on the effect of 25(OH)D maintained at the same level over two measurements taken 5 years apart yielding a similar result that lower values are more harmful. The other three studies demonstrated similar effects of 25(OH)D as a continuous variables per 10 ng/ml (66), 20 nmol/L (67), and one SD (68) change with the strongest effect observed for each 10 ng/ml increase at an HR of 0.72 [0.54,0.96].

Two forms of serum **C-reactive protein** (CRP) were reported to be risk factors for fractures in three studies. Two of these studies investigated the regular form but in different functional forms, one (69) dividing participants into six groups and the other (70) treating it as a continuous variable. Moreover, the effects presented were not consistent. The former one showed a U-shape relationship across groups while the latter demonstrated an HR of 1.07 [1.03,1.13] per 1 mg/L increase. The final study (71) examining high-sensitivity C-reactive protein (hs-CRP) reached a similar conclusion to the latter one suggesting that higher values were associated with a greater risk although the analysis was conducted in groups.

Two ways were used to estimate glomerular filtration rate in the three studies investigating the relationship between **estimated glomerular filtration rate**

(eGFR) and fractures. Regardless of the method employed, modification of diet in renal disease (72) or cystatin C (73, 74), the results were consistent across all studies indicating that an eGFR <60 ml/min/1.73m3 was generally associated with an increased risk although the effect sizes varied from an HR of 1.36 [1.15,1.60] to an OR of 2.46 [1.16,5.21] depending on the reference groups chosen.

Serum **bioavailable estradiol** (BioE2) was tested in two studies using tertiles (75) or below/ above the median (76) both supporting that higher values were protective against fractures. Plasma **sphingosine 1-phosphate** (S1P) was analyzed in two studies per SD increase (77) or above/ below the highest tertile threshold (78) with consistent results suggesting that higher values were associated with a higher risk.

The remaining 22 biomarkers were each identified in one study and can be divided into two groups according to their effects of one single measurement at baseline except for collagen type I N-telopeptide (79) which was computed as the rate of increase during menopause transition and showed a negative effect at higher rates. The first group includes androstenedione (80), androstenedione/ SHBG ratio (80), BioT (75), free estradiol index (46), hemoglobin (81), uric acid (82), vitamin B12 (83), and vitamin D metabolite ratio (84) which were found to be protective at higher values. The second group includes bone material strength index (85), cross-linked N-telopeptide of type I

collagen (86), C-terminal cross-linking telopeptide of type I collagen ratio (87), cystatin C (73), fluoride (88), HbA1c (89), HDL-C (90), homocysteine (91), IGFBP-1 (92), PTH (93), pentosidine (94), periostin (95), and triglycerides (96) which were protective at lower values.

### 2.2.3 Bone Mineral Density and Related Factors

BMD and related factors including bone mass, bone mineral content (BMC), bone mineral apparent density (BMAD), BMD, and BMD T-score were reported in 30 studies as risk factors for fractures. A detailed summary of the associations between these five risk factors and fractures are presented in Appendix 5.

**BMD** is the factor with the most evidence in this review reported in 23 studies. The hip region (17 studies) including total hip (42, 43, 51, 97-101), femoral neck (46, 60, 97, 99, 101-107), trochanter (97, 100), ward's angle (97), and intertrochanter (97) is the most frequently analyzed anatomical location followed by lumbar spine (60, 97, 100, 101, 103, 104, 107, 108), radius/ forearm (97, 101, 104, 109-111), hand (112, 113), and calcaneus (97, 104) in order of frequency. All of them supported the idea that higher BMD was associated with a lower risk of fractures. Among these studies, most (18 studies) tested one single BMD measurement at baseline per SD change and within these studies, the effect sizes varied from an HR of 1.26 [1.01,1.58] to an OR of 2.39 [1.92,2.97]

at the femoral neck, from a RR of 1.40 [1.20,1.63] to a RR of 1.68 [1.11,2.56] at the total hip, from an HR of 1.32 [1.25,1.41] to an OR of 1.65 [1.37,1.99] at the lumbar spine, from a RR of 1.32 [1.14,1.53] to a RR of 2.99 [1.06,8.41] at the radius, from an OR of 1.55 [1.17,2.06] to an OR of 1.91 [1.23,3.10] at the hand, and from a RR of 1.4 [1.3,1.5] to a RR of 1.7 [1.4,1.9] at the calcaneus. Within this group of studies, several also compared BMD at various anatomical locations in terms of its ability to predict fractures at multiple sites combined. However, the location with the strongest effect varied across studies including calcaneus for nonvertebral fractures (RR 1.51 [1.29,1.77]) (97), femoral neck for MOF (HR 1.68 [1.56,1.81]) (100), femoral neck for nonvertebral fractures (RR 1.5 [1.4,1.6] in participants aged 65-79 and RR 1.9 [1.6,2.4] in participants aged 80 and older) (104), and ultra distal radius for low trauma fractures (OR 2.15 [1.69,2.71]) (101). One other study (42) examined BMD at the total hip per 0.1 g/cm2 and reported an OR of 1.29 [1.20,1.38]. Two other studies investigated the change in BMD at the total hip over 15 years (98) and at the radius over 10 years (110) both suggesting that greater loss in BMD negatively impacts fracture risk.

**BMD T-score** was the second most investigated factor within this category reported in six studies. Among them, two studies obtained BMD T-score at the total hip while the other four studies each used one the following sites: femoral neck, nondominant hand, lumbar spine, or heel/ forearm/ finger. Four studies

tested BMD T-scores in groups three (114-116) of which selected the normal range -1.0 or higher as their reference groups while the fourth (52) used the osteoporosis cutoff of -2.5. The other two studies tested the relationship between BMD T-score per SD and any fracture with one showing an HR of 1.23 [1.13,1.35] per SD decrease at nondominant hand (49) and the other one presenting an HR of 0.63 [0.59,0.67] per SD (1.2) increase at total hip (117). Regardless of the way of comparison, the conclusion was consistent across all six studies indicating that a higher BMD T-score was associated with a lower risk of fracture.

The remaining three factors including BMAD (99), BMC (99), and bone mass (118) were each reported in one study published at least 20 years ago. All of these factors showed similar effects to BMD with higher values being protective against fractures. Bone mass was additionally calculated as the rate of loss per year over a span of two years and fast losers had an increased risk compared to normal losers (OR 2.0).

### 2.2.4 Dietary Habits

Dietary habits including calcium, dairy products, fat, fish oil, protein, soy isoflavone, tea, and vegetables were reported in 11 studies as risk factors for fractures. A detailed summary of the associations between these eight risk

factors and fractures are presented in Appendix 6.

**Dairy products** were reported in three studies with contradictory results regarding milk. The reference groups used in the two studies investigating milk were similar with less than 200 ml (208 grams) per day in one and less than 200 grams per day in the other. However, the former study (119) showed a protective effect for osteoporotic fractures at higher amounts (>= 400 ml/d) with an HR of 0.58 [0.36,0.95] while the latter (120) suggested a negative impact on any fracture at higher amounts (>= 400 g/d) with HRs of 1.16. The third study tested yogurts, milk, and cheese as a group and found a positive effect in dairy products on hip, vertebral, or wrist fractures when consumed in at least 17.9 servings a week (RR 1.51 [1.07,2.11]) (121).

**Soybeans** were reported to be associated with osteoporotic fractures in four forms: the compounds isoflavone primarily found in soybeans, its major components daidzein and genistein, and the fermented soybeans natto. When comparing the highest quartile of daily intake to the lowest quartile, isoflavone (HR 1.22 [1.01,1.48]) and genistein (HR 1.22 [1.01,1.48]) were positively associated with osteoporotic fractures in individuals without a history of bone fractures while daidzein (HR 0.75 [0.58,0.97]) was inversely associated with osteoporotic fractures in participants with bone fracture history as reported in the same study (122). Natto was revealed to be protective against osteoporotic fractures showing an HR of 0.56 [0.32,0.99] in individuals consuming at least

seven packs per week (40 grams per pack) compared to those who having less than one pack per week (123).

The remaining six dietary factors were each identified in one study and all were found to be protective at higher amounts or frequencies including dietary calcium intake (51), dietary protein intake (46), number of different vegetables consumed in one day (124), regular use of fish oil supplements (125), and having tea daily (126) except for total fat intake which had a negative impact on any fracture (45).

### 2.2.5 Diseases

Diseases including alcoholism, anemia, asthma, cancer, cardiovascular disease, celiac disease, chronic hepatic disease, chronic obstructive pulmonary disease (COPD), COVID-19, diabetes, epilepsy, giant cell arteritis, hypercholesterolemia, hypertension, hyperthyroidism, inflammatory bowel disease (IBD), kidney disease, multiple sclerosis, osteoarthritis, Parkinson's disease (PD), polymyalgia rheumatica, psoriasis, pulmonary embolism, respiratory tuberculosis, rheumatoid arthritis, schizophrenia, seasonal influenza, and thrombocytopenia were reported in 30 studies as risk factors for fractures. Suffering from any of the aforementioned diseases was positively associated with fractures when compared to individuals without the same disease, those

without any morbidity, or a healthy cohort. A detailed summary of the associations between these 28 risk factors and fractures are presented in Appendix 7.

Four types of **diabetes** were investigated in nine studies (100, 127-134) making it the most frequently reported risk factor within this category. The strongest effect identified for each type was as follows: gestational diabetes HR 1.60 [1.09,2.35] (127), type 1 diabetes HR 1.85 [1.50,2.28] (128), type 2 diabetes OR 2.49 [1.64,3.77] (133), and prediabetes HR 2.26 [1.13,4.49] (132). Six studies examined **osteoarthritis** regardless of the joint affected (44, 55, 128, 135, 136) with the exception of one study that focused exclusively on the hip (137). The strongest association reported was an HR of 1.9 (44). Four studies reported specific diagnoses within the **cardiovascular disease** category including cerebrovascular event (128), ischemic heart disease (128), coronary artery disease (138), stroke (139), and any cardiovascular disease (140). Effect sizes varied ranging from an HR of 1.18 [1.11,1.25] for cardiovascular disease to an HR of 2.02 [1.67,2.46] for cerebrovascular event.

Three studies that identified **anemia** all analyzed it as a risk factor for any fracture presenting HRs ranging from 1.07 [1.01,1.14] (141) and 1.1 [1.04,1.16] (142) to 1.80 [1.41,2.28] (81). Three studies that investigated **cancer** each tested a different type of cancer and used distinct reference groups in their analyses. One compared cancer to participants without any morbidity and

reported an HR of 1.61 [1.40,1.86] for any fracture (128). Another study compared invasive cancer survivor from the distant metastasis stage to those in the localized stage against individuals with no cancer history and presented an HR of 1.57 [1.38,1.79] for fragility fractures when comparing all cancer survivors to those without a cancer history (143). The last study examined the impact of receiving aromatase inhibitors in people with breast cancer on the risk of any fracture showing an OR of 3.36 [2.65,4.26] compared to a healthy cohort (144). Three studies investigated **multiple sclerosis** demonstrating HRs that ranged from 1.7 [1.2,2.6] for any fracture (135) and 1.9 for major fractures (44) to 2.70 [1.90,3.83] for any fracture (128) although one same cohort was used as their origins of participants.

Six diseases were each reported in two studies and all found to be associated with increased risk of fractures. This group includes celiac disease (44, 128), COPD (128, 135), hypertension (128, 138), hyperthyroidism and subclinical hyperthyroidism (138, 145), IBD (60, 128), PD (128, 135).

The remaining 16 diseases were each identified in one study and most of their effect sizes fall within the range of 1 to 2 including asthma (128), COVID-19 (146), epilepsy (138), giant cell arteritis (147), hypercholesterolemia (128), polymyalgia rheumatica (147), psoriasis (148), respiratory tuberculosis (149), schizophrenia (150), and seasonal influenza (151). The factors with greater effects are thrombocytopenia (138), chronic hepatic disease (138), pulmonary

embolism (138), alcoholism (138), kidney disease (60), and rheumatoid arthritis (128) listed in order of magnitude.

### 2.2.6 Genetic Factors

Genetic factors including eight single nucleotide polymorphisms (SNPs) and two haplotypes were reported in seven studies as risk factors for fractures. A detailed summary of the associations between these nine risk factors and fractures are presented in Appendix 8.

Two studies investigated the rs18000012 in type I alpha 1 collagen gene (COL1A1) using the same origin of participants. Both suggested that the genotype TT has a negative impact on fractures compared to the most common type GG reporting a RR of 2.33 [1.39,3.87] for fragility fractures (152) and an OR of 3.3 [1.3,8.4] for nonvertebral fractures (153). The former study analyzed the haplotype in the same gene as well which consists of two SNPs: promoter-1997 rs1107946 and intron 1 Sp1 rs18000012. Three haplotype combinations were observed in their population among which G-T was associated with an increased risk of fragility fractures at an OR of 2.12 [1.23,3.66] when compared to the most prevalent type G-G. The latter study also tested the haplotype in the vitamin D receptor gene (VDR) which was computed from three SNPs: Bsml rs1544410, Apal rs7975232, and Taql rs731236. A higher number of fracture

cases was observed in haplotype 1 in their cohort leading to a comparison between homozygous carriers (11) and women not carrying the haplotype (22, 23 and 33) resulting in an OR of 2.4 [1.2,4.8].

The remaining six SNPs were each identified in one study and can be divided into two groups according to the effects of their most common alleles. The first group includes methylenetetrahydrofolate reductase C677T rs1801133 (154), myostatin rs7570532 (155), glucose dependent insulinotropic polypeptide receptor rs1800437 (156), and prolactin T228C rs7739889 (157) genes where the most prevalent allele was found to be protective against fractures. The second group includes major histocompatibility complex class II transactivator rs3087456 (158) and C-type lectin domain 16A rs725613 (158) genes with the opposite effect.

### 2.2.7 Lifestyle Factors

Lifestyle factors including alcohol consumption, skipping breakfast, physical activity, and smoking were reported in 15 studies as risk factors for fractures. A detailed summary of the associations between these four risk factors and fractures are presented in Appendix 9.

**Physical activity** was analyzed in eight studies with six presenting results on overall levels of physical activity and five showing the effects of specific types

of activity. Regarding overall activity, five studies indicated that a higher level of engagement in exercises was protective against fractures regardless of whether it was assessed by frequency (159), metabolic equivalent hours (160), or simply time per week or day (51, 55, 161). For people who exercised regularly for at least 30 minutes per day, the risk was 42% lower compared to those who did not engage in regular exercise (RR 0.58 [0.34,0.98]) (55). However, one study presented a contradictory result suggesting that with each additional time of total physical activity per week, the odds of low-trauma fractures increased by 3% (OR 1.03 [1.01,1.06]) (162). Two studies specifically investigating walking reported conflicting results as well. One measured walking by the number of days participants walked for at least 20 minutes in the past 30 days and grouped them by comparing their numbers with other women of the same age. People who did not walk at all had a 60% higher risk of sustaining major fractures compared to those who were very active (HR 1.6) (44). In contrast, the other study demonstrated that with every additional session of walking per week, the odds of low-trauma fractures increased by 6% (OR 1.06 [1.02,1.09]) (162). The remaining types of physical activity examined individually include bicycling (163), physical activity at work (163), sitting (160), and yard work (160) all of which supported the idea that a lower level of movement was associated with a higher risk of fractures.

**Alcohol consumption** was the second most reported risk factor within this

category investigated by five studies. In the four studies investigating all types of alcohol combined, results were inconsistent. One indicated that consuming more than 5.7 grams of pure alcohol per day was associated with a 39% lower risk of hip, vertebral, or wrist fractures compared to 1.4-5.7 g/d (HR 0.61 [0.42,0.88]) (121) while the other three (55, 164, 165) suggested that alcohol use was associated with an increased risk of fractures. The largest effect presented was a RR of 2.07 [1.22,3.51] comparing individuals who consumed at least 1.82 units of alcohol per week to those who had less than this amount (55). One study tested beer and liquor separately and found that consuming at least 2 glasses per day of either was associated with a higher risk of any fracture compared to consuming less than 1 glass per month (166).

Two studies examined **smoking** in slightly different ways. One compared current smokers to nonsmokers finding that the odds of non hip fractures were 68% higher (OR 1.68 [1.08,2.60]) (50). The other compared current smokers who consumed at least 20 cigarettes per day to never smokers revealing an even higher risk of nonvertebral fractures with an HR of 1.93 [1.30,2.84] (167).

**Skipping breakfast** was positively associated with any fracture as reported in one study with an OR of 2.30 [1.41,3.74] based on the comparison between participants who seldom had breakfast and those who had breakfast almost every day (89).

### 2.2.8 Medical Conditions

Medical conditions including depressive symptoms, family history of diabetes, family history of fracture, family history of osteoporosis, personal history of fall, personal history of fracture, and self-perceived fracture risk were reported in 26 studies as risk factors for fractures. A detailed summary of the associations between these seven risk factors and fractures are presented in Appendix 10.

**Personal history of fracture** was the most investigated factor within this category reported in 14 studies (42, 43, 48, 52, 55, 56, 107, 108, 114, 164, 165, 168-170). The time duration for fracture history prior to baseline ranged from as short as one year (164) to any time in the participants' previous life while the conclusion was consistent across studies that individuals who had experienced fractures before had an increased risk of sustaining subsequent fractures. Among these studies, nine investigated previous fractures at any site as a risk factor for fragility, osteoporotic or any fracture (42, 52, 107, 108, 164, 165, 168-170). The effect sizes varied from an HR of 1.15 [1.06,1.23] of prior fractures between age 51 and 70 for any fracture after age 71 (168) to an HR of 2.9 [2.3,3.6] of any previous fracture for any fracture (52). One study looked further into the number of fractures as a risk factor for any fracture and presented an OR of 2.10 [1.03,4.26] of one fracture and an OR of 4.04 [1.72,9.50] of two or more fractures compared to zero fractures (108).

**Personal history of fall** was the second most frequently reported factor within this category investigated by nine studies (42, 44, 47, 48, 51, 102, 133, 171, 172). The time span for fall history prior to baseline varied from as short as four months (172) to any time in the participants' previous life (42). Similar to personal history of fracture, all studies supported the opinion that a history of fall was associated with a higher risk of fractures. Among these studies, four examined falls in the past 12 months as a risk factor for osteoporotic or any fracture (47, 51, 133, 171). The effect sizes ranged from an OR of 1.38 [1.14,1.66] (171) to an OR of 2.16 [1.81,2.59] (133). One study delved deeper into the number of falls in the past year as a risk factor for major fractures and found an OR of 1.1 of one fall and an OR of 1.6 for two or more falls compared to zero falls (44).

**Family history** was another aspect of concern reported in one study on diabetes (169), four studies on fractures (44, 89, 108, 173), and one study on osteoporosis (53). Family history of diabetes was revealed to be protective against any fracture with an OR of 0.66 [0.44,0.98]. As expected, a family history of fracture or osteoporosis was both associated with a higher risk of fractures. The strongest effect was observed for hip fracture history by maternal grandmother on any fracture with an OR of 3.70 [1.50,8.85] (108).

The remaining two factors depressive symptoms (174) and self-perceived fracture risk (128) were each identified in one study and both had a negative

impact on fractures.

### 2.2.9 Medications

Medications including antidepressants, antiepileptic drugs, antipsychotic drugs, beta blockers, diuretics, drugs that increase fall risk, oral glucocorticoids, levothyroxine, nonsteroidal anti-inflammatory drugs (NSAIDs), polypharmacy, propiomazine, proton pump inhibitors (PPIs), statins, and z-drugs were reported in 24 studies as risk factors for fractures. A detailed summary of the associations between these 14 risk factors and fractures are presented in Appendix 11.

**PPIs** was investigated in seven studies (114, 169, 175-179) most of which supported the opinion that current users had an increased risk of fractures compared to nonusers or never users. Four studies (114, 169, 175, 176) compared current users against nonusers with the largest effect size observed for any fracture at an OR of 2.53 [1.28,4.99] (169). One study suggested that both current and past users were at a higher risk of any fracture reporting an HR of 1.29 [1.08,1.55] (178) while another study found that the risk of MOF was elevated only in individuals with at least one year of use but not in those not on long-term use (OR 2.07 [1.14,3.77]) (177).

Antidepressants and polypharmacy were both the second most investigated factor within this category each reported in three studies. However, none of the

three studies examining the same factor had an identical scope. From the narrowest coverage to the broadest, **antidepressants** were analyzed as fluoxetine (HR 2.07 [1.28,3.32]) (180), selective serotonin reuptake inhibitors (SSRIs) (HR 1.30 [1.04,1.62]) (181) and any antidepressant (HR 1.22 [1.15,1.30]) (182) all of which were associated with a higher risk of fracture when comparing current users to nonusers. In terms of **polypharmacy**, the number of medications taken simultaneously was counted within different categories from fall-related drugs, nonpsychotropic drugs to any. The first one includes five medication categories and the risk increase of any fracture for individuals taking one category versus none was 26%, about 47.5% for two or three categories and surged dramatically to 123% in those taking four categories (183). Taking more than three nonpsychotropic drugs (50) or using a pre-packaged drug dispensing system (114), a service offered to people on regular multiple medication use who have difficulty managing their drugs independently, was associated with a similar risk increase compared to nonusers with an OR of 1.36 [1.04,1.78] and an HR of 1.4 [1.1,1.7], respectively. The following three medications were each tested in two studies: **antiepileptic drugs** were consistently associated with an increased fracture risk (54, 184), **statins** showed a protective effect in both studies (185, 186), while **beta blockers** were protective in one study (187) but associated with a higher risk in the other (188).

The remaining eight medications were each identified in one study and can be grouped according to their effects on fractures. Comparisons were made between current users and nonusers except for antipsychotic drugs where was between ever users and never users. Only diuretics was revealed to be protective against nonvertebral fractures (60). The rest seven medications including antipsychotic drugs (189), drugs that increase fall risk (114), oral glucocorticoids (190), levothyroxine (191), NSAIDs (192), propiomazine (193), and z-drugs (193) were all found to have a negative impact on any fracture.

### 2.2.10 Physical Capability

Physical capability including balance, body sway, daily living activities, hand grip strength, quadriceps strength, quality of life physical component (SF-36 PCS), and vision were reported in 13 studies as risk factors for fractures. A detailed summary of the associations between these seven risk factors and fractures are presented in Appendix 12.

**Hand grip strength** was investigated in five studies all of which demonstrated that the risk of fracture increases with less strength or in groups with lower strength. One study reported that for every 5 kilograms reduction in strength, the HR of osteoporotic fractures was 1.33 [1.11,1.60] (194). The other four studies each used different thresholds to group participants with all representing

effect sizes ranging from 1.6 to 2.2 (51, 56, 195, 196).

Three factors in this category were each analyzed in two studies. **Body sway** was examined in two studies using the same origin of participants. One study tested the risk per SD increase in natural logarithmic transformed body sway (105) while the other published 14 years later updated the risk to an HR of 1.08 [1.02,1.15] per 40 cm2 (47). Impairment in **daily living activities** was associated with an increased risk of any fracture (HR 1.54 [1.13,1.92]) (54) and the risk was even higher (HR 3.2 [1.8,5.5]) in individuals with more than one functional limitation compared to those with no more than one limitation (196). The two studies on **quadriceps strength** presented consistent results although one measured the risk for each 1-kilogram decrease (197) and the other measured it for every SD decrease based on natural logarithmic transformation of kilograms (105). **Vision** was investigated in two studies both showing that impaired visual ability is associated with a higher risk of fractures. One study assessed vision through binocular visual field loss (198) while the other measured the ability to recognize faces from a distance of four meters (199).

The remaining two factors balance (200) and quality of life (60) were each reported in a single study and both had a negative impact on fractures when impairment in the capability was present.

### 2.2.11 Other radiographic parameters

Other radiographic parameters including aortic calcification score (ACS), appendicular skeletal muscle index (ASMI), broadband ultrasound attenuation (BUA), cortical area 66% slice, fat mass, lean mass, lumbar spine trabecular bone score (TBS), lumbar vertebra attenuation, speed of sound (SOS), stiffness index (SI), and vertebral deformity were reported in 16 studies as risk factors for fractures. A detailed summary of the associations between these 11 risk factors and fractures are presented in Appendix 13.

**SOS** as a parameter of ultrasound velocity through the bone tissue measured by quantitative ultrasound (QUS) was investigated in five studies at three different anatomical locations all of which supported the idea that the risk of fractures increased with each 1 SD decrease. The three studies that examined SOS at the calcaneus reported HRs of 1.19 [1.06,1.34] (103), 1.20 [1.08,1.34] (201) and 1.95 [1.30,2.94] (202), respectively. Two other studies investigated SOS at the distal radius (109, 203) and one of them also tested SOS at the patella (109).

**BUA** measured by QUS at the calcaneus was the second most frequently reported other radiographic factor investigated in four studies with similar effects to SOS. For every 1 SD decrease, the risk increased by 72% for any fracture (OR 1.72 [1.30,2.31]) (113), 33% for nonvertebral fractures (HR 1.33 [1.17,1.51])

(201), and 47% (HR 1.47 [1.26,1.71]) (103) or 53% (HR 1.53 [1.01,2.33]) (202) for low trauma fractures. **Lean mass** was reported in three studies each using a different way to quantify it but all indicated that a higher amount of lean mass was protective against fractures regardless of whether it was measured as lean mass index (204), appendicular lean mass index (205), or total percent lean mass loss during menopause transition (206).

Two studies analyzed the relationship between **ACS** and fractures but used different thresholds to categorize it. One study compared at least 2 to 0 and 1 combined and reported an HR of 1.40 [1.08,1.81] for low trauma fractures (207). The other one compared more than 6 to 0 and presented an HR of 1.93 [1.54,3.26] for nonvertebral fractures (208). **Lumbar spine TBS** was also identified in two studies. Although the comparisons were both made per SD and the absolute values of the SDs were nearly identical (0.12 and 0.115, respectively), the HRs reported were distinct with 1.19 [1.13,1.26] for MOF (100) and 1.87 [1.38,2.54] for fragility fractures (209).

The remaining six factors were each identified in one study and can be classified according to their effect on fractures except for fat mass which was measured as total percent gain during the menopause transition and showed a negative impact on any fracture per SD (206). Vertebral deformity was the only one that was harmful for nonvertebral fractures when present (210). The rest four factors including ASMI (204), cortical area 66% slice (211), lumbar vertebra

attenuation (212), and SI at calcaneus (202) were all found to be protective against fractures at higher values.

### 2.2.12 Reproductive History

Reproductive history including amenorrhea, breastfeeding, cycle length, menopause hormone therapy (MHT), hysterectomy, menarche age, menopause status, oral contraceptive use, parity, and reproductive lifespan were reported in 20 studies as risk factors for fractures. A detailed summary of the associations between these 10 risk factors and fractures are presented in Appendix 14.

**MHT** was investigated in nine studies (107, 165, 213-219) all of which supported the idea that current users had a lower risk of fractures compared to never users or nonusers with effect sizes ranging from an RR of 0.28 [0.09,0.89] (216) to an HR of 0.78 [0.73,0.83] (214). However, one study suggested that the protective effect against any fracture was only present in participants taking at least 0.3 defined daily dose per day either currently or in the past 5 years (218) while another indicated that the effect was only present after at least 2 years of use (219). Defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults. It was used in the former study to compare different medications used as MHT in a standardized way. Within

these studies, the impact of past use was found to vary with dose or time. Four (165, 214, 218, 219) proposed that either current or past use was beneficial but current or past use of less than 0.3 defined daily dose per day (OR 1.12 [1.04,1.19]) (218) or past use more than 10 years ago (HR 2.03 [1.25,3.29]) (215) may be associated with an increased risk compared to never use. One study investigated the duration of MHT and demonstrated that for every additional year of use, the odds of low energy fractures were 6% lower (OR 0.94 [0.88,0.99]) (165) while another study presented a similar conclusion for any fracture by comparing women with 2 to 4 years (HR 0.93 [0.91,0.95]) or more than 5 years (HR 0.85 [0.83,0.88]) of use to never users (219).

**Menopause status** was the second most reported factor within this category investigated in seven studies all of which were in favor of the idea that the later the final menstrual period, the lower the fracture risk. Three of them made a direct comparison between post menopause or not at baseline with effect sizes ranging from an OR of 1.98 [1.02,3.56] (53), an HR of 3.50 [1.05,11.67] (53), to an RR of 3.59 [1.06,12.19] (55), respectively. The other four delved further into the age at menopause and found that the risk of fracture increased with younger age (220) or age groups (62, 219, 221). The largest effect presented in this group of studies was an OR of 2.9 [1.4,5.7] for fragility fractures for a 10 year difference in menopausal age (221).

Three studies demonstrated that an older **menarche age** or older age groups

with around 12 years old as the reference (219, 222) was a risk factor of facture. The increase in age was associated with a 57% higher odds of osteoporotic fractures (OR 1.57 [1.04,2.37]) (173). Two factors were each identified in two studies with consistent results across studies. Ever use of **oral contraceptives** was associated with a higher risk of any fracture compared to never users with an HR of 1.07 [1.01,1.15] (223). While the other study suggested that the effect only manifested after 1 year of use, the direction was the same with an HR of 1.03 [1.01,1.05] (219). A longer **reproductive span** showed a protective effect against any fracture either tested per 5 years (OR 0.89 [0.80,0.98]) (133) or in groups (219).

The remaining five factors were each identified in one study and can be grouped based on their effects on fractures. The presence of **amenorrhea** at any time during the reproductive span (173) or **hysterectomy** (224) had a negative impact on fractures. In contrast, **parity** of one was protective against any fracture compared to nulliparity (219). A mean **cycle length** over 30.5 days between age 28 and 32 was found to be associated with an increased risk of wrist, hip or vertebrae fractures compared to 26.6-30.5 days (222). Lastly, the effect of **breastfeeding** varied with duration (219). When less than six months was compared to never, it was protective against any fracture. However, when it comes to more than a year, the risk became higher than never.

# Chapter 3 Methods

This chapter presents the methodology used to develop models for assessing first incident fragility fracture risk in postmenopausal women using data from the Canadian Longitudinal Study on Aging (CLSA).

## 3.1 Overview of the CLSA

The Canadian Longitudinal Study on Aging (CLSA) is a large-scale, national, long-term study designed to follow 51338 individuals who were between 45 and 85 years old at the time of recruitment with planned follow-up at least 20 years (225). The baseline data collection started from 2010 and lasted until 2015 and served as the baseline. The whole study population is composed of two cohorts. The tracking cohort including 21241 participants who were randomly selected from all 10 Canadian provinces and provided core information through structured telephone interviews. The comprehensive cohort consists of 30097 participants who were randomly selected from individuals residing within 25 to 50 kilometres of one of the 11 data collection sites located in seven provinces. In addition to core questionnaire information, members of the comprehensive cohort contributed in-depth information through in-person physical

examinations and biological specimen collection at data collection sites.

Participants recruitment was carried out through three sources: (a) a subset of participants in the Statistics Canada's Canadian Community Health Survey-Healthy Aging (CCHS-HA); (b) provincial health care system registries; (c) random digit dialing of landline telephones. Individuals living in institutions such as long-term care facilities were excluded at recruitment; however, participants who became institutionalized after enrolment remain part of the study and are followed until study completion, loss to follow-up or death. Participation in the study is voluntary, and written informed consent was obtained from all participants at the time of enrolment.

Follow-up assessments are conducted at three-year intervals with the first follow-up completed by mid-2018 and the second follow-up concluded in 2021. Subsequent waves of data collection are ongoing. For the present analysis, data from baseline, follow-up 1, and follow-up 2 were used. Ethical approval for this analysis was obtained from the Hamilton Integrated Research Ethics Board under project ID 17988.

### 3.2 Selection of Outcome and Risk Factors

Cases of first incident fragility fracture were identified through the question 'Have you ever broken a bone in your adult life that resulted from a minor fall or

low level of injury (e.g. a simple fall from standing height)?' which was asked from baseline through follow-up 2. Female participants who answered 'No' at baseline and responded 'Yes' at either follow-up 1 or follow-up 2 were considered cases while those who answered "No" at all time points were considered non-cases.

Regarding risk factors, baseline measures of the comprehensive cohort were used as the data collection in tracking cohort did not involve physical assessments, blood withdrawal, or DXA scans. The only exception was hormone contraceptives for which data from follow-up 1 were used. Questions about hormone contraceptives were added at follow-up 1 and it was deemed unlikely that this information would change from baseline given the minimum age for inclusion into the CLSA study was 45 years old.

Factors were identified from the CLSA dataset as consistent as possible with those reported in the literature. If multiple formats of one factor were identified through literature review and they were measuring different constructs (e.g. weight and weight change, lean mass percentage and lean mass index, BMD at different anatomical locations), all of them were included.

### 3.3 Statistical Analysis

The data analysis for this thesis consisted of five parts. Firstly, descriptive

statistics were used to understand the distribution of the sample, the outcome, and each risk factor identified in the CLSA dataset. Mean (SD) or frequency (percentage) were reported as appropriate. Secondly, univariate analysis was performed between each risk factor and the fracture outcome to select for factors suitable for the multivariate analysis. Thirdly, logistic regression models were fitted to the eligible factors found in the second step to identify independent risk factors for fragility fractures. Two separate models were developed at this stage, one with factors that could be obtained during a single primary care visit (primary model A) and the other with all the factors selected. The fourth step was multiple imputation as sensitivity analysis to assess whether the logistic models were robust in the presence of missing values. Two models were developed during this step as well corresponding to the two constructed in step three. Lastly, receiver operating characteristic (ROC), sensitivity, and specificity analysis was conducted to evaluate the performance of the two new models constructed in step two. All statistical analyses were performed using SAS (version 9.4 on Windows). A flow chart outlining the statistical analysis process is shown in Figure 2.2.

During the univariate analysis, the unadjusted associations between each risk factor and the fragility fracture outcome were examined by fitting logistic regression models for each pair. Risk factors were always first tested in the original forms they were collected. For categorical variables with more than two

categories, the number of groups were reduced to the smallest possible number whenever clinically and statistically reasonable following the initial test. In terms of continuous variables that were not normally distributed, they were divided into five groups based on quintiles or into other numbers of groups if established thresholds were available such as reference ranges for biomarkers. Regarding factors collected in multiple units, such as weekly frequency and daily hours of physical activities, all available form were tested before determining which one to include. The version subsequently used in multivariate models was determined according to Akaike information criterion (AIC) value, Bayesian information criterion (BIC) value and clinical relevance. Odds ratios (OR) and 95% confidence interval (CI) were reported for each factor. The inclusion criterion for risk factors to be included in multivariate analysis was a p-value less than 0.2 in the univariate analysis.

Prior to fitting multivariate models, the degree of multicollinearity among those factors selected in univariate analysis was measured using variance inflation factor (VIF). For factors with a VIF greater than 5, Pearson or Spearman correlation coefficients with other factors were then calculated as appropriate to determine which factors should be retained or excluded. A correlation coefficient with an absolute value greater than 0.8 was considered strong. Decisions were made based on the magnitude of their associations with the fracture outcome, VIF values, and the strength of correlations. After removing factors highly

correlated with others, all the other eligible factors were entered together into the multivariate logistic regression model and underwent backward elimination with factors retained if their p-values were less than 0.05. A final model including all the factors retained during the backward elimination process was estimated using complete cases only.

To assess the impact of missing values, 10 datasets were imputed for sensitivity analysis as the number of imputed datasets was sufficient to achieve a relative efficiency greater than 0.98 given the proportion of missing data. Fully conditional specification approach was used in multiple imputation with predictive mean matching specified for continuous variables and discriminant function or logistic regression specified for categorical variables with more than two levels or with just two levels, respectively. Two rounds of factor selection were performed. A logistic regression model was first fitted to all the factors excluding highly correlated ones and then a new model was fitted using factors with p-values less than 0.2. The final model was constructed using factors with p-values less than 0.5 in the previous model.

After completing the complete case analysis and the multiple imputation analysis, ROC, sensitivity and specificity analysis was conducted for each model as a means to evaluate and compare their performance. The area under the ROC curve (AUC) was reported from the ROC analysis. The optimal cutoff values for each model were determined based on sensitivity, specificity, the

Youden J index, positive predictive value (PPV), and negative predictive value (NPV). Given the intended use of the models was screening, sensitivity and NPV were prioritized. AUC, sensitivity and specificity were also reported for BMD T-score total hip using a cutoff value of -2.5 based on the diagnostic criteria for osteoporosis.

The previous three steps, multivariate analysis, sensitivity analysis, and model evaluation were repeated twice, one incorporating factors that could be gathered during a single primary care visit (primary model A) and the other including all the factors identified in the CLSA dataset (extended model B).

# Chapter 4 Results

This chapter presents the results of the data analysis which include factor and outcome selection, sample characteristics, univariate analysis, and multivariate logistic regression. Furthermore, multiple imputation plus bootstrapping as sensitivity analysis and AUC values were provided as means to evaluate the models.

## 4.1 Sample Characteristics

In total, 137 factors were identified through literature review among which an exact match in the CLSA dataset was able to be located for 82 factors. Regarding diseases reported by less than 100 participants or diseases collected in the open-ended question, they were combined as other comorbidities. This group includes 14 diseases as follows: multiple sclerosis (n=95), psoriasis (n=67), chronic hepatic disease (fatty liver, liver cyst, hepatitis) (n=59), celiac disease (n=44), anemia (n=37), Parkinson's disease (n=28), polymyalgia rheumatica (n=18), hypercholesterolemia (n=12), schizophrenia (n=5), pulmonary embolism (n=3), thrombocytopenia (n=2), tuberculosis (n=2), alcoholism (n=1), and giant cell arteritis (n=0). Two additional factors were not

applicable to this analysis. First, due to the timing of the CLSA study which was initiated in 2010, COVID-19 was not a concern at that time; therefore, does not apply to this analysis. Similar for personal history of fracture, since this analysis focuses on first incident fragility fractures, participants with a history of fragility fracture were excluded making it impossible to investigate this factor. For the remaining factors, an alternative was sought and the closest functional substitute was successfully found for 37 factors. A list of pairs of the original measurement and its substitute is presented in Table 4.1. However, neither a match nor a substitute was acquired for 18 factors including soybeans, tea, the nine genetic factors, family history of diabetes, family history of osteoporosis, amenorrhea, breastfeeding, cycle length, menarche age, and reproductive lifespan.

Most factors were provided in the same unit or groups in the CLSA dataset as reported in the literature except for some in the dietary habits category and physical activities. Due to the way they were collected in the nutrition risk questionnaire, frequencies of calcium-fortified foods, dairy products, fat, vegetables, and protein were used instead of amount. Calcium-fortified foods include calcium-fortified foods, calcium-fortified juice, calcium-fortified milk, and other calcium-fortified beverages. Dairy products consist of whole milk, skim milk, regular cheese, low-fat cheese, regular yogurt, and low-fat yogurt. Fat includes sausages, bacon, pates, butter, margarine, dressings, and sauces.

Vegetables consist of green salad, carrots, potatoes, and other vegetables. Protein includes beef, pork, other meats, chicken, turkey, fish, omega-3 eggs, all egg dishes, sausages, and pates. In addition, physical activities in the past 7 days were grouped by intensity into sitting, walking, light sports, moderate sports, strenuous sports, and muscle exercise, rather than individual activity or the overall level. As a result, 93 factors divided into 10 categories were selected for the data analysis. A summary of these factors is provided in Table 4.2.

In terms of the outcome, 2438 and 2002 fragility fracture events were reported at follow-up 1 and follow-up 2, respectively. However, some reports were not consistent such as participants who reported an event at follow-up 1 but denied a history of fracture at follow-up 2. The full comprehensive cohort in the CLSA study consisted of 15320 female participants. After excluding participants lost to follow-up (n=1195), those with a fragility fracture history in their adult life at baseline (n=821), and those with inconsistent records (n=2374), the sample size was reduced to 10930 with 1048 first incident fragility fracture events during the six-year follow-up. Of these, 430 events happened during the first three years and the remaining 618 occurred in the second three years.

The characteristics of participants included in this analysis are presented in Table 4.3. The mean age of the sample was 61.70 (10.00). Most of the participants were postmenopausal (81.01%). The missing rates for the biomarkers are all high above 10% as 147 (0.96%) participants did not consent

to have blood withdrawal plus blood sample was not collected from 1486 (9.70%) participants. Since prediabetes or diabetes was derived from HbA1c and medications, this factor also has a high missing rate of 11.05%. 931 participants did not complete a hand grip strength test resulting in a missing rate of 8.52%. Similarly, 693 (6.33%) participants did not have a valid BMD T-score at total hip recorded in the dataset. No other factor has a missing rate exceeding 5%.

### 4.2 Univariate analysis

In total, 65 of the 93 factors tested met the inclusion criteria for multivariate analysis. The unadjusted OR and p-values of all the factors tested are presented in Table 4.3. The remainder of this section elaborates on the factors selected in each category as well as modifications made to the format or grouping of some variables during the univariate analysis.

Eight **anthropometric factors** including age, BMI, height, hip circumference, ethnic group, waist circumference, weight, and weight change in the past 6 months were tested. Ethnic group was initially recorded as every single ethnicity and multiracial but was then regrouped to white and non-white because less than 100 participants identified themselves as each other single ethnicity. The amount of weight change was also tested but did not provide more information than simply gained or lost; therefore, it was discarded. All the eight factors in

this category met the inclusion criteria for multivariate analysis.

Six **dietary habits** including calcium-fortified foods, dairy products, fat, vegetables, fish oil supplements in the past month, and protein were tested. Calcium-fortified foods was initially tested as frequency per day but due to the large percentage of zeros (66.43%) in the dataset, it was dichotomized into yes or no. Three factors, calcium-fortified foods, vegetables and protein, in this category met the inclusion criteria for multivariate analysis.

Fourteen **diseases** including asthma, cancer, cerebrovascular event, emphysema chronic bronchitis COPD or chronic changes in lungs due to smoking, prediabetes or diabetes, epilepsy, hypertension, hyperthyroidism, Crohn's disease ulcerative colitis or irritable bowel syndrome, kidney disease or failure, osteoarthritis, rheumatoid arthritis, flu in the past year, and other comorbidities were tested. Participants were asked to specify the type of cancer they had if they indicated that a doctor had diagnosed them with it. However, due to the low number of cases in some cancer types, participants were grouped as either having cancer or not. Cerebrovascular event was initially one group in the broader term cardiovascular disease along with heart disease but the latter one did not show an effect on fractures thus this factor was narrowed down to cerebrovascular event. Gestational diabetes, prediabetes, and diabetes were tested as separate groups at first. However, since the first one did not appear to affect fracture risk, it was removed while prediabetes and

diabetes showing similar effects were combined into one group. Osteoarthritis was initially tested at each individual site and later regrouped into yes or no because the effect was similar regardless of the anatomical locations affected. 12 factors in this category met the inclusion criteria for multivariate analysis except for hyperthyroidism and flu in the past year.

Eleven **lifestyle factors** including alcohol consumption in the past year, skipping meals, worked in the past 7 days, smoking, yard work in the past 7 days, sitting in the past 7 days, walking in the past 7 days, light sports in the past 7 days, moderate sports in the past 7 days, strenuous sports in the past 7 days, and muscle exercise in the past 7 days were tested. The analysis of alcohol consumption began with details such as overall frequency and number of drinks of each kind per week. However, since they did not provide additional predictive value for fractures beyond yes or no, they were not used. Similarly, active level at work was not used because its effect was not different from that of worked or not. All the six physical activities were tested initially in frequency and daily hours and the more informative format was selected. Eight factors in this category met the inclusion criteria for multivariate analysis except for sitting, light sports, and moderate sports.

Four **medical conditions** including depressive symptoms, parent hip fracture after age 50, personal history of fall, and self-perceived general health were tested. The effect of parent hip fracture after age 50 was initially analyzed in

four groups: no, dad, mom or both. However, since no difference was found in predicting fractures, these groups were combined into no and yes. all the four factors in this category met the inclusion criteria for multivariate analysis.

Fourteen **medications** including antidepressants, antiepileptics, antipsychotics, beta blockers, diuretics, drugs that increase fall risk, oral glucocorticoids, levothyroxine, NSAIDs, polypharmacy, propiomazine, PPIs, and z-drugs (zolpidem/ zopiclone/ zaleplon) were tested. Medications taken at baseline were recorded along with their corresponding anatomical therapeutic chemical (ATC) codes and drug identification number (DIN) codes in the CLSA dataset. Use of a certain medication was identified through searching the ATC and DIN codes. Drugs that increase fall risk includes antihypertensive agents, diuretics, beta blockers, sedatives and hypnotics, neuroleptics and antipsychotics, antidepressants, benzodiazepines, narcotic analgesics, and NSAIDs as reported in the literature (114). Polypharmacy was defined as the number of DIN codes in a participant's record as each DIN code is a unique number assigned to a product sold in Canada while the ATC code is used to classify drugs according to their chemical properties. In terms of propiomazine, no participants were taking this medication at baseline; therefore, it was not possible to test it in this analysis. Eight factors, antidepressants, antiepileptics, diuretics, drugs that increase fall risk, oral glucocorticoids, polypharmacy, PPIs, and statins, in this category met the inclusion criteria for multivariate analysis.

Seven **physical capability** including activities of daily living, balance, chair rise time, eyesight rating, hand grip strength, standing balance, and timed get up and go were tested. Activities of daily living was originally recorded as the number of some and complete dependence but were divided into groups by severity due to the imbalanced distribution across the numbers. They were then dichotomized because of the small number of cases in the severe and total impairment groups. Similarly, although standing balance was recorded in seconds, since there were no substantial differences in participants who could not reach the goal of 60 seconds in 15-second intervals when compared to those who did, it was converted into a binary variable. Six factors in this category met the inclusion criteria for multivariate analysis except for eyesight rating.

Five **reproductive history** factors including hormone contraceptives, menopause hormone therapy, hysterectomy, menopause status, and parity number were tested. Menopause age was also recorded in the dataset. However, neither the age at menopause nor the method of menopause (natural or surgical) provided additional information to menopause status. Four factors in this category met the inclusion criteria for multivariate analysis except for hysterectomy.

Ten **biomarkers** including 25(OH)D, albumin, creatinine, hs-CRP, ferritin, HbA1c, HDL-C, hemoglobin, triglycerides, and eGFR were tested. All of them were analyzed in two ways: in their original continuous forms and categorized

according to reference ranges. Nine factors in this category met the inclusion criteria for multivariate analysis except for HDL-C.

Fourteen **BMD and related measures** including total fat mass percentage, total lean mass percentage, lean mass index, appendage lean mass index, appendage pure lean mass index, BMC pelvic, BMD left arm, BMD right arm, BMD lumbar spine, BMD pelvic, BMD left leg, BMD right leg, BMD nondominant arm, and BMD T-score total hip were tested. 12 factors in this category met the inclusion criteria for multivariate analysis except for appendage lean mass index and appendage pure lean mass index. However, only total fat mass percentage, lean mass percentage, and BMD T-score total hip were entered into the multivariate models since the remaining BMD measurements would be highly correlated with BMD T-score total hip making it inappropriate to include them in the same model.

### 4.3 Multivariate Analysis

To summarize, the 65 factors considered for multivariate analysis are as follows: age, BMI, height, hip circumference, ethnic group, waist circumference, weight, weight change, calcium-fortified foods, protein, vegetables, asthma, cancer, cerebrovascular event, emphysema chronic bronchitis COPD or chronic changes in lungs due to smoking, prediabetes or diabetes, epilepsy,

hypertension, Crohn's disease ulcerative colitis or irritable bowel syndrome, kidney disease or failure, osteoarthritis, rheumatoid arthritis, other comorbidities, alcohol consumption, skipping meals, smoking, worked in the past 7 days, yard work, walking, strenuous sports, muscle exercise, depressive symptoms, parent hip fracture, personal history of fall, self-perceived general health, antidepressants, antiepileptics, diuretics, drugs that increase fall risk, oral glucocorticoids, polypharmacy, PPIs, statins, activities of daily living, balance, chair rise test, hand grip strength, timed get up and go, hormone contraceptives, menopause hormone therapy, menopause status, parity number, 25(OH)D, albumin, creatinine, eGFR, ferritin, HbA1c, hemoglobin, hs-CRP, triglycerides, total fat mass percentage, total lean mass percentage, and BMD T-score total hip. The first 53 variables were used in the primary model A while all of them were incorporated into the extended model B.

### 4.3.1 Primary Model A

As a first step, VIF values for all the 53 variables were examined. High VIF values were found for weight (184.27), BMI (175.50), height (26.44), hip circumference (7.92), and waist circumference (5.44) listed from largest to smallest. Variables that were strongly correlated with them were identified by correlation coefficients and weight, BMI, and hip circumference were

considered for removal to reduce multicollinearity. Following this adjustment, the remaining 50 variables exhibited no VIF values exceeding 5.

During the backward selection process, all 50 candidate variables were initially included in the model. After several iterations, 12 factors were retained including age, alcohol consumption, antidepressants, balance, epilepsy, hand grip strength, height, menopause hormone therapy, osteoarthritis, parent hip fracture, personal history of fall, and smoking. However, the protective effect of menopause hormone therapy (OR 0.98 [0.97, 1.00]) became non-significant in the complete case analysis.

Following that, a logistic regression model was constructed using complete cases consisting of a sample of 9274 participants with 892 events. 11 factors were retained in the final model. Alcohol consumption and hand grip strength appeared to be protective against fractures while the other nine variables had a negative impact. The strongest effect was found in epilepsy presenting an OR of 2.18 [1.28, 3.73] suggesting the odds of first incident fragility fracture were about 2.2 times higher for people with epilepsy compared to those without the disease. Following was a personal history of fall which resulted in 78% higher odds of fractures comparing to people who did not fall in the past 12 months. Regardless of the frequency of smoking, the harmful impact was consistent with an OR of 1.63 [1.23, 2.16] for daily smokers and an OR of 1.22 [1.05, 1.43] for occasional of former smokers compared to people who never smoke. The odds

of fractures were 36% higher among people aged 55 to 64 years old compared to those aged 45 to 54 years old and increased further to around 55% in those aged 65 and above. However, the odds appeared to plateau after age 65 as the ORs for the age group 65 to 74 and the 75 and older group were similar. Balance, alcohol consumption, parent hip fracture, and antidepressant, were associated with similar effects, each showing approximately a 30% difference compared to the reference group. The OR of osteoarthritis comparing individuals with the disease to those without 1.19 [1.02, 1.39]. The remaining two factors, hand grip strength and height were both continuous variables and demonstrated a 3% change in odds of developing incident first fragility fracture over 6 years for every 1-unit change. Primary model A is presented in full detail in Table 4.4.

### 4.3.2 Extended Model B

As a first step, VIF values for all the 65 variables were examined. High VIF values were found for weight (185.90), BMI (176.50), height (26.97), hip circumference (8.41), waist circumference (5.68), and eGFR (5.32) listed from largest to smallest. Variables that were strongly correlated with them were identified and weight, BMI, hip circumference, and eGFR were considered for removal to reduce multicollinearity. In addition, total fat mass percentage was also excluded because it was perfectly correlated with total lean mass

percentage as total fat mass percentage is equal to one minus total lean mass percentage. Following this adjustment, the remaining 60 variables exhibited no VIF values exceeding 5.

During the backward selection process, all 60 candidate variables were initially included in the model. After several iterations, 11 factors were retained including alcohol consumption, antidepressants, balance, BMD T-score total hip, epilepsy, hand grip strength, height, osteoarthritis, parent hip fracture, personal history of fall, waist circumference. However, the protective effect of alcohol consumption (OR 0.78 [0.62, 0.98]) became non-significant in the complete case analysis.

Following that, a logistic regression model was constructed using complete cases consisting of a sample of 8811 participants with 837 events. In the backward selection process, all 60 candidate variables were initially included in the model. 10 factors were retained in the final model. Hand grip strength and BMD T-score total hip appeared to be protective against fractures while the other eight variables had a negative impact. The strongest effect was found in epilepsy presenting an OR of 2.12 [1.21, 3.70] suggesting the odds of first incident fragility fracture were about 2.1 times higher for people with epilepsy compared to those without the disease. Following was a personal history of fall which resulted in 79% higher odds of fractures comparing to people who did not fall in the past 12 months. Balance, antidepressant, parent hip fracture, and osteoarthritis were associated with similar effects, each showing approximately

a 28% increase. Three continuous factors, hand grip strength, height, and waist circumference, demonstrated a 2 to 3% increase in odds for every 1-unit change. The last one BMD T-score total hip was associated with a 4% reduction in odds of developing incident first fragility fracture over 6 years for every 0.1-unit increase. Extended Model B is presented in full detail in Table 4.5.

### 4.4 Multiple Imputation

Using the 10 imputed datasets, the 11 factors retained in primary model A all showed the same direction and similar effect sizes. Four additional risk factors for fist incident fragility fractures were identified including other comorbidities, polypharmacy, asthma, and weight change listed from the strongest to the weakest effect. The odds of fracture were 1.4 times higher for people with any of the other 14 comorbidities compared to those without those diseases. Taking 1 to 2 medications at baseline was associated with a 38% increase in odds while the effect of taking 3 or more medications did not reach statistical significance comparing to taking zero medications. Asthma and weight loss in the past 6 months both showed a negative impact on fractures with ORs around 1.2 while the other category in wight change, weight gain, was not associated with fractures. Multiple imputation model A is presented in full detail in Table 4.4. Using another 10 imputed datasets, the 10 factors retained in extended model

B all showed the same direction and similar effect sizes. Five additional risk factors for fist incident fragility fractures were identified including polypharmacy, smoking, asthma, muscle exercise and weight change listed from the strongest to the weakest effect. Taking 1 to 2 medications at baseline was associated with a 38% increase in odds while the effect of taking 3 or more medications did not reach statistical significance comparing to taking zero medications. Both daily smokers and occasional or former smokers were associated with increased odds presenting ORs of 1.35 [1.04, 1.76] and 1.16 [1.01, 1.34], respectively. Asthma, muscle exercise 0 to 0.5 hours a day, and weight loss in the past 6 months showed similar effects, each demonstrating approximately a 21% difference in odds while muscle exercise of more than 0.5 hours a day and weight gain in the past 6 months were not associated with fractures. Multiple imputation model B is presented in full detail in Table 4.5.

### 4.5 Model Performance

The performance of BMD T-score total hip was utilized as the reference. This sample consisted of 10238 participants and 972 events. Based on the diagnostic criterion for osteoporosis, a BMD T-score <= -2.5 was classified as a case while values above this threshold were classified as non-cases. Using this standard, AUC yielded 0.60 (0.58, 0.61), sensitivity 3.50%, and specificity 98.04%

indicating that BMD T-score alone was excellent at identifying participants who did not sustain a fracture during follow-up but missed most cases.

To maintain sensitivity at least 80% and optimize specificity, the threshold chosen for primary model A was a fracture probability of 7.30%. Sensitivity was prioritized because the model was intended for use as a first screening tool where capturing as many true cases as possible was more important at this stage. Moreover, individuals flagged by the model would likely undergo a BMD test as a follow-up screen. Given that BMD is effective in confirming low fracture risk, it can refine the initial assessment and reduce unnecessary interventions. The resulting AUC of primary model A was 0.63 (0.61, 0.65) demonstrating a 0.03 improvement from the BMD T-score only model. Sensitivity was 80.49% while specificity was 34.61% showing +76.99% and -63.43% changes respectively.

Applying the same standard, the threshold chosen for extended model B was a fracture probability of 7.15%. The resulting AUC was 0.65 (0.63, 0.67) demonstrating a 0.05 improvement from the BMD T-score only model. Sensitivity was 80.17% while specificity was 38.86% showing +76.67% and -59.18% changes respectively. An increase of 0.02 in AUC and 4% in specificity were also observed compared to primary model A.

# Chapter 5 Discussion and Conclusions

This chapter summarizes the findings of this thesis and compares them with those reported in publications. Clinical implications, strengths and limitations as well as future directions for research are discussed.

## 5.1 Discussion

This thesis developed models for assessing the risk of first incident fragility fractures in postmenopausal women by identifying independent risk factors reported in literature, then testing them separately using the CLSA dataset, and finally combing them to construct the models. The results of these analyses suggest that personal information (age, alcohol consumption, antidepressants, balance, epilepsy, height, osteoarthritis, history of fall, and smoking), family history (parent hip fracture) plus a simple physical examination (hand grip strength) could be used to screen women with higher risk. The associations observed for these factors are generally expected and plausible and most remained significant after controlling for BMD T-score total hip. This model outperformed the BMD T-score alone model in terms of AUC, sensitivity, and specificity.

### 5.1.1 Comparison between Models

Primary model A includes 11 factors without taking biomarkers or radiographic measures into account while Extended model B consists of 10 factors including the BMD T-score total hip. The eight factors common to both models are antidepressants, balance, epilepsy, hand grip strength, height, osteoarthritis, parent hip fracture after age 50, and personal history of fall. The directions of effects are identical in both models and their effect sizes are very similar with all the differences in ORs within 0.06 indicating that their effects are independent of BMD. The addition of biomarkers and radiographic measures to extended model B did not improve the model performance substantially compared to primary model A in terms of AUC, sensitivity or specificity.

After adjusting for BMD T-score, the effect of age, alcohol consumption, and smoking attenuated probably because they served as indicators of BMD in model A. In general, an older age or heavier smoking behavior is associated with a lower BMD or an increased risk of osteoporosis (226-232). However, the impact of alcohol consumption on osteoporosis or BMD was not consistent across studies. Increased total spine BMD was reported to be associated with more frequent alcohol intake in women above 20 years old even in heavy

drinkers (233). Similarly, higher femoral neck BMD was observed in postmenopausal women who had at least one drink per day but not binge drinking (234). Several studies found that the effect was amount-dependent with greater harm associated with higher values and positive or no effect at the lighter end (235-237). Some of them also suggested that the relationship was type specific.

### 5.1.2 Comparison with Previous Studies

The majority of factors retained in primary model A demonstrated identical directions and similar effects to those reported in the literature. Although the units or groupings used for comparison was not identical, older age was consistently associated with an increased risk of fractures. The effect of antidepressants (182) and epilepsy (138) comparing yes to no in the current analysis and in the literature was comparable at OR 1.29 [1.08, 1.55] vs HR 1.22 [1.15, 1.30] and OR 2.18 [1.28, 3.73] vs HR 1.97 [1.08, 3.62], respectively.

By simply asking about balance, individuals who perceived their balance as poor or impaired consistently exhibited a higher risk of fracture both in primary model A and the literature (200). However, the strength of association was notably greater in prior study with an OR of 4.45 [1.50, 13.20] compared to an

OR of 1.35 [1.10, 1.65] observed in the present sample. The discrepancy in effect sizes may be partly explained by differences in sample size and model covariates. The previous study included 370 participants and 67 osteoporotic fracture events which likely produced a less stable estimate as reflected in the wide confidence interval. Additionally, although both this analysis and the previous study adjusted for fall history which may be closely related to balance, the time frames were different. The current model considered fall in the past 12 months while the previous study used a 10-year window. The shorter time frame may reflect recent balance status more accurately potentially attenuating the observed association.

Although the way of comparing hand grip strength was different, the beneficial effect of greater strength was consistently observed across previous studies (51, 56, 194-196) and current analysis. The effect of height per centimeter was consistent at 1.03 (49). In studies on osteoarthritis comparing yes to no, the effect sizes reported varied from an HR of 1.16 [1.08, 1.25] to an HR of 1.90 in previous studies (44, 55, 135, 136). The magnitude observed in the current analysis was closer to the lower end of this range with an OR of 1.19 [1.02, 1.39]. Similarly, the associations reported for fall in the past year comparing yes to no varied between an OR of 1.38 [1.14, 1.66] and OR of 2.16 [1.81, 2.59]. The effect in primary model A fell within the range with an OR of 1.78 [1.47, 2.15]. Although the site and age of fracture were not specified, the

reported association between parental fracture and any fracture was an OR of 1.42 (1.04, 1.94) (89) which is comparable to that observed for parent hip fracture after age 50 in primary model A with an OR of 1.30 (1.08, 1.57). Variation was observed for two factors. Alcohol consumption in the past year showed a protective effect against fracture which contrasts with findings in literature comparing yes to no (164, 165). However, further investigation into the amount or type of alcohol consumed yielded inconsistent results. In studies defined alcohol consumption based on quantity, a harmful effect was generally observed only beyond a certain intake threshold. In the sample of our study, only approximately 4% participants consumed more than two standard drinks per day, a level often used as the cutoff value to classify heavy drinkers. The predominance of light alcohol consumption in our dataset might be the reason why alcohol consumption presented a protective effect against fractures. These discrepancies suggest that the relationship between alcohol consumption and fracture may depend on the quantity, similar to the relationship between alcohol intake and BMD or osteoporosis (233-237). Comparing daily smokers to never smokers, model A presented a statistically significant effect in all with an OR of 1.63 [1.23, 2.16] regardless of the number of cigarettes smoked per day. In contrast, the previous study (167) reported a significant association only among individuals who smoked at least 20 cigarettes per day with an HR of 1.93 [1.30, 2.84].

## 5.2 Clinical Implications

The findings of this thesis have several clinical implications for the assessment and management of fracture risk. The AUC and sensitivity improvements from BMD alone model indicate that the 11 factors in model A combined is a better way to screen women at higher risk of first incident fragility fracture. The BMD-based diagnostic criterion for osteoporosis is not ideal for population screening due to its low sensitivity, only 3% in the current analysis, and similar findings have been reported in previous studies. With the proposed fracture probability threshold of 7.26%, the model A reached a sensitivity of 80% and a specificity of 35% meaning that 80% of people who would sustain a fracture without intervention could be captured. Although ideally a good screening test should also have high specificity, trade-offs between sensitivity and specificity can be acceptable depending on the purpose of the tool. In the context of this thesis, people who screened positive by this tool were intended to undergo further evaluations such as a BMD test rather than receive immediate treatment. Given the BMD testing has high specificity, it can effectively refine risk assessment and filter out those at truly low risk. Moreover, BMD testing is non-invasive, relatively safe and widely accepted in clinical practice. Therefore, the potential harm for false positive at

the individual level is minimal.

These findings also highlight areas that individuals and healthcare provider can focus on to help prevent fractures since some factors are modifiable. To start with, education efforts could emphasize fracture prevention in individuals who are older, taller, have epilepsy or osteoarthritis, are currently taking antidepressants, have family history of hip fracture, report poor balance, or smoke daily. In addition, treating or stabilizing underlying diseases where feasible may help reduce the fracture risk. Smoking cessation, fall prevention and weight bearing exercise to improve hand grip strength could also be recommended.

### 5.3 Strengths, Limitations and Future Directions

The major strength of the model is that most factors included can be easily obtained through routine clinical practice, either by reviewing medical records or by asking straightforward questions. Notably, even after controlling for BMD, most factors remained statistically significant and their effect sizes showed minimal changes. This makes the model not only highly practical and accessible for use in primary care or similar settings but also easy to implement without requiring additional resources or specialized equipment. In the CLSA study, age was calculated based on participants' exact date of birth.

Alcohol consumption was collected by asking “About how often during the past 12 months did you drink alcohol?”. Antidepressants were obtained by searching the DIN and ATC codes in participants’ records. Balance was assessed by asking “Is your balance poor?”. Epilepsy and osteoarthritis were specifically asked as “Has a doctor ever told you that you have epilepsy/ osteoarthritis?”. Height was measured in a standing position and the final value was the average of two measurements. Hand grip strength was measured in a sitting position using the dominant hand with a wireless dynamometer and the measurements were repeated three times. Parent hip fracture after age 50 was a combination of two questions “Did your mother have a hip fracture after age 50?” and “Did your father have a hip fracture after age 50?”. Personal history of fall was collected by asking “In the past 12 months, did you have any falls?”. Smoking was derived from a series of questions from “Have you smoked at least 100 cigarettes in your life?”, “Have you ever smoked a whole cigarette?” to “At the present time, do you smoke cigarettes daily, occasionally or not at all?”. Having a simple screening tool which identifies individuals at risk before a first fracture occurs is valuable for both clinical practice and population health. Early identification and intervention can not only prevent the initial injury but also reduce the risk of subsequent fractures ultimately lowering healthcare costs and improving quality of life.

One more strength is that this thesis attempted to reduce recall bias by excluding participants who reported their fracture history inconsistently. Considering that the question on fragility fractures was phrased to capture any fracture occurring during adult life rather than those occurring since last study visit and that the dataset was not linked to official health service records, the accuracy of self-reported fracture events could not be fully verified. By excluding inconsistent responses, the credibility of other self-reported factors was likely improved as well.

This thesis also has several limitations. The overall missing rate was relatively high at 15.15% as these participants had at least one missing value in any of the variables used in the analysis. As a result, it was not possible to split the dataset and conduct internal validation to evaluate the model performance. The differences in the number of factors retained in complete case analysis and the multiple imputation analysis also suggested that the smaller sample size of complete cases might have limited statistical power as more factors were identified when the larger imputed dataset was used. In addition, not all the factors identified in the literature review were included in the analysis and some included factors were not analyzed in the exact format reported in previous studies, therefore, certain effects may have been missed and the observed associations for included factors may have been influenced. Moreover, because the outcome of interest was the first incident fragility

fracture during follow-up, participants with a history of fracture before baseline were excluded. The analysis was not able to adjust for prior fractures which is a well-established independent risk factor for subsequent fractures.

In terms of future directions, the discrepancies observed in the relationship between alcohol consumption and fracture risk could be further explored by using more detailed data on quantity, type or combined. One of the initial aims was to explore biologically women specific factors that may contribute to the higher fracture risk in postmenopausal women. Although some of these factors were included in the analysis, such as parity and MHT, none remained statistically significant after adjusting for other variables. This suggests that future research could target the potentially different impact of gender-neutral factors on facture risk between women and men. Additionally, the analysis could also be expanded to include male participants since all the factors retained in the final model are not specific to women. Such research could help determine whether the same risk factors apply across genders or whether distinct risk profiles exist for women and men. Lastly, to fully understand the model performance and generalizability, comparisons with existing fracture risk assessment tools could be conducted, and external datasets could be sought for validation.

## 5.4 Conclusions

This thesis identified risk factors for fragility fractures in postmenopausal women through a literature review and constructed models for assessing first incident fragility fracture risk based on these risk factors. The resulting model along with the proposed probability threshold demonstrated improved performance compared to BMD classification. It could be easily implemented as a screening tool in primary care and similar settings since it does not require laboratory tests, radiographic imaging or complex equipment. This new model has the potential to support early intervention and to help prevent fractures in postmenopausal women potentially improving both their quantity and quality of life. Further validation is needed to assess the generalizability of the model in other populations.

**Figure 2.1** Literature Review Flow Chart

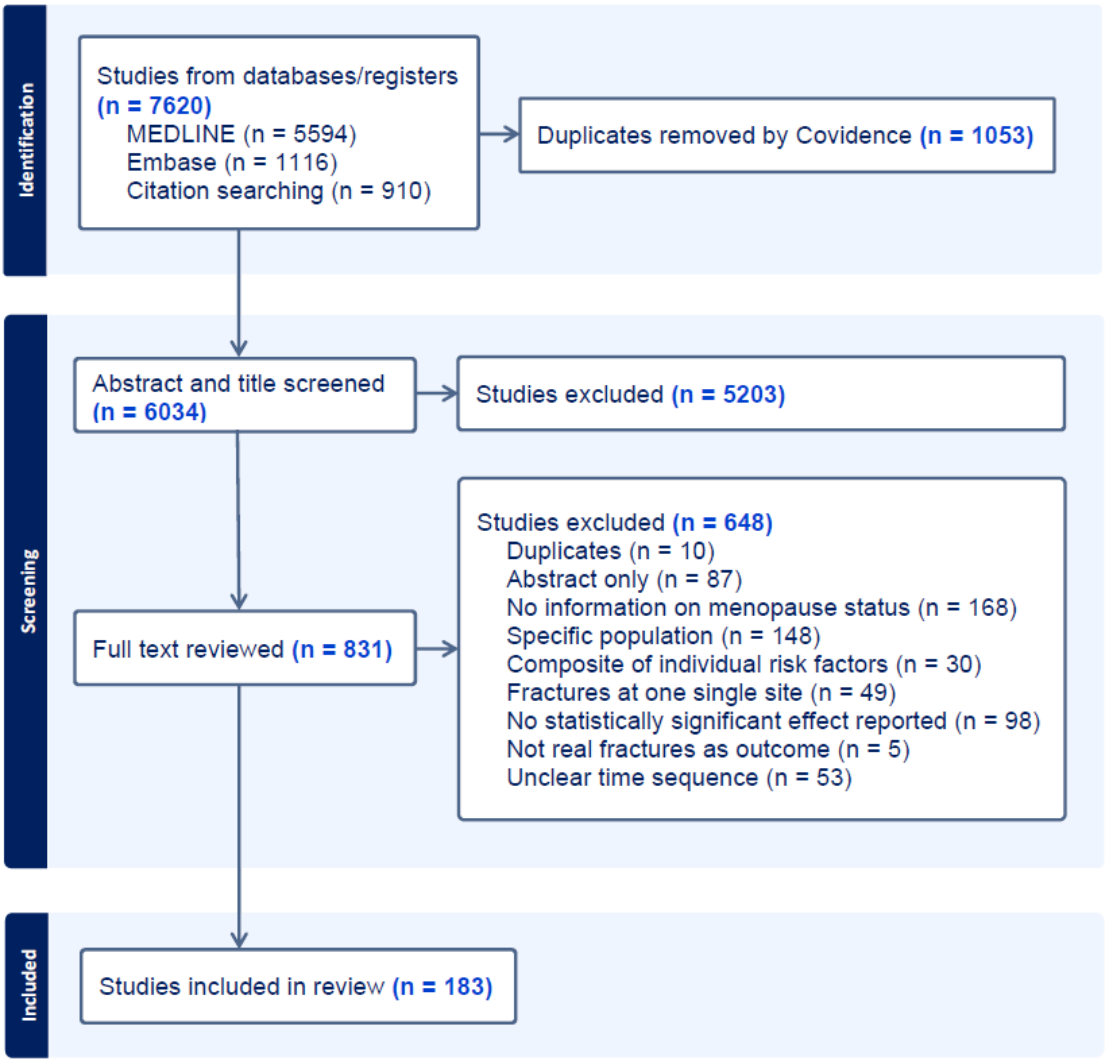

**Figure 2.2** Methods Flow Chart

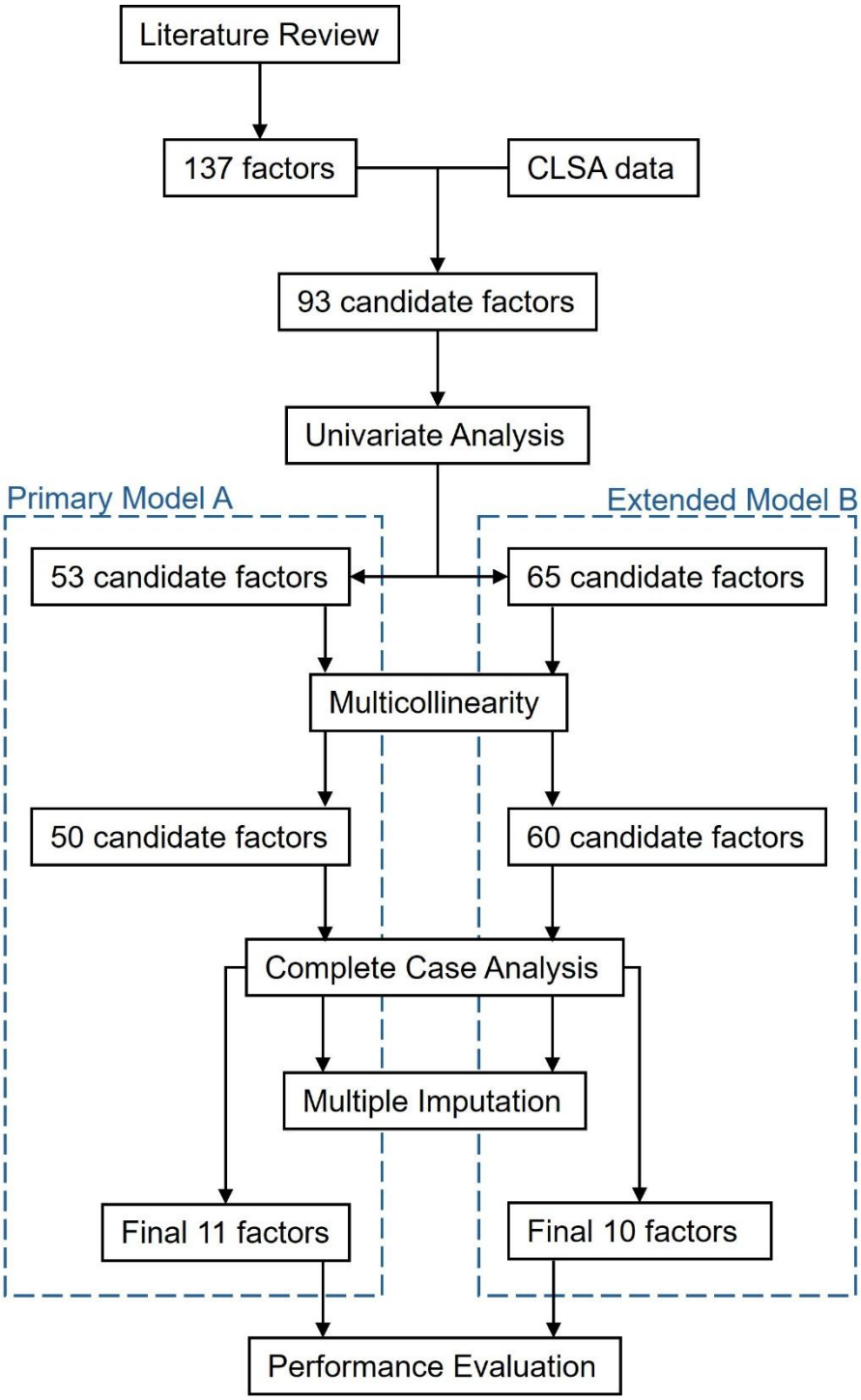

**Table 2.1** Risk Factors Identified through Literature Review by Category

| Category | Factors |
|---|---|
| **Anthropometric factors** | Age, body mass index (BMI), ethnic group, height, hip circumference, waist circumference, weight |
| **Biomarkers** | 25(OH)D, androstenedione, androstenedione/ SHBG ratio, bioavailable estradiol (BioE2), bioavailable testosterone (BioT), bone material strength index, C-reactive protein (CRP), collagen type I N-telopeptide, cross-linked N-telopeptide of type I collagen, C-terminal cross-linking telopeptide of type I collagen ratio, cystatin C, estimated glomerular filtration rate (eGFR), fluoride, free estradiol index, hemoglobin, HbA1c, homocysteine, insulin-like growth factor-binding protein 1 (IGFBP-1), high-density lipoprotein cholesterol (HDL-C), pentosidine, periostin, parathyroid hormone (PTH), sphingosine 1-phosphate (S1P), triglycerides, uric acid, vitamin B12, vitamin D metabolite ratio |
| **BMD and related factors** | Bone mass, bone mineral apparent density (BMAD), bone mineral content (BMC), bone mineral density (BMD), BMD T-score |
| **Dietary habits** | Calcium, dairy products, fat, fish oil, protein, soybeans, tea, vegetables |
| **Diseases** | Alcoholism, anemia, asthma, cancer, cardiovascular disease, celiac disease, chronic hepatic disease, chronic obstructive pulmonary disease (COPD), COVID-19, diabetes, epilepsy, giant cell arteritis, hypercholesterolemia, hypertension, hyperthyroidism, inflammatory bowel disease, kidney disease, multiple sclerosis, osteoarthritis, Parkinson's disease, polymyalgia rheumatica, psoriasis, pulmonary embolism, respiratory tuberculosis, rheumatoid arthritis, schizophrenia, seasonal influenza, thrombocytopenia |
| **Genetic factors** | Major Histocompatibility Complex class II transactivator (MHC2TA, CIITA)_rs3087456, C-type lectin domain 16A (CLEC16A)_rs725613, collagen type Ia1 (COLIA1)_haplotype, collagen type Ia1 (COLIA1)_rs1800012, Glucose Dependent Insulinotropic Polypeptide Receptor (GIPR)_rs1800437, methylenetetrahydrofolate reductase (MTHFR)_ rs1801133, Myostatin (MSTN)_ rs7570532, prolactin PRL_T228C, vitamin D receptor (VDR)_haplotype |
| **Lifestyle** | Alcohol consumption, skipping breakfast, physical activity, |

| | |
|---|---|
| **factors** | smoking |
| **Medical conditions** | depressive symptoms, family history of diabetes, family history of fracture, family history of osteoporosis, personal history of fall, personal history of fracture, self-perceived fracture risk |
| **Medications** | antidepressants, antiepileptic drugs, antipsychotic drugs, beta blockers, diuretics, drugs that increase fall risk, oral glucocorticoids, levothyroxine, nonsteroidal anti-inflammatory drugs (NSAIDs), polypharmacy, propiomazine, proton pump inhibitors (PPIs), statins, z-drugs |
| **Physical capability** | balance, body sway, daily living activities, hand grip strength, quadriceps strength, quality of life physical component (SF-36 PCS), vision |
| **Other radiographic parameters** | aortic calcification score (ACS), appendicular skeletal muscle index (ASMI), broadband ultrasound attenuation (BUA), cortical area 66% slice, fat mass, lean mass, lumbar spine trabecular bone score (TBS), lumbar vertebra attenuation, speed of sound (SOS), stiffness index (SI), vertebral deformity |
| **Reproductive history** | Amenorrhea, breastfeeding, cycle length, menopause hormone therapy (MHT), hysterectomy, menarche age, menopause status, oral contraceptive use, parity, reproductive lifespan |

**Table 4.1** Alternative selection

| **Original Measurement** | **Closest Functional Substitutes** |
|---|---|
| Parathyroid hormone (PTH) | 25(OH)D |
| Vitamin D metabolite ratio | |
| Androstenedione | albumin |
| Androstenedione/ SHBG ratio | |
| Bioavailable estradiol (BioE2) | |
| Bioavailable testosterone (BioT) | |
| Free estradiol index | |
| Insulin-Like Growth Factor-Binding Protein 1 (IGFBP-1) | |
| Bone mass | BMD |
| Bone Material Strength Index | |
| Broadband Ultrasound Attenuation (BUA) | |
| Cortical Area 66% Slice | |
| Lumbar Vertebra Attenuation | |
| Stiffness Index (SI) | |
| aortic calcification score (ACS) | BMD T-score |
| Bone Mineral Apparent Density (BMAD) | |
| Lumbar Spine TBS | |
| Speed of Sound (SOS) | |
| Vertebral Deformity | |
| Quadriceps strength | Chair Rise |
| Cystatin C | Creatinine |
| Uric acid | |
| Fluoride | eGFR |
| Vision | Eyesight rating |
| Homocysteine | High Sensitivity C-Reactive Protein (hs-CRP) |
| Sphingosine 1-phosphate (S1P) | |
| Oral contraceptive use | Hormonal contraceptives |
| C-terminal cross-linking telopeptide of type I collagen ratio | Ferritin |
| Collagen type I N-telopeptide | |
| Cross-linked N-telopeptide of type I collagen | |
| Pentosidine | |
| Periostin | |
| Vitamin B12 | Hemoglobin |
| Self-perceived fracture risk | Self-perceived general health |
| Skipping breakfast | Skipping meals |

| | |
|---|---|
| Body sway | Standing balance |
| quality of life physical component (SF-36 PCS) | Timed get up and go |

**Table 4.2** Factors Tested by Category

| Category | Factor |
|---|---|
| Anthropometric factors | Age, BMI, height, hip circumference, ethnic group, waist circumference, weight, weight change in the past 6 months |
| Dietary habits | Calcium-fortified foods, dairy products, fat, vegetables, fish oil supplements in the past month, protein |
| Diseases | Asthma, cancer, cerebrovascular event, emphysema chronic bronchitis COPD or chronic changes in lungs due to smoking, prediabetes or diabetes, epilepsy, hypertension, hyperthyroidism, Crohn's disease ulcerative colitis or irritable bowel syndrome, kidney disease or failure, osteoarthritis, rheumatoid arthritis, flu in the past year, other comorbidities |
| Lifestyle factors | Alcohol consumption in the past year, skipping meals, worked in the past 7 days, smoking, yard work in the past 7 days, sitting in the past 7 days, walking in the past 7 days, light sports in the past 7 days, moderate sports in the past 7 days, strenuous sports in the past 7 days, muscle exercise in the past 7 days |
| Medical conditions | Depressive symptoms, parent hip facture after age 50, personal history of fall, self-perceived general health |
| Medications | Antidepressants, antiepileptics, antipsychotic, beta blockers, diuretics, drugs that increase fall risk, oral glucocorticoids, levothyroxine, NSAIDs, polypharmacy, propiomazine, PPIs, statins, z-drugs |
| Physical capability | Activities of daily living, balance, chair rise time, eyesight rating, hand grip strength, standing balance, timed get up and go |
| Reproductive history | Hysterectomy, menopause status, parity number, menopause hormone therapy, hormone contraceptives |
| Biomarkers | 25(OH)D, Albumin, Creatinine, hs-CRP, Ferritin, HbA1c, HDL-c, Hemoglobin, Triglycerides, eGFR |
| BMD and related measures | Total fat mass percentage, Total lean mass percentage, Lean mass index, Appendage lean mass index, Appendage pure lean mass index, Total hip t-score, BMC pelvic, BMD left arm, BMD right arm, BMD lumbar spine, BMD pelvic, BMD left leg, BMD right leg, BMD nondominant arm |

**Table 4.3** Sample Characteristics and Unadjusted OR from Univariate Analysis

| **Factor** | **Unit/ Group** | **Mean (SD) / frequency (percentage)** | **Missing frequency (percentage)** | **Unadjusted OR (95%CI)** | **p-value** |
|---|---|---|---|---|---|
| **Anthropometric factors** | | | | | |
| Age | 45-54 | 3140(28.73) | 0(0) | ref | |
| | 55-64 | 3756(34.36) | | 1.43 (1.20, 1.70) | <.0001 |
| | 65-74 | 2494(22.82) | | 1.72 (1.43, 2.06) | <.0001 |
| | >=75 | 1540(14.09) | | 1.84 (1.50, 2.26) | <.0001 |
| BMI | kg/cm2 | 27.81(11.06) | 33(0.3) | 1.01 (1.00, 1.02) | 0.0932 |
| Height | cm | 161.80(6.49) | 23(0.21) | 1.01 (1.00, 1.02) | 0.0565 |
| Hip circumferemce | cm | 105.41(12.50) | 62(0.57) | 1.01 (1.00, 1.01) | 0.0047 |
| Ethnic group | white | 10345(94.71) | 7(0.06) | ref | |
| | non-white | 578(5.29) | | 0.77 (0.56, 1.05) | 0.0976 |
| Waist circumferemce | cm | 87.84(13.84) | 62(0.57) | 1.01 (1.00, 1.01) | 0.0001 |
| Weight | kg/cm2 | 72.56(16.06) | 32(0.29) | 1.01 (1.00, 1.01) | 0.0198 |
| Weight change in the past 6 months | same | 6877(63.82) | 154(1.41) | ref | |
| | gained | 1904(17.67) | | 1.10 (0.93, 1.30) | 0.2863 |
| | lost | 1995(18.51) | | 1.27 (1.08, 1.50) | 0.0040 |
| **Dietary habits** | | | | | |
| Calcium-fortified foods | No | 7156(66.43) | 168(1.54) | ref | |
| | Yes | 3616(33.57) | | 0.85 (0.74, 0.98) | 0.0209 |
| Dairy products | times per day | 1.96(1.18) | 97(0.89) | 0.99 (0.94, 1.04) | 0.6818 |
| Fat | times per day | 1.74(1.04) | 53(0.48) | 1.03 (0.97, 1.10) | 0.2836 |

| | | | | | |
|---|---|---|---|---|---|
| Fish Oil supplements in the past month | No | 10310(95.65) | 151(1.38) | ref | |
| | Yes | 469(4.35) | | 1.02 (0.75, 1.40) | 0.8927 |
| Protein | times per day | 1.33(0.60) | 107(0.98) | 0.87 (0.78, 0.98) | 0.0206 |
| Vegetables | times per day | 2.44(1.17) | 61(0.56) | 0.96 (0.91, 1.01) | 0.1137 |
| **Diseases** | | | | | |
| Asthma | No | 9254(85.07) | 52(0.48) | ref | |
| | Yes | 1624(14.93) | | 1.32 (1.12, 1.56) | 0.0010 |
| Cancer | No | 9334(85.67) | 35(0.32) | ref | |
| | Yes | 1561(14.33) | | 1.25 (1.05, 1.48) | 0.0110 |
| Cerebrovascular event | No | 10451(96.60) | 111(1.02) | ref | |
| | Yes | 365(3.40) | | 1.77 (1.33, 2.37) | 0.0001 |
| Emphysema, chronic bronchitis, COPD or chronic changes in lungs due to smoking | No | 10283(94.66) | 67(0.61) | ref | |
| | Yes | 580(5.34) | | 1.20 (0.92, 1.57) | 0.1751 |
| Prediabetes or diabetes | No | 8457(86.99) | 1208(11.05) | ref | |
| | Yes | 1265(13.01) | | 1.18 (0.97, 1.42) | 0.0936 |
| Epilepsy | No | 10795(99.04) | 30(0.27) | ref | |
| | Yes | 105(0.96) | | 2.24 (1.37, 3.67) | 0.0013 |
| Hypertension | No | 7284(67.00) | 59(0.54) | ref | |
| | Yes | 3587(33.00) | | 1.12 (0.98, 1.28) | 0.0894 |
| Hyperthyroidism | No | 10376(96.21) | 59(0.54) | ref | |
| | Yes | 409(3.79) | 145(1.33) | 0.91 (0.64, 1.29) | 0.5911 |
| Crohn’s disease, ulcerative colitis | No | 9533(87.65) | 54(0.49) | ref | |

| | | | | | |
|---|---|---|---|---|---|
| or irritable bowel syndrome | | | | | |
| | Yes | 1343(12.35) | | 1.25 (1.04, 1.49) | 0.0180 |
| Kidney disease or failure | No | 10618(97.61) | 52(0.48) | ref | |
| | Yes | 260(2.39) | | 1.29 (0.88, 1.88) | 0.1943 |
| Osteoarthritis | No | 7442(69.47) | 217(1.99) | ref | |
| | Yes | 3271(30.53) | | 1.45 (1.27, 1.66) | <.0001 |
| Rheumatoid arthritis | No | 10398(96.34) | 137(1.25) | ref | |
| | Yes | 395(3.66) | | 1.63 (1.22, 2.17) | 0.0009 |
| Flu in the past year | No | 10146(93.22) | 46(0.42) | ref | |
| | Yes | 738(6.78) | | 1.16 (0.91, 1.48) | 0.2262 |
| Other comorbidities | No | 10560(96.65) | 0(0) | ref | |
| | Yes | 366(3.35) | | 1.55 (1.15, 2.10) | 0.0044 |
| **Lifestyle factors** | | | | | |
| Alcohol consumption in the past year | No | 1543(14.12) | 5(0.05) | ref | |
| | Yes | 9387(85.88) | | 0.75 (0.63, 0.89) | 0.0008 |
| Skipping meals | rarely or never | 8155(75.76) | 166(1.52) | ref | |
| | almost everyday, often or sometimes | 2609(24.24) | | 1.15 (1.00, 1.33) | 0.0578 |
| Smoking | Never | 3869(35.56) | 165(1.51) | ref | |
| | Occasionally or former | 6310(58.00) | | 1.19 (1.03, 1.36) | 0.0171 |
| | Daily | 700(6.43) | | 1.44 (1.12, 1.86) | 0.0049 |
| Worked in the past 7 days | No | 4638(43.08) | 165(1.51) | ref | |

| | | | | | |
|---|---|---|---|---|---|
| | Yes | 6127(56.92) | | 0.83 (0.73, 0.94) | 0.0044 |
| Yard work in the past 7 days | Yes | 4360(40.41) | 140(1.28) | ref | |
| | No | 6430(59.59) | | 1.11 (0.98, 1.27) | 0.1130 |
| Sitting in the past 7 days | daily hours 0 | 46(0.43) | 184(1.68) | ref | |
| | <0.5 | 38(0.35) | | 1.24 (0.33, 4.66) | 0.7475 |
| | 0.5-1 | 273(2.54) | | 0.55 (0.19, 1.56) | 0.2566 |
| | 1-2 | 1659(15.44) | | 0.82 (0.32, 2.09) | 0.6711 |
| | 2-4 | 4569(42.52) | | 0.83 (0.33, 2.12) | 0.7040 |
| | >=4 | 4161(38.72) | | 0.94 (0.37, 2.40) | 0.9013 |
| Walking in the past 7 days | No | 1566(14.52) | 143(1.31) | ref | |
| | Yes | 8221(85.48) | | 0.83 (0.70, 0.99) | 0.0389 |
| Light sports in the past 7 days | daily hours 0 | 8253(76.52) | 145(1.33) | ref | |
| | <0.5 | 678(6.29) | | 0.89 (0.68, 1.18) | 0.4227 |
| | 0.5-1 | 606(5.62) | | 1.05 (0.80, 1.38) | 0.7351 |
| | 1-2 | 798(7.40) | | 0.99 (0.77, 1.26) | 0.9118 |
| | 2-4 | 319(2.96) | | 1.05 (0.72, 1.52) | 0.8187 |
| | >=4 | 131(1.21) | | 1.21 (0.70, 2.09) | 0.4884 |
| Moderate sports in the past 7 days | daily hours 0 | 9259(85.83) | 143(1.31) | ref | |
| | <0.5 | 125(1.16) | | 1.39 (0.82, 2.36) | 0.2244 |
| | 0.5-1 | 287(2.66) | | 1.23 (0.85, 1.78) | 0.2757 |
| | 1-2 | 570(5.28) | | 0.85 (0.63, 1.15) | 0.2961 |
| | 2-4 | 411(3.81) | | 1.10 (0.80, 1.53) | 0.5478 |
| | >=4 | 135(1.25) | | 1.01 (0.57, 1.79) | 0.9811 |

| | | | | | |
|---|---|---|---|---|---|
| Strenuous sports in the past 7 days | Daily hours <0.5 | 7885(73.12) | 143(1.31) | ref | |
| | >=0.5 | 2899(26.88) | | 0.77 (0.66, 0.90) | 0.0009 |
| Muscle exercise in the past 7 days | Daily hours 0 | 7665(71.11) | 151(1.38) | ref | |
| | 0-0.5 | 1428(13.25) | | 1.18 (0.98, 1.41) | 0.0799 |
| | >=0.5 | 1686(15.64) | | 0.90 (0.75, 1.09) | 0.2827 |
| **Medical conditions** | | | | | |
| Depressive symptoms | CES-D <10 points | 8941(82.12) | 50(0.46) | ref | |
| | >=10 | 1947(17.88) | | 1.24 (1.06, 1.46) | 0.0072 |
| Parent hip fracture after age 50 | No | 9139(86.86) | 408(3.73) | ref | |
| | Yes | 1383(13.14) | | 1.47 (1.23, 1.74) | <.0001 |
| Personal history of fall | No in the past 12 months | 9598(88.96) | 141(1.29) | ref | |
| | Yes | 1191(11.04) | | 1.90 (1.60, 2.25) | <.0001 |
| Self-perceived general health | Poor | 131(1.20) | 6(0.05) | ref | |
| | fair good or very good | 8403(76.92) | | 0.74 (0.44, 1.23) | 0.2455 |
| | excellent | 2390(21.88) | | 0.61 (0.36, 1.03) | 0.0632 |
| **Medications** | | | | | |
| Antidepressants | No | 9270(84.81) | 0(0) | ref | |
| | Currently taking | 1660(15.19) | | 1.39 (1.18, 1.64) | <.0001 |
| Antiepileptics | No | 10408(95.15) | 0(0) | ref | |
| | Currently taking | 530(4.85) | | 1.37 (1.05, 1.78) | 0.0219 |
| Antipsychotics | No | 10765(98.49) | 0(0) | ref | |

| | | | | | |
|---|---|---|---|---|---|
| | Currently taking | 165(1.51) | | 1.16 (0.71, 1.90) | 0.5618 |
| Beta blockers | No | 10128(92.66) | 0(0) | ref | |
| | Currently taking | 802(7.34) | | 0.94 (0.73, 1.21) | 0.6273 |
| Diuretics | No | 9296(85.05) | 0(0) | ref | |
| | Currently taking | 1634(14.95) | | 1.18 (1.00, 1.40) | 0.0522 |
| Drugs that increase fall risk | No | 5356(49.00) | 0(0) | ref | |
| | Currently taking | 5574(51.00) | | 1.26 (1.10, 1.43) | 0.0005 |
| Levothyroxine | No | 9069(82.97) | 0(0) | ref | |
| | Currently taking | 1861(17.03) | | 0.97 (0.82, 1.15) | 0.7038 |
| NSAIDs | No | 9359(85.63) | 0(0) | ref | |
| | Currently taking | 1571(14.37) | | 1.11 (0.93, 1.32) | 0.2522 |
| Oral glucocorticoids | No | 10826(99.05) | 0(0) | ref | |
| | Currently taking | 104(0.95) | | 1.73 (1.01, 2.95) | 0.0463 |
| Polypharmacy | currently taking no medications | 1328(12.15) | 0(0) | ref | |
| | 1-2 | 2416(22.10) | | 1.56 (1.20, 2.03) | 0.0009 |
| | >=3 | 7186(65.75) | | 1.75 (1.38, 2.21) | <.0001 |
| Propiomazine | No | 10930(100) | 0(0) | NA | |
| | Currently taking | 0(0) | | | |
| PPIs | No | 9159(83.80) | 0(0) | ref | |
| | Currently taking | 1771(16.20) | | 1.31 (1.11, 1.54) | 0.0011 |
| Statins | No | 8910(81.52) | 0(0) | ref | |
| | Currently taking | 2020(18.48) | | 1.16 (0.99, 1.35) | 0.0746 |
| Z-drugs (zolpidem/ zopiclone/ zaleplon) | No | 10507(96.13) | 0(0) | ref | |

| | | | | | |
|---|---|---|---|---|---|
| | Currently taking | 423(3.87) | | 0.82 (0.57, 1.17) | 0.2703 |
| **Physical capability** | | | | | |
| Activities of daily living | No functional impairment | 9631(88.41) | 50(0.46) | ref | |
| | Yes | 1263(11.59) | | 1.53 (1.29, 1.83) | <.0001 |
| Balance | No | 9602(88.33) | 60(0.55) | ref | |
| | Impaired | 1268(11.67) | | 1.81 (1.53, 2.14) | <.0001 |
| Chair rise time | 0-2.4 seconds | 4160(39.37) | 363(3.32) | ref | |
| | >2.4 | 6407(60.63) | | 1.34 (1.17, 1.54) | <.0001 |
| Eyesight rating | excellent | 2441(22.35) | 7(0.06) | ref | |
| | very good | 4326(39.60) | | 0.96 (0.81, 1.13) | 0.5954 |
| | good | 3393(31.06) | | 1.04 (0.87, 1.24) | 0.6672 |
| | fair | 639(5.85) | | 0.84 (0.62, 1.15) | 0.2762 |
| | poor or non-existent (blind) | 124(1.14) | | 1.18 (0.67, 2.10) | 0.5635 |
| Hand grip strength | kg | 25.52(5.79) | 931(8.52) | 0.96 (0.95, 0.98) | <.0001 |
| Standing balance | can stand 60 seconds | 5147(49.17) | 463(4.23) | ref | |
| | less than 60 | 5320(50.83) | | 1.45 (1.27, 1.66) | <.0001 |
| Timed get up and go | 0-10.5 seconds | 8602(79.49) | 108(0.99) | ref | |
| | >10.5 | 2220(20.51) | | 1.47 (1.27, 1.70) | <.0001 |
| **Reproductive history** | | | | | |
| Hormone contraceptives | year in use | 7.63(8.07) | 291(2.66) | 0.99 (0.98, 1.00) | 0.0396 |
| Menopause hormone therapy | year in use | 2.81(6.23) | 125(1.14) | 1.01 (1.00, 1.02) | 0.1355 |
| Hysterectomy | No | 9212(84.83) | 70(0.64) | ref | |

| | | | | | |
|---|---|---|---|---|---|
| | Yes | 1648(15.17) | | 1.18 (0.99, 1.40) | 0.5820 |
| Menopause status | Pre/peri | 2062(18.99) | 70(0.64) | ref | |
| | Post | 8798(81.01) | | 1.69 (1.40, 2.04) | <.0001 |
| Parity Number | 0 | 1988(18.29) | 59(0.54) | 1.15 (0.98, 1.35) | 0.0956 |
| | 1-3 | 7790(71.66) | | ref | |
| | >3 | 1093(10.05) | | 1.30 (1.06, 1.58) | 0.0116 |
| **Biomarkers** | | | | | |
| 25(OH)D | 20 nmol/L | 93.70(38.35) | 1206(11.03) | 1.03 (1.00, 1.07) | 0.0685 |
| Albumin | g/L | 39.71(2.70) | 1205(11.02) | 0.98 (0.95, 1.00) | 0.0617 |
| Creatinine | 20 umol/L | 71.98(17.36) | 1205(11.02) | 1.06 (1.00, 1.12) | 0.0715 |
| hs-CRP | <3 mg/L | 7184(73.87) | 1205(11.02) | ref | |
| | >=3 | 2541(26.13) | | 1.13 (0.97, 1.31) | 0.1110 |
| Ferritin | 30 ug/L | 114.94(95.22) | 1214(11.11) | 1.02 (1.00, 1.04) | 0.0299 |
| eGFR | mL/min/1.73m2 | 83.69(15.12) | 1205(11.02) | 0.99 (0.99, 1.00) | 0.0030 |
| HbA1c | percent | 5.56(0.64) | 1291(11.81) | 1.10 (1.00, 1.21) | 0.0481 |
| HDL-c | mmol/L | 1.69(0.48) | 1205(11.02) | 1.04 (0.91, 1.20) | 0.5702 |
| Hemoglobin | >=115 g/L | 8900(97.16) | 1770(16.19) | ref | |
| | <115 | 260(2.84) | | 1.59 (1.12, 2.25) | 0.0100 |
| Triglycerides | mmol/L | 1.64(0.88) | 1205(11.02) | 1.08 (1.00, 1.16) | 0.0417 |
| **BMD and related measures** | | | | | |
| Total fat mass percentage | percent | 38.94(6.19) | 429(3.92) | 1.02 (1.00, 1.03) | 0.0070 |
| Total lean mass percentage | percent | 61.06(6.19) | 429(3.92) | 0.99 (0.98, 1.00) | 0.0070 |
| Lean mass index | kg/m2 | 16.79(2.37) | 429(3.92) | 1.00 (0.97, 1.03) | 0.8361 |
| Appendage lean mass index | kg/m2 | 6.86(1.06) | 429(3.92) | 0.98 (0.92, 1.04) | 0.4798 |
| Appendage pure lean mass index | kg/m2 | 6.46(1.03) | 429(3.92) | 0.99 (0.93, 1.06) | 0.8000 |

| | | | | | |
|---|---|---|---|---|---|
| BMC pelvic | 50 grams | 218.35(57.11) | 429(3.92) | 0.81 (0.76, 0.86) | <.0001 |
| BMD left arm | 0.1 g/cm2 | 0.70(0.08) | 429(3.92) | 0.67 (0.61, 0.74) | <.0001 |
| BMD right arm | 0.1 g/cm2 | 0.71(0.07) | 429(3.92) | 0.66 (0.60, 0.73) | <.0001 |
| BMD lumbar spine | 0.1 g/cm2 | 1.00(0.19) | 429(3.92) | 0.89 (0.85, 0.93) | <.0001 |
| BMD pelvic | 0.1 g/cm2 | 1.19(0.18) | 429(3.92) | 0.89 (0.85, 0.93) | <.0001 |
| BMD left leg | 0.1 g/cm2 | 1.11(0.17) | 429(3.92) | 0.89 (0.85, 0.93) | <.0001 |
| BMD right leg | 0.1 g/cm2 | 1.12(0.16) | 429(3.92) | 0.87 (0.83, 0.91) | <.0001 |
| BMD nondominant arm | 0.1 g/cm2 | 0.70(0.08) | 429(3.92) | 0.66 (0.60, 0.72) | <.0001 |
| BMD T-score total hip | 1 | -0.55(1.04) | 693(6.33) | 0.71 (0.67, 0.76) | <.0001 |

**Table 4.4** Primary Model A

| | | complete case (n=9274) | | | | multiple imputation (n=109300) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | unit/ group | OR | lower limit | upper limit | p-value | OR | lower limit | upper limit | p-value |
| **Age** | 55-64 vs 45-54 | 1.36 | 1.12 | 1.65 | 0.0020 | 1.32 | 1.10 | 1.59 | 0.0029 |
| | 65-74 vs 45-54 | 1.56 | 1.25 | 1.94 | <.0001 | 1.51 | 1.23 | 1.86 | <.0001 |
| | >=75 vs 45-54 | 1.53 | 1.18 | 1.98 | 0.0015 | 1.53 | 1.20 | 1.96 | 0.0006 |
| **Alcohol consumption in the past year** | Yes vs No | 0.76 | 0.63 | 0.92 | 0.0046 | 0.79 | 0.67 | 0.95 | 0.0101 |
| **Antidepressants** | currently taking vs no | 1.29 | 1.08 | 1.55 | 0.0060 | 1.20 | 1.01 | 1.42 | 0.0417 |
| **Asthma** | Yes vs No | / | / | / | / | 1.22 | 1.03 | 1.45 | 0.0233 |
| **Balance** | Impaired vs No | 1.35 | 1.10 | 1.65 | 0.0041 | 1.36 | 1.13 | 1.63 | 0.0009 |
| **Epilepsy** | Yes vs No | 2.18 | 1.28 | 3.73 | 0.0043 | 2.02 | 1.23 | 3.33 | 0.0055 |
| **Hand grip strength** | kg | 0.97 | 0.96 | 0.99 | <.0001 | 0.97 | 0.96 | 0.99 | 0.0001 |
| **Height** | cm | 1.03 | 1.01 | 1.04 | <.0001 | 1.03 | 1.02 | 1.04 | <.0001 |
| **Osteoarthritis** | Yes vs No | 1.19 | 1.02 | 1.39 | 0.0234 | 1.16 | 1.00 | 1.34 | 0.0442 |
| **Other comorbidities** | Yes vs No | / | / | / | / | 1.40 | 1.03 | 1.91 | 0.0328 |
| **Parent hip fracture after age 50** | Yes vs No | 1.30 | 1.08 | 1.57 | 0.0045 | 1.34 | 1.12 | 1.61 | 0.0016 |
| **Personal history of fall in the past 12 months** | Yes vs No | 1.78 | 1.47 | 2.15 | <.0001 | 1.69 | 1.42 | 2.01 | <.0001 |
| **Polypharmacy** | currently taking 1-2 medications vs 0 | / | / | / | / | 1.38 | 1.06 | 1.80 | 0.0178 |
| | currently taking >=3 medications vs 0 | / | / | / | / | 1.22 | 0.95 | 1.57 | 0.1127 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Smoking** | Occasionally or former vs Never | 1.22 | 1.05 | 1.43 | 0.0112 | 1.17 | 1.02 | 1.35 | 0.0280 |
| | Daily vs Never | 1.63 | 1.23 | 2.16 | 0.0008 | 1.51 | 1.16 | 1.96 | 0.0020 |
| **Weight change in the past 6 months** | Gained vs Same | / | / | / | / | 1.07 | 0.89 | 1.27 | 0.4802 |
| | Lost vs Same | / | / | / | / | 1.20 | 1.02 | 1.41 | 0.0320 |

**Table 4.5** Extended Model B

| | | complete case (n=8811) | | | | multiple imputation (n=109300) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | unit/ group | OR | lower limit | upper limit | p-value | OR | lower limit | upper limit | p-value |
| **Antidepressants** | currently taking vs no | 1.31 | 1.08 | 1.58 | 0.0051 | 1.20 | 1.01 | 1.42 | 0.0426 |
| **Asthma** | Yes vs No | / | / | / | / | 1.22 | 1.02 | 1.44 | 0.0260 |
| **Balance** | Impaired vs No | 1.31 | 1.06 | 1.62 | 0.0125 | 1.30 | 1.08 | 1.57 | 0.0048 |
| **BMD T-score total hip** | 1 | 0.68 | 0.62 | 0.73 | <.0001 | 0.69 | 0.64 | 0.75 | <.0001 |
| **Epilepsy** | Yes vs No | 2.12 | 1.21 | 3.70 | 0.0084 | 1.93 | 1.17 | 3.20 | 0.0103 |
| **Hand grip strength** | kg | 0.98 | 0.96 | 0.99 | 0.0009 | 0.98 | 0.97 | 0.99 | 0.0013 |
| **Height** | cm | 1.03 | 1.02 | 1.04 | <.0001 | 1.03 | 1.02 | 1.04 | <.0001 |
| **Muscle exercise in the past 7 days** | 0-0.5 vs 0 daily hours | / | / | / | / | 1.21 | 1.01 | 1.46 | 0.0424 |
| | >=0.5 vs 0 daily hours | / | / | / | / | 0.97 | 0.81 | 1.18 | 0.7887 |
| **Osteoarthritis** | Yes vs No | 1.25 | 1.07 | 1.47 | 0.0052 | 1.20 | 1.05 | 1.39 | 0.0100 |
| **Parent hip fracture after age 50** | Yes vs No | 1.26 | 1.03 | 1.53 | 0.0219 | 1.24 | 1.04 | 1.48 | 0.0177 |
| **Personal history of fall in the past 12 months** | Yes vs No | 1.79 | 1.47 | 2.18 | <.0001 | 1.66 | 1.39 | 1.98 | <.0001 |
| **Polypharmacy** | currently taking 1-2 medications vs 0 | / | / | / | / | 1.38 | 1.05 | 1.80 | 0.0188 |
| | currently taking >=3 medications vs 0 | / | / | / | / | 1.24 | 0.97 | 1.59 | 0.0852 |
| **Smoking** | Occasionally or former vs never | / | / | / | / | 1.16 | 1.01 | 1.34 | 0.0398 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Daily vs never | / | / | / | / | 1.35 | 1.04 | 1.76 | 0.0240 |
| **Waist circumference** | cm | 1.02 | 1.01 | 1.02 | <.0001 | 1.01 | 1.01 | 1.02 | <.0001 |
| **Weight change in the past 6 months** | Gained vs Same | / | / | / | / | 1.08 | 0.91 | 1.29 | 0.3725 |
| | Lost vs Same | / | / | / | / | 1.20 | 1.01 | 1.42 | 0.0339 |

**Table 4.6** Model Performance

| | AUC | lower limit | upper limit | sensitivity | specificity |
|---|---|---|---|---|---|
| BMD T-score | 0.60 | 0.58 | 0.61 | 3.50% | 98.04% |
| Primary Model A | 0.63 | 0.61 | 0.65 | 80.49% | 34.61% |
| Extended Model B | 0.65 | 0.63 | 0.67 | 80.17% | 38.86% |

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# Appendices

## **Appendix 1** Literature Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to September 19, 2024>

1 exp *Menopause/ or exp *Postmenopause/ 32747
2 (postmenopaus* or perimenopaus* or premenopaus* or post menopaus* or post-menopaus* or menopaus* or early menopaus*).mp. 136638
3 1 or 2 136638
4 exp *Women/ 31083
5 (female or woman or women).mp. 10338229
6 4 or 5 10338229
7 limit 6 to "middle aged (45 plus years)" 4457678
8 3 or 7 4520903
9 exp *Risk Assessment/ or exp *Risk Factors/ or exp *Risk Adjustment/ 38002
10 (risk assessment* or risk factor* or risk management or risk adjustment* or risk model* or risk reduction* or fracture risk* or fracture prediction* or fracture prevention).mp. 1790729
11 9 or 10 1791009
12 fracture*.mp. 381555
13 exp *Cohort Studies/ or exp *Longitudinal Studies/ or exp *Case-Control Studies/ 6066
14 (cohort stud* or longitudinal stud* or case-control stud* or case control stud*).mp. 1126973
15 13 or 14 1128301
16 8 and 11 and 12 and 155732
17 limit 16 to (humans and english) 5594

Embase <1974 to 2024 September 20>

1 exp *menopause/ or exp *early menopause/ or exp *postmenopause/ 49631
2 (postmenopaus* or perimenopaus* or premenopaus* or post menopaus* or post-menopaus* or menopaus* or early menopaus*).mp. 224300
3 1 or 2 224300
4 exp *female/ 144601
5 (female or woman or women).mp. 12762857
6 4 or 5 12766511

7 exp *middle aged/ or exp *aged/ 52453
8 6 and 7 17720
9 3 or 8 241615
10 exp *risk factor/ or exp *risk assessment/ or exp *risk model/ or exp *risk reduction/ or exp *fracture risk assessment/239550
11 (risk assessment* or risk factor* or risk management or risk adjustment* or risk model* or risk reduction* or fracture risk* or fracture prediction* or fracture prevention).mp.2655650
12 10 or 11 2655842
13 exp *fracture/ 199093
14 fracture*.mp. 497034
15 13 or 14 499761
16 exp *cohort analysis/ or exp *longitudinal study/ or exp *case control study/ 69218
17 (cohort stud* or longitudinal stud* or case-control stud* or case control stud*).mp. 1045401
18 16 or 17 1058568
19 9 and 12 and 15 and 18 1194
20 limit 19 to (human and english) 1116

**Appendix 2** Characteristics of Included Studies

| first author | country of study | origin of participants | study design | sample size | percentage of female participants | menopause status | Mean (SD)/ median (IQR) age | Follow-up duration |
|---|---|---|---|---|---|---|---|---|
| Abrahamsen, 2003 | Denmark | DOPS | cohort | 869 | 100 | peri, post | 49.9 (2.9) | 5 years |
| Afrin, 2020 | Finland | OSTPRE | cohort | 8744 | 100 | post | 62.2(2.9) | 5 years |
| Ahmadi-Abhari, 1993 | UK | EPIC – Norfolk cohort | cohort | 18586 | 55.3 | pre, peri, post | case 63.8(8.8)/ non case 58.5(9.1) | 14.8(13.6-16.1) |
| Ahmeidat, 2021 | UK | EPIC – Norfolk cohort | cohort | 10526 | 100 | pre, peri, post | exposed 56.7(8.8)/ not exposed 58.7(9.2) | up to 23 years |
| Ahn, 2014 | South Korea | NR | cohort | 2769 | 100 | pre, post | 56.7(6.9) | 11 |
| Amouzegar, 2021 | Iran | TLGS | cohort | 396 | 100 | post | 45.9(11.5) | 15.9(11.8-16.5) |
| Appleby, 2008 | UK | EPIC - Oxford cohort | cohort | 9166 | 100 | post | NR | 5 years |
| Ardawi, 2018 | Saudi Arabia | CEOR | cohort | 707 | 100 | post | Case 67.6(7.1)/ non case 59.4(5.7) | 5.2(1.3) |

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|---|---|---|---|---|---|---|---|---|
| Axelsson, 2022 | Sweden | NR | cohort | 336804 | 50.1 | post | 80.9(8.1) | 1 year |
| Bach-Mortensen, 2006 | Denmark | CCHS | case control | 1370 | 100 | post | 65.1(8.8) | 6.1 years |
| Bae, 2016 | South Korea | NR | cohort | 248 | 100 | post | 58.4(6.3) | 3.7(1.2) |
| Banefelt, 2022 | Sweden | NR | cohort | 11973 | 100 | post | 68.2(8.5) | 2 years |
| Barad, 2005 | US | WHI | cohort | 80947 | 100 | post | exposed 60(6.5)/ not exposed 65.9(6.9) | 2.5(1.2) years |
| Black, 1999 | US | SOF | cohort | 9575 | 100 | post | 69.8 | 8.3 years |
| Black, 1992 | US | SOF | cohort | 8134 | 100 | post | 71.4 | 0.72 years |
| Buchebner, 2014 | Sweden | OPRA - Malmö cohort | cohort | 1011 | 100 | post | 75.2(0.1) | 13.1 years |
| Carbone, 2010 | US | WHI | cohort | 138667 | 100 | post | 63.22(7.19) | 7.7 years |
| Carriere, 2016 | France | NR | cohort | 6811 | 59.58 | post | case 74(71-78)/ non case 73(69-77) | 3.6 (3.4-3.8) |

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|---|---|---|---|---|---|---|---|---|
| Castano-Betancourt, 2013 | the netherlands | Rotterdam Study | cohort | 5006 | 56.7 | post | 67.6 | 9.6 years |
| Cauley, 2017 | US | WHI Observational Study | case control | 2232 | 100 | post | 64.5 | 8.6 years |
| Cauley, 2015 | US | SWAN | cohort | 1756 | 100 | pre, peri | 48.5(2.7) | 9.5(2.62) years |
| Cauley, 2012 | US | SWAN | cohort | 2305 | 100 | pre, peri | 45.7(2.7) | 7.6(1.6) years |
| Cauley, 2009 | US | SOF | cohort | 8224 | 100 | post | 71.2 | 8 years |
| Cauley, 2005 | US | SOF | cohort | 7334 | 100 | post | 73.4 | 6.1 (1.5) |
| Cauley, 1995 | US | SOF | cohort | 9568 | 100 | post | 71.7 | 4.6 years |
| Chan, 2000 | US | health maintenance organisations | case control | 3675 | 100 | post | 76.1 | NR |
| Chang, 2016 | US | SWAN | cohort | 2062 | 100 | pre, peri | 46(44-48) | 2-5 years |
| Charles, 2023 | Belgium | FRISBEE | cohort | 3299 | 100 | post | 69.1(64.6-75.2) | 9.1(7.2-10.6) years |
| Chen, 2018 | the Netherlands | LASA | cohort | 1477 | 51.6 | post | 75.8(6.6) | 6 years |
| Chen, 2010 | US | WHI | cohort | 160080 | 100 | post | 63.2(7.2) | 7.8 years |
| Coleman, 2009 | US | SOF | cohort | 4773 | 100 | post | 79.3 | 8.1 (2.7) years |

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|---|---|---|---|---|---|---|---|---|
| Colon-Emeric, 2002 | US | EPESE Duke and Iowa | cohort | 4149 | 65 | post | 73.4(6.7) | 10 years |
| Compston, 2000 | Multiple | GLOW | cohort | 40179 | 100 | post | 68(8.3) | up to 5 years |
| Cooper, 1997 | US | Menstruation and Reproductive History Study | cohort | 832 | 100 | post | 73 (range 63-81) | NR |
| Cui, 2022 | China | SWHS | cohort | 36613 | 100 | post | 61.4 (range 43.3-76.7) | 10.1(9.3-11) years |
| Daya, 2022 | US | ARIC | cohort | 10946 | 54.3 | pre, post | 57(5.7) | 21(13-27.3) years |
| deBoer , 2004 | the netherlands | LASA | cohort | 1453 | 51.7 | post | 75.8 | 3 years |
| Dennison, 2014 | UK | Hertfordshire Cohort Study | cohort | 202 | 100 | post | 75.8(2.6) | 5 years |
| Dennison, 2012 | multiple | GLOW | cohort | 40614 | 100 | post | NR | 2 years |
| Dhonukshe-Rutten, 2005 | the Netherlands | LASA | cohort | 651 | 100 | post | 75.4(6.5) | 3 years |
| Diem, 2011 | US | SOF | cohort | 8217 | 100 | post | 77 | 7.93(4.64) years |
| Diez-Perez, 2007 | Spain | NR | cohort | 5146 | 100 | post | 72.3(5.4) | 2.83 (0.73) |
| Ding, 2014 | US | PACE | cohort | 25276 | 78.3 | post | 78.6 | 3 years |

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|---|---|---|---|---|---|---|---|---|
| Domiciano, 2021 | Brazil | SPAH | cohort | 449 | 100 | post | 72.9 | 4.3(0.8) years |
| Edwards, 2013 | UK | Hertfordshire Cohort Study | cohort | 388 | 100 | post | 66.6(2.7) | 5.0(1.1) years |
| Engel, 2011 | France | E3N | cohort | 70182 | 100 | post | 53.8(4.5) | 11.5(4.4) years |
| Ensrud, 2012 | US | WHI | case control | 790 | 100 | post | 66.2(7.3) | 8.60(1.61) years |
| Feart, 2013 | France | 3C | cohort | 1435 | 62.9 | post | 76 | 4.64(1.72) years |
| FitzGerald, 2012 | multiple | GLOW | cohort | 54229 | 100 | post | 71 | 3 years |
| Gafoor, 2019 | UK | CPRD | cohort | 153304 | 61.3 | post | 83 | 681,221.1 person-years |
| Gardsell, 1991 | Sweden | NR | cohort | 488 | 100 | post | 60 | NR |
| Garnero, 2002 | France | OFELY | cohort | 408 | 100 | post | 64.5 | 5.9(2) years |
| Ginsberg, 2021 | US | Health ABC | cohort | 786 | 52 | post | 75 | 10(5) years |
| Gnudi, 2000 | Italy | NR | cohort | 254 | 100 | post | 58.06(7.67) | 5.47(1.05) years |
| Gregson, 2014 | multiple | GLOW | cohort | 43832 | 100 | post | NR | 3 years |

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|---|---|---|---|---|---|---|---|---|
| Hansen, 2000 | US | Iowa Women's Health Study | cohort | 34703 | 100 | post | 61.6 | 6.5 years |
| Hars , 2016 | Switzerland | GERICO | cohort | 913 | 79.9 | post | 65.0(1.4) | 3.4(0.9) years |
| Harslof, 2013 | Denmark | DOPS | cohort | 1717 | 100 | peri | 50.6 | 10 years |
| Heesch, 2008 | Australia | Australian Longitudinal Study on Women's Health | cohort | 8188 | 100 | post | NR | fx in the 15th year from baseline |
| Helte, 2021 | Sweden | SMC–Clinical | cohort | 3478 | 100 | post | 67.7 | 9.3 years |
| Holloway, 2015 | Australia | GOS | cohort | 870 | 100 | post | NR | NR |
| Huang, 1998 | US | Hawaii Osteoporosis Study | cohort | 251 | 100 | post | 73.7(4.9) | 2.7(0.6) years |
| Hundrup, 2004 | Denmark | Danish Nurse Cohort Study | cohort | 7082 | 100 | post | NR | 40190 person-years |
| Huopio, 2004 | Finland | OSTPRE | cohort | 422 | 100 | pre, post | 59.6(3) | 2.6(0.7) years |
| Huopio, 2000 | Finland | OSTPRE | cohort | 3068 | 100 | peri | 53.4 | 3.6(0.78) years |
| Huopio, 2000 | Finland | OSTPRE | cohort | 3068 | 100 | peri | 53.4 | 3.6(0.78) years |

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|---|---|---|---|---|---|---|---|---|
| Hussain, 2023 | Australia and US | ASPREE clinical trial and ASPREE fracture substudy | cohort | 8945 | 100 | post | 75(4) | 4.0(0.02-7.0) years |
| Jacqmin-Gadda, 1998 | France | Paquid cohort study on mental and physical aging | cohort | 3216 | 57.9 | post | 74.8(6.7) | 5 years |
| Jaiswal, 2023 | Sweden | SUPERB | cohort | 2778 | 100 | post | 77.8(1.6) | 6.4(5.7-7.3) years |
| Jaiswal, 2023 | Sweden | SUPERB | cohort | 647 | 100 | post | 77.2(1.4) | 6.0(5.5-6.4) years |
| Jiajue, 2019 | China | PK-VF | cohort | 982 | 100 | post | 62(15) | 5.2(1.0) years |
| Jorgensen, 2011 | Norway | Tromsø Study | cohort | 3947 | 100 | post | 67.2 | 7.6 years (range 4 days -10.3 years) |
| Julian, 2016 | UK | EPIC Norfolk cohort | cohort | 14624 | 55.7 | pre, peri, post | 62.1 | 15(2.3) years |
| Kamiya, 2019 | Japan | JPOS | cohort | 1342 | 100 | post | 63.4(8.5) | 15.2(10.1-15.4) years |

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|---|---|---|---|---|---|---|---|---|
| Karkkainen, 2008 | Finland | OSTPRE | cohort | 2928 | 100 | post | 59.1(2.9) | 8.37 (range 6.43-9.86) years |
| Kato, 2000 | US | New York University Women's Health Study | cohort | 5817 | 100 | post | 58.1 | 8.6 (range 0-12.4) years |
| Kim, 2022 | US | SOF | cohort | 9704 | 100 | post | 71.9(5.3) | up to 4 months |
| Kim, 2020 | Korea | NHIS | case control | 65262 | 100 | post | 74 | up to 3 years |
| Kojima, 2023 | Japan | JPOS | cohort | 1414 | 100 | post | 63.3(8.6) | 15.1(10.1-15.4) years |
| Kojima, 2020 | Japan | JPOS | cohort | 1417 | 100 | post | 63.5(8.4) | 15.2(10.1-15.4) years |
| Kuchuk, 2007 | the Netherlands | LASA | cohort | 634 | 100 | post | 75.5(6.6) | 6 years |
| Lafferty, 1994 | US | NR | cohort | 157 | 100 | post | 53.6 | 11.5 years |
| Lai, 2013 | Taiwan | NHI | cohort | 41426 | 100 | pre, post | 65.1 | 6.4 years |
| LaMonte, 2019 | US | WHI | cohort | 77206 | 100 | post | 63.4(7.3) | 14.0(5.2) years |

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|---|---|---|---|---|---|---|---|---|
| Lasschuit, 2020 | Australia | DOES | cohort | 809 | 50 | post | 71 (68–76) | 15.5(8.0-21.0) years |
| Lauppe, 2019 | Sweden | NORD | cohort | 17815 | 100 | post | 68.7 | 66695 person years |
| Lee, 2019 | Korea | NHIS - National Health Screening | cohort | 37857 | 100 | post | 70.4 | 8 years |
| Lee, 2018 | US | NR | cohort | 507 | 54.6 | post | 73.4(6.3) | 5.8(2.1-11.0) years |
| Lee, 2015 | US | WHI clinical trials | cohort | 68125 | 100 | post | 61.7 | 8.1 years |
| Lee, 2010 | Korea | KHGS | cohort | 4619 | 100 | pre, post | 52.2 | 46.3(2.2) months |
| Leslie, 2013 | Canada | Manitoba Bone Density Program | cohort | 29407 | 100 | post | 65.4(9.4) | 4.7 years |
| Lewis, 2019 | Australia | PLSA | cohort | 1024 | 100 | post | 75.0(2.6) | 10 years |
| Lewis, 2014 | Australia | CAIFOS | cohort | 1025 | 100 | post | 79.9(2.6) | 5 years |
| Liang, 2023 | China | PK-VF | cohort | 754 | 100 | post | 63.7(13.0) | 5 years |
| Looker, 2013 | US | NHANES III | cohort | 2316 | 100 | post | 73.5 | up to 10 years |
| Lui, 2024 | Hong Kong | electronic health records | cohort | NR | 54.1 | post | NR | 11 months |

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| | | of the Hong Kong Hospital Authority | | | | | | |
| Lundin, 2016 | Sweden | PRIMOS | cohort | 351 | 100 | post | 72.8(2.31) | 10.1 years |
| Malmgren, 2020 | Sweden | OPRA | cohort | 981 | 100 | post | 75.2(0.1) | 10.4(8.8) years |
| Mei, 2021 | UK | UK Biobank | cohort | 190816 | 53.9 | post | NR | 8.1(7.4-8.8) years |
| Meier, 2000 | UK | UK based GPRD | case control | 13068 | 75 | post | NR | NR |
| Meisinger, 2007 | Germany | MONICA | cohort | 1793 | 46.7 | post | 62 | 10.7 years |
| Melton, 2007 | US | Rochester Epidemiology Project | cohort | 18516 | 100 | post | 46.2(12.5) | 13.6 years |
| Melton, 2003 | US | Rochester Epidemiology Project | cohort | 225 | 100 | post | 68.0(13.6) | 16.2 years (range 54 days to 20.6 years) |
| Michaelsson, 2014 | Sweden | SMC | cohort | 61433 | 100 | pre, post | 53.7 | 20.1 years |
| Mitama, 2017 | Japan | Hiroshima Atomic Bomb Casualty Council | cohort | 3771 | 100 | post | 68.3(7.5) | 7.4 years |

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|---|---|---|---|---|---|---|---|---|
| Moberg, 2022 | Sweden | MDCS | cohort | 12018 | 100 | pre, post | 56 | 13.8 (9.3-18.2) years |
| Moberg, 2014 | Sweden | WHILA | cohort | 6416 | 100 | post | 56.4 (range 50-64) | 14.4 years |
| Moberg, 2013 | Sweden | WHILA | cohort | 3363 | 100 | post | 56.8 (50-64) | 8.4 years |
| Morseth, 2012 | Norway | Tromsø Study | cohort | 4072 | 100 | post | 66.7(8.2) | 11.6 (IQR 9.4) years |
| Muka, 2415 | the Netherlands | Rotterdam Study | cohort | 5074 | 61.5 | post | 70.3(9.1) | 10.9 years |
| Nakamura, 2011 | Japan | NR | cohort | 751 | 100 | post | 74.5 | 5.5 years |
| Nakamura, 2011 | Japan | NR | cohort | 773 | 100 | post | 74.6(4.4) | 5.5 years |
| Naves, 2005 | Spain | EVOS | cohort | 250 | 100 | pre, post | 65(9) | 8 years |
| Nevitt, 1994 | US | SOF | cohort | 8966 | 100 | post | 72(5) | 4.9(1.0) years |
| Nguyen, 2007 | Australia | DOES | cohort | 924 | 100 | post | 69 | 10 years |
| Nguyen, 2004 | Australia | DOES | cohort | 549 | 100 | post | 65.2(12.3) | NR |
| Nguyen, 1993 | Australia | DOES | cohort | 1080 | 100 | post | 69.2(6.6) | up to 5 years |
| Nikander, 2011 | Australia | AusDiab | cohort | 2780 | 100 | post | 60.3 | up to 5 years |

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|---|---|---|---|---|---|---|---|---|
| Nordstrom, 2019 | Sweden | Prescribed Drug Registry | cohort | 216614 | 57.5 | post | 69.2(9.9) | up to 1 year |
| Ojo, 2007 | US | EPESE hispanic | cohort | 2621 | 58.6 | post | 72.4 | 7 years |
| Ostbye, 2004 | Canada | CSHA | cohort | 3381 | 100 | post | 78(6) | fracture in the 5th-6th year |
| Otonari, 2021 | Japan | Kyushu University Fukuoka Cohort Study | cohort | 4427 | 100 | post | 61.8(6.2) | 5.3 years |
| Pan, 2014 | Taiwan | NHI research database | case control | 19087 | 100 | post | 74.8 | 1 year |
| Papaioannou, 2005 | Canada | CaMos | cohort | 5143 | 100 | post | 66.6 | 3 years |
| Paskins, 2018 | UK | CPRD | cohort | 119039 | 49.1 | post | 58.9 | 11.4 years |
| Paskins, 2018 | UK | CPRD | cohort | 58374 | 69.5/71.3 | post | 71.6 | 9.5 years |
| Piirtola, 2008 | Finland | Lieto Study | cohort | 695 | 100 | post | 73.8(7.0) | 12 years |
| Popp, 2016 | Switzerland | SEMOF | cohort | 556 | 100 | post | 76.1(3.0) | 2.7(0.8) years |
| Porthouse, 2004 | UK | NR | cohort | 4292 | 100 | post | 76.9(5.14) | up to 24 months |
| Prieto-Alhambra, 2013 | multiple | GLOW | cohort | 51386 | 100 | post | 68.2(8.6) | 2.9 (2.1-3.0) years |
| Randell, 2002 | Finland | OSTPRE | cohort | 7217 | 100 | post | 53.3(2.7) | 5 years |

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|---|---|---|---|---|---|---|---|---|
| Rees-Punia, 2023 | US | CPS II and CPS II Nutrition Cohort | cohort | 92431 | 56.1 | post | NR | 1 year |
| Rejnmark, 2011 | Denmark | DOPS | cohort | 1011 | 100 | peri, post | 51(45-57) | 16 years |
| Rejnmark, 2004 | Denmark | DOPS | case control | 2016 | 100 | peri, post | 50 | 5 years |
| Riis, 1996 | NR | NR | cohort | 182 | 100 | post | 51 | 15 years |
| Rousseau, 2014 | France | OFELY | cohort | 607 | 100 | post | 66.6(8.4) | 7(6.8-7.1) years |
| Rouzi, 2012 | Saudi Arabia | CEOR | cohort | 707 | 100 | post | 61.3(7.2) | 5.2(1.3) years |
| Schuit, 2004 | the Netherlands | Rotterdam Study | cohort | 3357 | 100 | post | 68.3 | 6.8(2.3) years |
| Schwartz, 2001 | US | SOF | cohort | 9654 | 100 | post | 71.7 | 9.4(2.4) years |
| Shen, 2018 | china | CKB | cohort | 453625 | 60 | pre, post | 51.4(10.6) | 10.1 years |
| Shieh, 2023 | US | SWAN | cohort | 1690 | 100 | pre, post | 49.7(3.1) | 12(6) years |
| Shieh, 2023 | US | SWAN | cohort | 539 | 100 | pre, peri | 55.7(2.8) | 14.6 (range 0.8 to 22.8) years |
| Shieh, 2022 | US | SWAN | cohort | 1554 | 100 | pre, peri | 46.5(2.7) | 22 years |

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|---|---|---|---|---|---|---|---|---|
| Shieh, 2020 | US | SWAN | cohort | 484 | 100 | pre, peri | 53.4(2.4) at first follow up visit after MT | NR |
| Sim, 2018 | Australia | PLSA in women | cohort | 1429 | 100 | post | 75.2(2.7) | 10.9(4.2) years |
| Siris, 2006 | US | NORA | cohort | 59017 | 100 | post | NR | 36 (range 10-46) months |
| Sirola, 2008 | Finland | OSTPRE | cohort | 687 | 100 | peri, post | 53.3(2.9) | 15 years |
| Sornay-Rendu, 2017 | France | OFELY | cohort | 595 | 100 | post | 66(8) | 13.1(1.9) |
| Sornay-Rendu, 2014 | France | OFELY | cohort | 790 | 100 | pre, post | 58.7 | 19.9(2.9) years |
| Sornay-Rendu, 2005 | France | OFELY | cohort | 671 | 100 | post | 62.2(9) | 11.2(1.1) years |
| Spangler, 2008 | US | WHI Observational Study | cohort | 82410 | 100 | post | 64 | 7.4 years |
| Steinbuch, 2004 | US | Market Scan database | cohort | 5832 | 100 | post | NR | 1 year |
| Stel, 2004 | the Netherlands | LASA | cohort | 1477 | 51.6 | post | 75.8(6.6) | 3 years |
| Stumpf, 2020 | UK | IQVIA Disease Analyzer database | cohort | 8230 | 100 | post | 68.6(9.4) | 5 years |

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|---|---|---|---|---|---|---|---|---|
| Svejme, 2013 | Sweden | NR | cohort | 390 | 100 | pre, post | 48.3 | 25.9 years |
| Swanberg, 2012 | Sweden | OPRA | cohort | 1006 | 100 | post | 75.2(0.1) | 5 years |
| Tanaka, 2011 | Japan | Nagano Cohort Study | cohort | 765 | 100 | post | 63.3(10.8) | 5.1 years |
| Tanaka , 2014 | Japan | Nagano Cohort Study | cohort | 1470 | 100 | post | 63.7 | 7.2 years |
| Tanislav, 2020 | Germany | IQVIA Disease Analyzer database | cohort | 24530 | 48.1 | post | 67.3(13.5) | 5 years |
| Thong, 2021 | australia | ALSWH | cohort | 11313 | 100 | pre, post | 47 | 13.5 years |
| Tolea, 2007 | US | EPESE hispanic | cohort | 1350 | 100 | post | 75 | 7 years |
| Torekov, 2014 | Denmark | DOPS | cohort | 1424 | 100 | peri | 50.6 | 16 years |
| Torgerson, 1996 | UK | CHI | cohort | 1857 | 100 | pre, post | NR | 2 years |
| Tranah, 2008 | US | SOF | cohort | 6752 | 100 | post | 71.7(5.3) | 14.5 years |
| Tsai, 2014 | Taiwan | NHI research database | cohort | 151675 | 50.13 | pre, post | 51.11(9.83) | 10 years |
| Tuppurainen, 1995 | Finland | OSTPRE | cohort | 3140 | 100 | peri | 53.4(2.8) | 2.4 years (range 2 days to 3.4 years) |

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|---|---|---|---|---|---|---|---|---|
| Uitterlinden, 2001 | the netherlands | The Rotterdam Study | cohort | 1004 | 100 | post | 67.1 | 3.8 years |
| vanderHoorn, 2015 | Australia | ALSWH | cohort | 4432 | 100 | post | 78.2 | 7.6 years |
| vanGeel, 2007 | the Netherlands | NR | cohort | 2372 | 100 | post | 61.6(6.8) | 10 years |
| vanMeurs, 2004 | the Netherlands | LASA | cohort | 2406 | 53.7 | post | 73.9 | 4.65 years |
| Vestergaard, 2012 | Denmark | DOPS | cohort | 2016 | 100 | peri, post | 50.6 | 6.5 (0.5) years |
| Vestergaard, 2006 | Denmark | National Hospital Discharge Register and the Civil Registration System | case control | 258189 | 100 | post | NR | up to 5 years |
| Viniol, 2016 | Germany | Health Risk Institute research database | cohort | 414115 | 100 | post | 71.4 | 5 years |
| Wagner, 2009 | Sweden | Swedish Twin Registry | cohort | 343 | 100 | post | 64.9(7.8) | 5-7 years |

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|---|---|---|---|---|---|---|---|---|
| Wilczek, 2021 | Sweden | general mammography screening program | cohort | 14841 | 100 | pre, post | 53.1 | 48011 person years |
| Xin, 2024 | US | FHS | cohort | 1772 | 57.7 | post | NR | 17.1(8.6) years |
| Yazdanpanah, 2007 | the netherlands | the Rotterdam Study | cohort | 3374 | 100 | post | 68.3(8.2) | 7.4(3.3) years |
| Yeh, 2016 | Taiwan | LHID | cohort | 19832 | 30.3 | post | NR | 7.65 years |
| Yenchek, 2012 | US | Health ABC | cohort | 2167 | 50 | post | 73.5(2.9) | 11.3 years |
| Yoo, 2021 | Korea | NHIS | cohort | 1272115 | 100 | post | 61(8.1) | 8.3(8-8.6) years |
| Yu, 2008 | US | SOF | cohort | 5339 | 100 | post | 79 | 7.6 years |
| Zhou, 2014 | China | NR | cohort | 1724 | 100 | post | 69.3(9.3) | 5 years |
| Zoulakis, 2024 | Sweden | SUPERB | cohort | 3008 | 100 | post | 77.8 | 7.3 (4.4-8.4) years |

**Appendix 3** Anthropometric Factors and Fractures

| first author | fracture site | factor, detail | comparison (exposed vs unexposed) | effect measure | effect size | adjusted for |
|---|---|---|---|---|---|---|
| Charles, 2023 | fragility excluding toes, fingers or nose | age, / | per year | OR | 1.03 (1.02, 1.04) | Age, history of fall, history of fracture, corticoids use, osteoporosis treatment and BMD |
| Domiciano, 2021 | nonvertebral | age, / | each 10-year increase | RR | 2.07 (1.13, 3.82) | age, weight, BMI, prevalence of any osteoporotic fracture, prevalence of non-vertebral fracture, eGFR, BMD at lumbar spine, BMD at femoral neck, BMD at total hip |
| FitzGerald, 2012 | major | age, / | per 10 years | HR | 1.5 (NR, NR) | age, weight, BMI, any baseline fracture, maternal hip fracture, paternal hip fracture, current smoker, weight loss in 12 months, falls in past year, comorbidities, general health, physical activity, drinks/week) |
| Jacqmin-Gadda, 1998 | nonhip | age, / | 75-84 vs 65-74 | OR | 1.50 (1.13, 2.00) | none |
| Kato, 2000 | any | age, / | per year | RR | 1.03 (1.01, 1.04) | age, race, height, BMI, no. of cigarettes/ day, fat intake |

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|---|---|---|---|---|---|---|
| Melton, 2003 | osteoporotic | age, / | per 10-year increase | HR | 1.42 (1.14, 1.75) | Multivariate models combining the independent predictors from all of these risk factor domains were created |
| Nguyen, 2007 | osteoporotic | age, / | per 5-year increase | HR | 1.09 (1.01, 1.18) | age, postural sway, quadriceps strength, FNBMD, fall, and prior fracture |
| Porthouse, 2004 | nonvertebral excluding fingers, toes, ribs | age, / | per year increase | OR | 1.03 (1.01, 1.05) | NR |
| Rouzi, 2012 | osteoporotic | age, / | >=60 vs <60 | RR | 2.43 (1.49, 3.95) | Binary logistic regression with forward stepwise analysis for multiple factors was used to assess relationships with incident of ORFs |
| vanGeel, 2007 | any | age, / | >60 vs 50-59 | HR | 1.5 (1.2, 1.9) | none |
| Wilczek, 2021 | any excluding skull, fingers, toes | age, / | per year | HR | 1.02 (1.01, 1.03) | T-score, age, height, weight, parental hip fracture, smoking, alcohol, rheumatic disease, diabetes, stand without arms, fallen during last month, right handedness, fracture due to low energy trauma, height loss >3cm, menopause< 45 years, cortisone treatment, hyperparathyroidism, anorexia, malabsorption, angina or myocardial infarction, other disease related to |

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|---|---|---|---|---|---|---|
| | | | | | | osteoporosis, hemiplegia, reduced mobility |
| Ahn, 2014 | fragility | BMI, / | <18.5 vs >=18.5 | HR | 2.66 (1.13, 6.24) | age, body mass index, previous fracture history, parental history of osteoporosis, dietary calcium intake, menopausal status, duration of total breast-feeding, and bone mineral density |
| Colon-Emeric, 2002 | any | BMI, / | lowest quartile | HR | 1.23 (1.09, 1.56) | multivariable analysis identified correlations and interactions among the significant variables. |
| Kato, 2000 | any | BMI, / | <=28 vs <22 kg/m2 | RR | 0.80 (0.66, 0.98) | age, race, height, BMI, no. of cigarettes/ day, fat intake |
| Lee, 2010 | hip, wrist, humerus, rib, pelvis | BMI, / | <18.5 vs 18.5-22.9 kg/m2 | RR | 2.61 (1.06, 6.45) | Age, body mass index, menopausal state, history of previous fracture, hip circumference, weekly dairy product consumption, regular exercise duration, alcohol intake, and history of RA and OA, SoSR, SoST |
| Piirtola, 2008 | any | BMI, / | 25-29.9 vs >=30 | RR | 1.9 (1.3, 2.7) | Age, handgrip strength, BMI, occurrence of a previous fracture after 45 years of age and compression of thoracic or upper lumbar vertebrae |
| Piirtola, 2008 | any | BMI, / | <25 vs >30 | RR | 2.0 (1.4, | Age, handgrip strength, BMI, occurrence of a previous fracture after 45 years of age and |

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|---|---|---|---|---|---|---|
| | | | | | 2.9) | compression of thoracic or upper lumbar vertebrae |
| Liang, 2023 | nonvertebral | BMI, change (follow up minus baseline) | per 1kg/m2 increase in change | HR | 0.61 (0.39, 0.96) | age, years since menopause, previous fractures, hypertension, coronary heart disease, and fast plasma glucose, BMI category (normal weight, overweight, and obesity), BMI at baseline, BMD L2-4 |
| Xin, 2024 | any excluding finger, toe, face, skull | BMI, trajectory between age 35-64 | high level overweight 29.5 dropped to normal 22 from age 50 VS normal 24 increased to slightly overweight 26 | HR | 2.14 (1.08, 4.24) | sex, fracture history, drinking, type II diabetes, smoking, and hypertension status at baseline |
| Colon-Emeric, 2002 | any | ethnic group, / | white vs other | HR | 2.20 (1.74, 2.51) | multivariable analysis identified correlations and interactions among the significant variables. |
| Kato, 2000 | any | ethnic group, / | black vs caucasian | RR | 0.45 (0.32, 0.63) | age, race, height, BMI, no. of cigarettes/ day, fat intake |
| Kato, 2000 | any | height, / | 165-170 vs <=155 cm | RR | 1.26 (1.02, 1.56) | age, race, height, BMI, no. of cigarettes/ day, fat intake |

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|---|---|---|---|---|---|---|
| Kato, 2000 | any | height, / | >170 vs <=155 cm | RR | 1.64 (1.24, 2.17) | age, race, height, BMI, no. of cigarettes/ day, fat intake |
| Papaioannou, 2005 | nonvertebral | height, / | per SD increase | RR | 1.282 (1.100, 1.494) | age, current height, height loss, current weight, weight loss, BMI, lumbar spine and femoral neck BMD, SF-36 PCS, and prevalent vertebral fracture status |
| Wilczek, 2021 | any excluding skull, fingers, toes | height, / | per cm | HR | 1.03 (1.01, 1.05) | T-score, age, height, weight, parental hip fracture, smoking, alcohol, rheumatic disease, diabetes, stand without arms, fallen during last month, right handedness, fracture due to low energy trauma, height loss >3cm, menopause< 45 years, cortisone treatment, hyperparathyroidism, anorexia, malabsorption, angina or myocardial infarction, other disease related to osteoporosis, hemiplegia, reduced mobility |
| Lee, 2010 | nonvertebral | hip circumference, / | >=89.8 cm vs <89.7 | RR | 3.59 (1.06, 12.19) | multivariate |
| Amouzegar, 2021 | any | waist circumference, / | >=95 vs <95 cm | HR | 2.43 (1.53, 3.86) | age, smoking status, education, physical activity, steroid usage, marital status, each other MetS component, BMI |
| FitzGerald, 2012 | major | weight, unexplained loss in 12 | >= 10 lbs vs N | HR | 1.3 (NR, NR) | age, weight, BMI, any baseline fracture, maternal hip fracture, paternal hip fracture, current smoker, weight loss in 12 months, falls |

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|---|---|---|---|---|---|---|
| | | months | | | | in past year, comorbidities, general health, physical activity, drinks/week) |
| Compston, 2016 | any | weight, unintentional loss | >=10lb/ 4.5kg vs no | HR | 1.49 (1.34, 1.65) | none |
| FitzGerald, 2012 | major | weight, / | per 10 kg | HR | 0.9 (NR, NR) | age, weight, BMI, any baseline fracture, maternal hip fracture, paternal hip fracture, current smoker, weight loss in 12 months, falls in past year, comorbidities, general health, physical activity, drinks/week) |
| Moberg, 2022 | any excluding skull and face | weight, change since age 20 | gradually decreasing vs been the same | HR | 1.39 (1.17, 1.65) | age, BMI, previous fracture and all variables with a significant impact ($p<0.05$) on fracture risk from the basic model analysis |

**Appendix 4** Biomarkers and Fractures

| first author | fracture site | factor, detail | comparison (exposed vs unexposed) | effect measure | effect size | adjusted for |
|---|---|---|---|---|---|---|
| Buchebner, 2014 | MOF | 25(OH)D, maintained serum 25(OH)D in two measurements 5 years apart | <50 vs >75 nmol/L | HR | 1.7 (1.1, 2.6) | none |
| Buchebner, 2014 | MOF | 25(OH)D, maintained serum 25(OH)D in two measurements 5 years apart | <50 vs >75 nmol/L | IRR | 1.91 (1.24, 2.89) | none |
| Buchebner, 2014 | MOF | 25(OH)D, maintained serum 25(OH)D in two measurements 5 years apart | <50 vs 50-75 nmol/L | HR | 1.8 (1.2, 2.8) | none |
| Buchebner, 2014 | MOF | 25(OH)D, serum | Q1 vs Q5 | RR | 1.53 (1.16, 2.01) | none |
| Buchebner, 2014 | MOF | 25(OH)D, serum | Q1 vs Q4 | RR | 1.46 (1.12, 1.96) | none |
| Cauley, 2015 | nontraumatic | 25(OH)D, serum | per 10 ng/ml increase | HR | 0.72 (0.54, 0.96) | age, site, race, fracture history, prior and current menopausal hormone therapy, BMI, physical activity, SF-36 Role–physical functioning score, education, lumbar spine BMD, calcium and vitamin D supplements, |

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|---|---|---|---|---|---|---|
| | | | | | | corticosteroids, diabetes, and dietary calcium |
| Julian, 2016 | hip, spine, wrist at year 10 | 25(OH)D, serum | per 20nmol/L increase | HR | 0.92 (0.85, 0.99) | age, sex, month, BMI, smoking, alcohol, supplement use, history of fractures and physical activity |
| Nakamura, 2011 | limb or vertebral | 25(OH)D, serum | <47.7 vs >=71 nmol/L | HR | 2.82 (1.09, 7.34) | age, body mass index, bone mineral density, medication of osteoporosis, and physical activity |
| Nakamura, 2011 | limb or vertebral | 25(OH)D, serum | 59.2-71 vs >=71 nmol/L | HR | 2.82 (1.09, 7.27) | age, body mass index, bone mineral density, medication of osteoporosis, and physical activity |
| Nakamura, 2011 | limb or vertebral | 25(OH)D, serum | >=71 vs <71 nmol/L | HR | 0.42 (0.18, 0.99) | age, body mass index, bone mineral density, medication of osteoporosis, and physical activity |
| Rouzi, 2012 | osteoporotic | 25(OH)D, serum | <=17.9 nmol/L vs >17.9 | RR | 1.63 (1.06, 2.51) | Binary logistic regression with forward stepwise analysis for multiple factors was used to assess relationships with incident of ORFs |

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| Tanaka , 2014 | long bone | 25(OH)D, serum | <25 ng/mL vs >=25 | RR | 2.20 (1.39, 3.53) | lumbar or femur BMD <-2.5 SD of the YAM, age, weight, diabetes mellitus, PTH, eGFR, prior fracture, presence of back pain, and treatments by bisphosphonates, SERMs, and active vitamin D3. |
| Looker , 2013 | MOF | 25(OH)D, serum | per SD decline | RR | 1.16 (1.01, 1.33) | age, survey, race/ethnicity, BMI, height, health status, prescription osteoporosis drug use, current physical activity compared to activity 10 years ago, milk intake |
| Moberg, 2013 | any | Androstenedione, serum | per 1 nmol/L increase | HR | 0.48 (0.34, 0.69) | age, body mass index and current smoking |
| Moberg, 2013 | any | Androstenedione/ SHBG ratio, serum | per 1 increase | HR | 0.57 (0.42, 0.77) | age, body mass index and current smoking |
| Cauley , 2017 | nonvertebral | bioavailable estradiol (BioE2), serum | tertile 3 vs tertile 1 | OR | 0.65 (0.50, 0.85) | weight, height, physical activity, total calcium intake, personal history of fracture, health status, diabetes treatment, and race/ ethnicity |
| Kuchuk, 2007 | osteoporotic | bioavailable estradiol (BioE2), serum | below median vs above. Median 18.2 | HR | 2.39 (1.28, 4.48) | age, BMI, corticosteroid use, alcohol use, current smoking, chronic disease, mobility and |

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| | | | pmol/l | | | exercise |
| Cauley, 2017 | nonvertebral | bioavailable testosterone (BioT), / | tertile 3 vs tertile 1 | OR | 0.76 (0.60, 0.96) | weight, height, physical activity, total calcium intake, personal history of fracture, health status, diabetes treatment, and race/ ethnicity |
| Jaiswal, 2023 | any | bone material strength index, by microindentation | per SD increase | HR | 1.29 (1.08, 1.54) | age, BMI, indentation stability, previous fracture, parent fractured hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol, FN BMD |
| Shieh, 2020 | any | collagen type I N-telopeptide, urine | rate of increase during menopause transition. Per SD increment. | HR | 1.25 (1.05, 1.50) | following covariates measured in early postmenopause (at the end of the MT, defined as the first study visit after 2 years following the final menstrual period): age, body mass index, race/ethnicity, fracture before the MT, current cigarette use (yes/ no), and Study of Women's Health Across the Nation study site, FN BMD |

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| Mitama, 2017 | fragility | C-reactive protein (CRP), serum | per 1 mg/L increase | HR | 1.07 (1.03, 1.13) | age, spine BMD, HbA1x, eGFR, albumin, exercise, smoking, alcohol, family history of fracture, IHD, CVD, previous fracture |
| Ahmadi-Abhari, 2013 | any | C-reactive protein (CRP), serum | 0.1-0.5 vs 1.1-2 mg/L | HR | 1.31 (1.03, 1.66) | age, sex, body mass index, smoking, alcohol intake, physical activity, past history of fractures, history of osteoporosis, use of NSAIDs and corticosteroid medication, medical history of arthritis, cancer, myocardial infarction, stroke and diabetes, and in women only menopausal status and postmenopausal Hormone Replacement Therapy. |
| Ahmadi-Abhari, 2013 | any | C-reactive protein (CRP), serum | 3.1-10 vs 1.1-2 mg/L | HR | 1.22 (1.00, 1.51) | age, sex, body mass index, smoking, alcohol intake, physical activity, past history of fractures, history of osteoporosis, use of NSAIDs and corticosteroid medication, medical history of arthritis, cancer, myocardial infarction, stroke and diabetes, and in women only menopausal status and postmenopausal Hormone Replacement Therapy. |

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| Nakamura, 2011 | limb or vertebral | C-reactive protein (CRP), serum high-sensitivity CRP (hs-CRP) | 0.25-0.59 vs <0.25 mg/L | HR | 2.22 (1.02, 4.84) | age, body mass index, bone mineral density, postural sway, calcium intake, vitamin D status, medication of osteoporosis, and physical activities |
| Nakamura, 2011 | limb or vertebral | C-reactive protein (CRP), serum high-sensitivity CRP (hs-CRP) | >=0.59 vs <0.25 mg/L | HR | 2.40 (1.10, 5.24) | age, body mass index, bone mineral density, postural sway, calcium intake, vitamin D status, medication of osteoporosis, and physical activities |
| Cauley, 2012 | any | cross-linked N-telopeptide of type I collagen, urinary | above median vs below. Median 31.9 nM BCE/nM Cr. | HR | 1.46 (1.05, 2.26) | time of collection, baseline age, race, site, fracture, history, lumbar spine BMD, height, weight, menopause status, education, alcohol use, smoking, and diabetes |
| Garnero, 2002 | nonvertebral | C-terminal cross-linking telopeptide of type I collagen ratio, Urinary | highest quartile vs other three | RR | 2.0 (1.04, 3.8) | age, presence of prevalent fracture, and physical activity, bone ALP, femoral neck BMD |
| Ensrud, 2012 | nonvertebral | Cystatin C, serum | per SD increase | OR | 1.23 (1.04, 1.46) | history of fracture |
| Ensrud, 2012 | nonvertebral | estimated glomerular filtration rate (eGFR), cyc-c | <60 vs >90 mL/min/1.73 m2 | OR | 2.46 (1.16, 5.21) | history of fracture |

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|---|---|---|---|---|---|---|
| Malmgren, 2020 | osteoporotic in 5 years | estimated glomerular filtration rate (eGFR), cyc-c | intermediate reduction 45-59 ml/min/1.73m2 vs normal >=60 | HR | 1.51 (1.04, 2.18) | weight, smoking, vitamin D levels, and FN BMD |
| Chen, 2018 | any excluding hand/finger, foot/toe, and heak/neck | estimated glomerular filtration rate (eGFR), MDRD | Quartile lowest vs highest | HR | 1.36 (1.15, 1.60) | age, sex, BMI, smoking, alcohol, number of chronic diseases, and PTH |
| Helte, 2021 | any | fluoride, urinary | highest tertile vs lowest tertile | HR | 1.25 (1.03, 1.51) | age, education, height, total fat mass, lean body mass, parity, smoking status, physical activity, alcohol intake, diabetes, eGFR, tertiles of urinary excretion of calcium, use of calcium supplements, use of vitamin D supplements, ever use of estrogen, and ever use of corticosteroids, serum Beta-CrossLaps (ng/L) |

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| Melton, 2003 | osteoporotic | free estradiol index, estradiol/SHBG | per SD decrease | HR | 1.40 (1.17, 1.67) | Multivariate models combining the independent predictors from all of these risk factor domains were created |
| Otonari, 2021 | any | HbA1c, / | 5-12.7% vs 3.3-4.9% | OR | 1.18 (1.01, 1.37) | multiple |
| Jaiswal, 2023 | any | hemoglobin, / | per SD decrease | HR | 1.23 (1.14, 1.33) | age, height, weight, FRAX CRFs, and FN BMD |
| Hussain, 2023 | any | high-density lipoprotein cholesterol (HDL-C), plasma | per SD increment | HR | 1.12 (1.06, 1.19) | age, physical activity, alcohol use, prefrailty/frailty status, education, body mass index, smoking status, aspirin use, diabetes, chronic kidney disease, use of lipid-lowering medication, and use of antiosteoporosis medications |
| vanMeurs, 2004 | osteoporotic | Homocysteine, plasma | per SD increment in the natural log transformed level | RR | 1.4 (1.2, 1.6) | age, sex, body-mass index, smoking status, and presence or absence of a history of recent falls, diabetes mellitus, dementia (in the Rotterdam Study) or cognitive impairment (in LASA), peripheral arterial disease, and serum creatinine level |

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| Lundin, 2016 | MOF | insulin-like growth factor-binding protein 1 (IGFBP-1), Serum | per SD increase | HR | 1.33 (1.05, 1.69) | age |
| Rejnmark, 2011 | osteoporotic | parathyroid hormone (PTH), plasma | >4.5 pmol/L vs <4.5 | HR | 1.69 (1.25, 2.29) | age, body mass index, use of hormone-replacement therapy, prior fracture (age[25 years), daily calcium intake, physical activity, plasma 25-hydroxyvitamin D levels, glomerular filtration rate, alcohol intake, and smoking habits |
| Tanaka, 2011 | long bone and vertebral | pentosidine, urinary | per SD increase | HR | 1.20 (1.07, 1.33) | age, body weight, diabetes mellitus, lumbar BMD, prior fracture, and presence of back pain |
| Rousseau, 2014 | nonvertebral | Periostin, Serum | highest quartile vs other three | OR | 2.05 (1.16, 3.63) | age, prevalent fracture, and hip BMD T-score |
| Ardawi, 2018 | osteoporotic | sphingosine 1-phosphate (S1P), Plasma | per SD above mean | HR | 6.12 (4.92, 7.66) | age, body mass index, physical activity score, dietary calcium intake, serum 25(OH)D, hand-grip strength, and bone mineral density of total hip |

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|---|---|---|---|---|---|---|
| Bae, 2016 | any | sphingosine 1-phosphate (S1P), Plasma | tertile 3 vs (1+2) | HR | 5.52 (1.04, 56.54) | age, height, weight, current smoking status, alcohol intake, regular outdoor exercise, family history of osteoporotic fracture, prevalent fracture, and antiosteoporotic medication (no medication, hormone replacement, and bisphosphonate treatment), FN BMD, annualized changes in FN BMD, C-terminal telopeptide of type I collagen |
| Chang, 2016 | nontraumatic | triglycerides, Fasting plasma | per 50 mg/dl | HR | 1.07 (1.02, 1.12) | age, race/ethinicity, study site, menopausal stage, smoking, alcohol use, physical activity, diabetes, BMI, lumbar spine BMD |
| Muka, 2016 | osteoporotic | uric acid, serum | per SD increase | HR | 0.905 (0.838, 0.977) | age, gender, height, weight, eGFR, index time, smoking status, Dutch Healthy Diet Index, physical activity, prevalent diabetes mellitus, prevalent cardiovascular disease, history of hip or knee surgery, diuretic drug use, hormone replacement therapy, corticosteroid drug use, thyroid therapy, anti-gout drugs, |

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| | | | | | | serum phosphate, serum total calcium, and dietary intake of vitamin C |
| Dhonukshe-Rutten, 2005 | osteoporotic excluding head, hand, fingers, foot, toes, ankle, vertebrae | Vitamin B12, serum | lowest quartile vs the other three | RR | 2.2 (1.1, 4.4) | age, BMI, smoking status, and recurrent falling |
| Ginsberg, 2021 | any | vitamin D metabolite ratio, vitamin D's catabolic product (24,25-dihydroxyvitamin D [24,25(OH)2D]) to 25(OH)D | per 50% lower | HR | 1.49 (1.06, 2.08) | age, sex, race, season of measurements, clinic site, BMI, baseline eGFR, serum calcium, phosphate, parathyroid hormone and fibroblast growth factor 23 |

**Appendix 5** BMD and Related Factors and Fractures

| first author | fracture site | factor, detail | comparison (exposed vs unexposed) | effect measure | effect size | adjusted for |
|---|---|---|---|---|---|---|
| Cauley, 2005 | nonvertebral | BMAD, femoral neck | per SD decrease | RR | 1.28 (1.20, 1.37) | age, body weight, height, fracture since age 50 years, walking as form of exercise, current calcium supplement use, current hormone therapy use, alcohol consumption in the past 30 days, diagnosis of osteoarthritis, diagnosis of chronic obstructive pulmonary disease, fallen 2 or more times in the past year, use arms to stand up from a chair, and current smoking |
| Cauley, 2005 | nonvertebral | BMC, femoral neck | per SD decrease | RR | 1.20 (1.13, 1.29) | age, body weight, height, fracture since age 50 years, walking as form of exercise, current calcium supplement use, current hormone therapy use, alcohol consumption in the past 30 days, diagnosis of osteoarthritis, diagnosis of chronic obstructive pulmonary disease, fallen 2 or more times in the past year, use arms to stand up from a chair, and current smoking |

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|---|---|---|---|---|---|---|
| Cauley, 2005 | nonvertebral | BMC, total hip | per SD decrease | RR | 1.25 (1.17, 1.35) | age, body weight, height, fracture since age 50 years, walking as form of exercise, current calcium supplement use, current hormone therapy use, alcohol consumption in the past 30 days, diagnosis of osteoarthritis, diagnosis of chronic obstructive pulmonary disease, fallen 2 or more times in the past year, use arms to stand up from a chair, and current smoking |
| Black, 1992 | nonvertebral | BMD, calcaneus | per SD | RR | 1.51 (1.29, 1.77) | age |
| Nevitt, 1994 | nonvertebral | BMD, calcaneus | per SD decrease | RR | 1.4 (1.3, 1.5) | age |
| Nevitt, 1994 | nonvertebral | BMD, calcaneus | per SD decrease | RR | 1.7 (1.4, 1.9) | age |
| Cauley, 2005 | nonvertebral | BMD, femoral neck | per SD decrease | RR | 1.42 (1.32, 1.52) | age, body weight, height, fracture since age 50 years, walking as form of exercise, current calcium supplement use, current hormone therapy use, alcohol consumption in the past 30 days, diagnosis of osteoarthritis, diagnosis of chronic obstructive pulmonary disease, |

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|---|---|---|---|---|---|---|
| | | | | | | fallen 2 or more times in the past year, use arms to stand up from a chair, and current smoking |
| Black, 1992 | nonvertebral | BMD, femoral neck | per SD | RR | 1.41 (1.20, 1.66) | age |
| Edwards, 2013 | any | BMD, femoral neck | per SD decrease | HR | 1.77 (1.16, 2.71) | age, weight, height, fracture after aged 45 but before baseline, parent or sibling having a fracture after aged 45, smoker status, diagnosis of rheumatoid arthritis since baseline, number of comorbidities, and alcohol consumption |
| Lasschuit, 2020 | low trauma | BMD, femoral neck | per SD reduction | HR | 1.39 (1.17, 1.64) | age, sex, BMI, fall count and previous fracture after age 50 |
| Leslie, 2013 | MOF | BMD, femoral neck | per SD | HR | 1.68 (1.56, 1.81) | age, BMI, glucocorticoids, prior major fracture, RA, COPD, alcohol abuse, and osteoporosis therapy |
| Melton, 2003 | osteoporotic | BMD, femoral neck | per SD decrease | HR | 1.26 (1.01, 1.58) | Multivariate models combining the independent predictors from all of these risk factor domains were created |
| Nevitt, 1994 | nonvertebral | BMD, femoral neck | per SD decrease | RR | 1.5 (1.4, 1.6) | age |

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|---|---|---|---|---|---|---|
| Nevitt, 1994 | nonvertebral | BMD, femoral neck | per SD decrease | RR | 1.9 (1.6, 2.4) | age |
| Nguyen, 2007 | osteoporotic | BMD, femoral neck | per SD decrease | HR | 1.55 (1.41, 1.7) | age, postural sway, quadriceps strength, FNBMD, fall, and prior fracture |
| Nguyen, 1993 | atraumatic | BMD, femoral neck | per SD decrease | OR | 2.39 (1.92, 2.97) | femoral neck BMD, quadriceps strength, body sway |
| Papaioannou, 2005 | nonvertebral | BMD, femoral neck | per SD decrease | RR | 1.336 (1.086, 1.645) | age, current height, height loss, current weight, weight loss, BMI, lumbar spine and femoral neck BMD, SF-36 PCS, and prevalent vertebral fracture status |
| Sornay-Rendu, 2014 | low trauma | BMD, femoral neck | per SD decrease | OR | 1.48 (1.2, 1.82) | age, previous fracture, parental hip fracture, falls, and medication use |
| Yenchek, 2012 | nonvertebral fragility | BMD, femoral neck | per SD decrease | HR | 2.15 (1.8, 2.57) | age, race, sex, BMI, parathyroid status, Vitamin D status |
| Black, 1992 | nonvertebral | BMD, femoral intertrochanteric | per SD | RR | 1.39 (1.19, 1.62) | age |
| Leslie, 2013 | MOF | BMD, femoral trochanter | per SD | HR | 1.56 (1.46, 1.65) | age, BMI, glucocorticoids, prior major fracture, RA, COPD, alcohol abuse, and osteoporosis therapy |

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|---|---|---|---|---|---|---|
| Black, 1992 | nonvertebral | BMD, femoral trochanter | per SD | RR | 1.38 (1.18, 1.61) | age |
| Black, 1992 | nonvertebral | BMD, femoral Ward's triangle | per SD | RR | 1.43 (1.22, 1.67) | age |
| Huang, 1998 | any | BMD, hand metacarpal | per SD decrease | OR | 1.55 (1.17, 2.06) | age |
| Huang, 1998 | any | BMD, hand phalangeal | per SD decrease | OR | 1.91 (1.23, 3.10) | age |
| Bach-Mortensen, 2006 | any | BMD, nondominant hand | per SD | OR | 1.6 (1.3, 1.9) | age and relation to either joint/bone pain group or control group |
| Black, 1992 | nonvertebral | BMD, total hip | per SD | RR | 1.40 (1.20, 1.63) | age |
| Cauley, 2005 | nonvertebral | BMD, total hip | per SD decrease | RR | 1.42 (1.33, 1.52) | age, body weight, height, fracture since age 50 years, walking as form of exercise, current calcium supplement use, current hormone therapy use, alcohol consumption in the past 30 days, diagnosis of osteoarthritis, diagnosis of chronic obstructive pulmonary disease, |

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|---|---|---|---|---|---|---|
| | | | | | | fallen 2 or more times in the past year, use arms to stand up from a chair, and current smoking |
| Charles, 2023 | fragility excluding toes, fingers or nose | BMD, total hip | 0.1 g/cm2 | OR | 1.29 (1.20, 1.38) | Age, history of fall, history of fracture, corticoids use, osteoporosis treatment and BMD |
| Domiciano, 2021 | nonvertebral | BMD, total hip | per SD decrease | RR | 1.68 (1.11, 2.56) | age, weight, BMI, prevalence of any osteoporotic fracture, prevalence of non-vertebral fracture, eGFR, BMD at lumbar spine, BMD at femoral neck, BMD at total hip |
| Leslie, 2013 | MOF | BMD, total hip | per SD | HR | 1.65 (1.55, 1.76) | age, BMI, glucocorticoids, prior major fracture, RA, COPD, alcohol abuse, and osteoporosis therapy |
| Rouzi, 2012 | osteoporotic | BMD, total hip | <=0.784 g/cm2 vs >0.784 | RR | 1.86 (1.26, 2.75) | Binary logistic regression with forward stepwise analysis for multiple factors was used to assess relationships with incident of ORFs |
| Sornay-Rendu, 2014 | low trauma | BMD, total hip | per SD decrease | OR | 1.62 (1.32, 1.97) | age, previous fracture, parental hip fracture, falls, and medication use |

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| Cauley, 2009 | nonvertebral | BMD, linear slope for change of BMD at total hip over 15 years | per SD decrease in the slope for BMD | HR | 1.14 (1.11, 1.18) | Further adjustment for other factors reduced the magnitude of the RH, but they remained statistically significant |
| Black, 1992 | nonvertebral | BMD, lumbar spine | per SD | RR | 1.35 (1.15, 1.58) | age |
| Lasschuit, 2020 | low trauma | BMD, lumbar spine | per SD reduction | HR | 1.43 (1.21, 1.69) | age, sex, BMI, fall count and previous fracture after age 50 |
| Leslie, 2013 | MOF | BMD, lumbar spine | per SD | HR | 1.32 (1.25, 1.41) | age, BMI, glucocorticoids, prior major fracture, RA, COPD, alcohol abuse, and osteoporosis therapy, diabetes, lumbar spine TBS and BMD |
| Nevitt, 1994 | nonvertebral | BMD, lumbar spine | per SD decrease | RR | 1.4 (1.2, 1.5) | age |
| Nevitt, 1994 | nonvertebral | BMD, lumbar spine | per SD decrease | RR | 1.5 (1.2, 1.8) | age |
| Papaioannou, 2005 | nonvertebral | BMD, lumbar spine | per SD decrease | RR | 1.364 (1.101, 1.689) | age, current height, height loss, current weight, weight loss, BMI, lumbar spine and femoral neck BMD, SF-36 PCS, and prevalent vertebral fracture status |

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| Sornay-Rendu, 2014 | low trauma | BMD, lumbar spine | per SD decrease | OR | 1.65 (1.37, 1.99) | age, previous fracture, parental hip fracture, falls, and medication use |
| Torgerson, 1996 | any | BMD, lumbar spine | lowest quarter vs highest | OR | 4.55 (1.53, 13.5) | stepwise logistic regression analysis was undertaken for all the variables |
| Huopio, 2000 | osteoporotic | BMD, lumbar spine and femoral neck | per SD decrease | RR | 1.6 (1.3, 2.0) | independent risk factor but did not specify confounders adjusted for |
| Black, 1992 | nonvertebral | BMD, distal radius | per SD | RR | 1.42 (1.21, 1.67) | age |
| Gnudi, 2000 | nonvertebral | BMD, distal radius | per SD decrease | RR | 2.99 (1.06, 8.41) | age, age at menopause, height, weight, treatment |
| Nevitt, 1994 | nonvertebral | BMD, distal radius | per SD decrease | RR | 1.5 (1.4, 1.6) | age |
| Nevitt, 1994 | nonvertebral | BMD, distal radius | per SD decrease | RR | 1.6 (1.3, 1.8) | age |
| Sornay-Rendu, 2014 | low trauma | BMD, distal radius | per SD decrease | OR | 1.84 (1.45, 2.34) | age, previous Fx, parental hip Fx, falls, and medication use |

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| Svejme, 2013 | fragility | BMD, forearm | per SD decrease | RR | 1.36 (1.15, 1.62) | early menopause, body weight, physical activity |
| Black, 1992 | nonvertebral | BMD, proximal radius | per SD | RR | 1.32 (1.14, 1.53) | age |
| Nevitt, 1994 | nonvertebral | BMD, proximal radius | per SD decrease | RR | 1.4 (1.3, 1.5) | age |
| Nevitt, 1994 | nonvertebral | BMD, proximal radius | per SD decrease | RR | 1.4 (1.2, 1.6) | age |
| Sornay-Rendu, 2014 | low trauma | BMD, ultradistal raidus | per SD decrease | OR | 2.15 (1.69, 2.71) | age, previous fracture, parental hip fracture, falls, and medication use |
| Sornay-Rendu, 2005 | low trauma | BMD, rate of BMD loss per year at distal radius over 10 years | tertile | HR | 1.55 (1.07, 2.26) | age, previous fractures, maternal history of fracture, physical activity, grip strength, falls, and baseline BMD |
| Sornay-Rendu, 2005 | low trauma | BMD, rate of BMD loss per year at mid-radius over 10 years | tertile | HR | 1.45 (1.03, 2.09) | age, previous fractures, maternal history of fracture, physical activity, grip strength, falls, and baseline BMD |

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|---|---|---|---|---|---|---|
| Sornay-Rendu, 2005 | low trauma | BMD, rate of BMD loss per year at ultra distal radius over 10 years | tertile | HR | 1.7 (1.14, 2.55) | age, previous fractures, maternal history of fracture, physical activity, grip strength, falls, and baseline BMD |
| Siris, 2006 | osteoporotic | BMD T-score, heel or forearm or finger | -1.99 to -1.0 vs >-1.0 | HR | 1.67 (1.49, 1.88) | personal history of prior fracture, health status, HRT usage, maternal history of fracture, ethnicity, education level, smoking status, and corticosteroid use |
| Siris, 2006 | osteoporotic | BMD T-score, heel or forearm or finger | <=-2.0 vs -1.0 | HR | 2.78 (2.44, 3.17) | personal history of prior fracture, health status, HRT usage, maternal history of fracture, ethnicity, education level, smoking status, and corticosteroid use |
| Siris, 2006 | osteoporotic | BMD T-score, heel or forearm or finger | -1.99 to -1.0 vs >-1.0 | HR | 1.52 (1.34, 1.72) | personal history of prior fracture, health status, HRT usage, maternal history of fracture, ethnicity, education level, smoking status, and corticosteroid use |
| Siris, 2006 | osteoporotic | BMD T-score, heel or forearm or finger | <=-2.0 vs -1.0 | HR | 2.37 (2.09, 2.68) | personal history of prior fracture, health status, HRT usage, maternal history of fracture, ethnicity, education level, smoking status, and corticosteroid use |
| Siris, 2006 | osteoporotic | BMD T-score, heel or forearm or finger | -1.99 to -1.0 vs >-1.0 | HR | 1.36 (1.04, 1.79) | personal history of prior fracture, health status, HRT usage, maternal history of fracture, ethnicity, education level, smoking status, and corticosteroid use |

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|---|---|---|---|---|---|---|
| Siris, 2006 | osteoporotic | BMD T-score, heel or forearm or finger | <=-2.0 vs -1.0 | HR | 1.97 (1.53, 2.53) | personal history of prior fracture, health status, HRT usage, maternal history of fracture, ethnicity, education level, smoking status, and corticosteroid use |
| Schuit, 2004 | nonvertebral | BMD T-score, femoral neck | <-2.5 vs >-1.0 | RR | 2.7 (2.0, 3.5) | none |
| Wilczek, 2021 | any excluding skull, fingers, toes | BMD T-score, nondominant hand | per SD decrease | HR | 1.23 (1.13, 1.35) | T-score, age, height, weight, parental hip fracture, smoking, alcohol, rheumatic disease, diabetes, stand without arms, fallen during last month, right handedness, fracture due to low energy trauma, height loss >3cm, menopause< 45 years, cortisone treatment, hyperparathyroidism, anorexia, malabsorption, angina or myocardial infarction, other disease related to osteoporosis, hemiplegia, reduced mobility |
| Banefelt, 2022 | any | BMD T-score, total hip | per SD greater | HR | 0.63 (0.59, 0.67) | none |
| Lauppe, 2019 | any | BMD T-score, total hip | <-1.0 vs >=-1.0 | HR | 1.5 (1.3, 1.7) | NR |

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|---|---|---|---|---|---|---|
| Lauppe, 2019 | any | BMD T-score, total hip | <-2.5 vs >=-1.0 | HR | 2.5 (2.2, 3) | NR |
| Lauppe, 2019 | any | BMD T-score, total hip | <-2.5 vs >=-1.0 | HR | 1.7 (1.4, 2.2) | NR |
| vanGeel, 2007 | any | BMD T-score, lumbar spine | <-2.5 vs >=-2.5 | HR | 1.7 (1.3, 2.1) | none |
| Riis, 1996 | any | bone mass, forearm within 3 years of menopause | low bone mass vs normal bone mass | OR | 1.9 (NR, NR) | NR |
| Riis, 1996 | any | bone mass, forearm loss rate per year over 2 years within 3 years of menopause | fast loser vs normal loser | OR | 2 (NR, NR) | NR |

**Appendix 6** Dietary Habits and Fractures

| first author | fracture site | factor, detail | comparison (exposed vs unexposed) | effect measure | effect size | adjusted for |
|---|---|---|---|---|---|---|
| Rouzi, 2012 | osteoporotic | calcium, dietary intake | <=391 mg/day vs >391 | RR | 1.66 (1.08, 2.53) | Binary logistic regression with forward stepwise analysis for multiple factors was used to assess relationships with incident of ORFs |
| Michaelsson, 2014 | any | dairy products, milk | 200-399 g/d vs <200 | HR | 1.07 (1.04, 1.11) | age, body mass index, height, total energy intake, total alcohol intake, healthy dietary pattern, calcium and vitamin D supplementation, ever use of cortisone, educational level, living alone, physical activity level estimated as metabolic equivalents, smoking status, Charlson's comorbidity index, use of oestrogen replacement therapy and nulliparity |
| Michaelsson, 2014 | any | dairy products, milk | 400-599 g/d vs <200 | HR | 1.16 (1.11, 1.21) | age, body mass index, height, total energy intake, total alcohol intake, healthy dietary pattern, calcium and vitamin D supplementation, ever use of cortisone, educational level, living alone, physical activity level estimated as metabolic equivalents, smoking status, Charlson's comorbidity index, use of oestrogen replacement therapy and nulliparity |
| Michaelsson, 2014 | any | dairy products, milk | >=600 g/d vs <200 | HR | 1.16 (1.08, 1.25) | age, body mass index, height, total energy intake, total alcohol intake, healthy dietary pattern, calcium and vitamin D supplementation, ever use of cortisone, educational level, living alone, physical activity level estimated as metabolic equivalents, |

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| | | | | | | smoking status, Charlson's comorbidity index, use of oestrogen replacement therapy and nulliparity |
| Feart, 2013 | hip, vertebral and wrist | dairy products, / | <17.9 vs >=17.9 servings/ week | HR | 1.51 (1.07, 2.11) | each individual food group component of the Mediterranean diet score, age, gender, physical activity, total energy intake, educational level, marital status, BMI, self-reported osteoporosis, osteoporosis treatment, calcium and/or vitamin D treatment |
| Kojima, 2023 | osteoporotic | dairy products, milk | >=400 ml/d vs <200 ml/d | HR | 0.58 (0.36, 0.95) | age, frequency of yogurt intake, frequency of cheese intake, BMI, history of osteoporotic fractures, frequency of natto intake, BMD |
| Kato, 2000 | any | fat, daily intake | >=75 vs <57.2 g | RR | 1.24 (1.01, 1.50) | age, race, height, BMI, no. of cigarettes/ day, fat intake |
| Mei, 2021 | any excluding skull, face, hands, feet, pathological, atypical, peripros | fish oil, supplements | regular use vs no | HR | 0.92 (0.87, 0.96) | age, sex, self-identified ethnic background, household income, BMI, standing height, smoking status, alcohol consumption, physical activity, cooked vegetable intake, salad/raw vegetable intake, fresh fruit intake, oily fish intake, nonoily fish intake, red and processed meat intake, type of milk consumed, coffee intake, calcium supplement use, vitamin D supplement use, overall health rating, diabetes, cardiovascular disease, cancer, and for women, menopause status and use of hormone |

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|---|---|---|---|---|---|---|
| | thetic, healed | | | | | replacement therapy |
| Melton, 2003 | osteoporotic | protein, dietary | per SD decrease | HR | 1.27 (1.05, 1.53) | Multivariate models combining the independent predictors from all of these risk factor domains were created |
| Cui, 2022 | osteoporotic | soybeans, daidzein | >17.6 mg/d vs <7.7 | HR | 0.75 (0.58, 0.97) | Age, income, educational level, cigarette smoking status, alcohol consumption, regular exercise, BMI, Charlson's Score, breasting time, calcium supplement use, daily dietary intake of calories, vitamin D, calcium and magnesium |
| Cui, 2022 | osteoporotic | soybeans, genistein | >=24.2 mg/d vs <10.6 | HR | 1.22 (1.01, 1.48) | Age, income, educational level, cigarette smoking status, alcohol consumption, regular exercise, BMI, Charlson's Score, breasting time, calcium supplement use, daily dietary intake of calories, vitamin D, calcium and magnesium |
| Kojima, 2020 | osteoporotic | soybeans, natto (fermented soybeans) | >=7 packs/wk vs <1 pack/wk | HR | 0.56 (0.32, 0.99) | age, BMD at total hip, BMI, history of osteoporotic fractures, history of myocardial infarction or stroke, presence of diabetes, current smoking, alcohol intake, frequency of intake of tofu and other soybean products, dietary calcium intake |
| Cui, 2022 | osteoporotic | soybeans, soy isoflavone | >42 mg/d vs <18.7 | HR | 1.22 (1.01, 1.48) | Age, income, educational level, cigarette smoking status, alcohol consumption, regular exercise, BMI, Charlson's Score, breasting time, calcium supplement use, daily dietary intake of calories, vitamin D, calcium and magnesium |

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|---|---|---|---|---|---|---|
| Shen, 2018 | any | tea, / | daily vs never | HR | 0.88 (0.83, 0.93) | sex, level of education, marital status, alcohol consumption, smoking status, physical activity, frequencies of red meat, fruits, vegetables, and dairy products intake, BMI, waist to hip ratio, prevalent hypertension, prevalent diabetes, menopausal status in women |
| Sim, 2018 | any excluding face, fingers, toes, those caused by motor vehicle injuries | vegetables, / | per number of different vegetables consumed daily | HR | 0.91 (0.84, 0.99) | age, BMI, treatment code, prevalent diabetes, socioeconomic status, physical activity, smoking history, energy, protein, calcium, alcohol |

**Appendix 7** Diseases and Fractures

| first author | fracture site | factor, detail | comparison (exposed vs unexposed) | effect measure | effect size | adjusted for |
|---|---|---|---|---|---|---|
| Huopio, 2005 | any | alcoholism, / | Y vs N | HR | 3.49 (1.29, 9.45) | age, weight, height, HRT-use, previous fracture history and femoral neck BMD |
| Chen, 2010 | any | anemia, / | Y vs N | HR | 1.07 (1.01, 1.14) | study arm assignment and interventions (observation study participants versus clinical trial controls or interventions), race/ ethnicity, age, height, weight, self reported general health (fair/poor health versus good/excellent health), baseline number of falls (none versus one, two, or three or more falls), diabetes ever, osteoporosis ever, cancer ever, total calcium intake, total vitamin D intake, total iron intake, physical function(< 80 score versus 80–90 score or 91–100 score), physical activity (total METS/wk), smoking (never versus past or current smoker), hormone therapy (never versus past or current user), fractured after age 55, and depression |
| Jaiswal, 2023 | any | anemia, / | Y vs N | HR | 1.80 (1.41, 2.28) | age, height, weight, FRAX CRFs, and FN BMD |

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|---|---|---|---|---|---|---|
| Lee, 2019 | any | anemia, / | Y vs N | HR | 1.10 (1.04, 1.16) | age, body mass index, alcohol, smoking, physical activity, income, hypertension, diabetes, dyslipidemia, stroke, chronic kidney disease, cancer, osteoporosis, and rheumatic arthritis |
| Gregson, 2014 | any | asthma, / | Y vs without any morbidities | HR | 1.58 (1.36, 1.84) | none |
| Stumpf, 2020 | any | cancer, breast | receiving aromatase inhibitors vs healthy cohort | OR | 3.36 (2.65, 4.26) | BMI, smoking behavior, comorbidities, and corticosteroid therapy |
| Gregson, 2014 | any | cancer, / | Y vs without any morbidities | HR | 1.61 (1.40, 1.86) | none |
| Rees-Punia, 2023 | fragility | cancer, invasive | survivor vs no cancer history | HR | 1.57 (1.38, 1.79) | age, sex, race and ethnicity, US Census region, moderate- to vigorous-intensity aerobic physical activity, body mass index, alcohol consumption, smoking, comorbidity score, diet quality score, age at menopause, hormone replacement therapy use, self-reported fracture history prior to baseline, radiotherapy, and chemotherapy |
| Rees-Punia, 2023 | fragility | cancer, invasive | localized stage cancer survivor vs no cancer history | HR | 1.15 (1.02, 1.29) | age, sex, race and ethnicity, US Census region, moderate- to vigorous-intensity aerobic physical activity, body mass index, alcohol consumption, smoking, comorbidity score, diet quality score, |

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|---|---|---|---|---|---|---|
| | | | | | | age at menopause, hormone replacement therapy use, self-reported fracture history prior to baseline, radiotherapy, and chemotherapy |
| Rees-Punia, 2023 | fragility | cancer, invasive | regional stage cancer survivor vs no cancer history | HR | 1.51 (1.25, 1.82) | age, sex, race and ethnicity, US Census region, moderate- to vigorous-intensity aerobic physical activity, body mass index, alcohol consumption, smoking, comorbidity score, diet quality score, age at menopause, hormone replacement therapy use, self-reported fracture history prior to baseline, radiotherapy, and chemotherapy |
| Rees-Punia, 2023 | fragility | cancer, invasive | distant metastasis stage cancer survivor vs no cancer history | HR | 2.12 (1.75, 2.58) | age, sex, race and ethnicity, US Census region, moderate- to vigorous-intensity aerobic physical activity, body mass index, alcohol consumption, smoking, comorbidity score, diet quality score, age at menopause, hormone replacement therapy use, self-reported fracture history prior to baseline, radiotherapy, and chemotherapy |
| Rees-Punia, 2023 | fragility | cancer, invasive | distant metastasis stage cancer survivor vs no cancer history | HR | 1.57 (1.19, 2.06) | age, sex, race and ethnicity, US Census region, moderate- to vigorous-intensity aerobic physical activity, body mass index, alcohol consumption, smoking, comorbidity score, diet quality score, age at menopause, hormone replacement therapy use, self-reported fracture history prior to baseline, radiotherapy, and chemotherapy |

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|---|---|---|---|---|---|---|
| Lai, 2013 | MOF | cardiovascular, cardiovascular disease | Y vs N | HR | 1.18 (1.11, 1.25) | age, hypertension, arrhythmia, hyperlipidemia, diabetes mellitus, dementia, Parkinson's disease, chronic kidney disease, osteoporosis, menopause, thiazolidinedione, glucocorticoid, bisphosphonate, calcitonin, estrogen, and raloxifene |
| Gregson, 2014 | any | cardiovascular, cerebrovascular event | Y vs without any morbidities | HR | 2.02 (1.67, 2.46) | none |
| Huopio, 2005 | any | cardiovascular, coronary artery disease | Y vs N | HR | 1.76 (1.13, 2.76) | age, weight, height, HRT-use, previous fracture history and femoral neck BMD |
| Gregson, 2014 | any | cardiovascular, ischemic heart disease | Y vs without any morbidities | HR | 1.86 (1.62, 2.14) | none |
| Tanislav, 2020 | any | cardiovascular, stroke | yes vs no stroke/ITA | HR | 1.29 (1.13, 1.47) | comorbidities and previous therapies |
| FitzGerald, 2012 | major | celiac disease, / | ever vs N | HR | 2.1 (NR, NR) | age, weight, BMI, any baseline fracture, maternal hip fracture, paternal hip fracture, currrent smoker, weight loss in 12 months, falls in past year, comorbidities, general health, physical activity, drinks/week) |
| Gregson, 2014 | any | celiac disease, / | Y vs without any morbidities | HR | 2.11 (1.43, 3.11) | none |

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|---|---|---|---|---|---|---|
| Huopio, 2005 | any | chronic hepatic disease, / | Y vs N | HR | 5.22 (1.66, 16.41) | age, weight, height, HRT-use, previous fracture history and femoral neck BMD |
| Dennison, 2012 | any | COPD, / | Y vs N | HR | 1.2 (1.1, 1.4) | FRAX risk factors, comorbidities (hypertension, heart disease, high cholesterol, asthma, chronic obstructive pulmonary disease [COPD], arthritis [reported osteoarthritis or rheumatoid arthritis], stroke, inflammatory bowel disease, celiac disease, Parkinson's disease, multiple sclerosis, cancer, and type I diabetes) |
| Gregson, 2014 | any | COPD, / | Y vs without any morbidities | HR | 1.95 (1.67, 2.28) | none |
| Lui, 2024 | MOF | COVID-19, / | Y vs N | HR | 1.16 (1.07, 1.26) | NR |
| Schwartz, 2001 | nonvertebral | diabetes, / | not using insulin vs nondiabetics | RR | 1.30 (1.10, 1.53) | age, BMI, calcaneal BMD, height, height loss since age 25, contrast sensitivity, resting pulse, history of stroke, use of long-acting benzodiazepines, grip strength, and fell in past year |
| Leslie, 2013 | MOF | diabetes, T1 and T2 | Y vs N | HR | 1.47 (1.25, 1.73) | age, BMI, glucocorticoids, prior major fracture, RA, COPD, alcohol abuse, and osteoporosis therapy, diabetes, lumbar spine TBS and BMD |

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|---|---|---|---|---|---|---|
| Ahmeidat, 2021 | any | diabetes, Gestational diabetes mellitus | Y vs N | HR | 1.60 (1.09, 2.35) | age at baseline, BMI, smoking status, ac tivity level, area deprivation index, self-reported stroke, diabetes mellitus prevalence, vitamin D nutrition, calcium nutrition, diuretics for > 3months, calcium and vitamin D supplement, social class and education, statin and total blood cholesterol, HT, menopausal status |
| Shieh, 2023 | any | diabetes, prediabetes | with before MT vs without | HR | 2.26 (1.13, 4.49) | age at start of the MT, body mass index at start of the MT, cigarette use at start of the MT, fracture before the MT, use of bone-detrimental medications before the MT, use of bone-detrimental medications during fracture observation, race and ethnicity, and study site, femoral neck BMD |
| Gregson, 2014 | any | diabetes, T1 | Y vs without any morbidities | HR | 1.85 (1.50, 2.28) | none |
| Jiajue, 2019 | nonvertebral | diabetes, T2 | Y vs N | OR | 2.25 (1.27, 3.98) | age, YSM, BMI, FN BMD, and any previous fractures |
| Lee, 2015 | any excluding hands, fingers, feet, toes | diabetes, T2 | Y vs N | HR | 1.20 (1.11, 1.30) | age, race, BMI, functional status, medical history, medications |

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|---|---|---|---|---|---|---|
| Thong, 2021 | any | diabetes, T2 | Y vs N | OR | 2.49 (1.64, 3.77) | diabetes, age, BMI, MHT use, reproductive lifespan, falls |
| Zoulakis, 2024 | any excluding skull, fingers, toes | diabetes, T2 | Y vs N | HR | 1.26 (1.04, 1.54) | age, body mass index (BMI), CRFs (previous fragility fracture, parental hip fracture, smoking, alcohol consumption, glucocorticoids, rheumatoid arthritis, and secondary osteoporosis), previous osteoporosis medications, femoral neck BMD |
| Huopio, 2005 | any | epilepsy, / | Y vs N | HR | 1.97 (1.08, 3.62) | age, weight, height, HRT-use, previous fracture history and femoral neck BMD |
| Paskins, 2018 | MOF | giant cell arteritis, / | Y vs N | HR | 1.79 (1.40, 2.3) | age, sex, BMI, alcohol consumption, smoking status, Charlson comorbidity index and PPI use |
| Paskins, 2018 | MOF | giant cell arteritis, / | Y vs N | HR | 1.65 (1.39, 1.95) | age, sex, BMI, alcohol consumption, smoking status, Charlson comorbidity index and PPI use |
| Paskins, 2018 | MOF | giant cell arteritis, / | Y vs N | HR | 1.48 (1.13, 1.94) | age, sex, BMI, alcohol consumption, smoking status, Charlson comorbidity index and PPI use |
| Gregson, 2014 | any | Hypercholesterolemia, / | Y vs without any morbidities | HR | 1.35 (1.19, 1.52) | none |

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|---|---|---|---|---|---|---|
| Gregson, 2014 | any | hypertension, / | Y vs without any morbidities | HR | 1.39 (1.23, 1.57) | none |
| Huopio, 2005 | any | hypertension, / | Y vs N | HR | 1.42 (1.06, 1.90) | age, weight, height, HRT-use, previous fracture history and femoral neck BMD |
| Daya, 2022 | any | hyperthyroidism, subclinical | Y vs euthyroidism | HR | 1.34 (1.09, 1.65) | age, sex, race by center, s diabetes, high-density lipoprotein cholesterol, antihypertensive treatment, heart rate, body mass index, smoking status, alcohol consumption, physical activity, menopause, and vitamin D level. |
| Huopio, 2005 | any | hyperthyroidism, / | Y vs N | HR | 1.70 (1.01, 2.86) | age, weight, height, HRT-use, previous fracture history and femoral neck BMD |
| Gregson, 2014 | any | inflammatory bowel disease, / | Y vs without any morbidities | HR | 2.00 (1.56, 2.57) | none |
| Papaioannou, 2005 | nonvertebral | inflammatory bowel disease, / | Y vs N | RR | 1.683 (1.084, 2.613) | age, current height, height loss, current weight, weight loss, BMI, lumbar spine and femoral neck BMD, SF-36 PCS, and prevalent vertebral fracture status |
| Papaioannou, 2005 | nonvertebral | kidney disease, / | Y vs N | RR | 3.084 (1.560, 6.099) | age, current height, height loss, current weight, weight loss, BMI, lumbar spine and femoral neck BMD, SF-36 PCS, and prevalent vertebral fracture status |

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|---|---|---|---|---|---|---|
| Dennison, 2012 | any | multiple sclerosis, / | Y vs N | HR | 1.7 (1.2, 2.6) | FRAX risk factors, comorbidities (hypertension, heart disease, high cholesterol, asthma, chronic obstructive pulmonary disease [COPD], arthritis [reported osteoarthritis or rheumatoid arthritis], stroke, inflammatory bowel disease, celiac disease, Parkinson's disease, multiple sclerosis, cancer, and type I diabetes) |
| FitzGerald, 2012 | major | multiple sclerosis, / | ever vs N | HR | 1.9 (NR, NR) | age, weight, BMI, any baseline fracture, maternal hip fracture, paternal hip fracture, current smoker, weight loss in 12 months, falls in past year, comorbidities, general health, physical activity, drinks/week) |
| Gregson, 2014 | any | multiple sclerosis, / | Y vs without any morbidities | HR | 2.70 (1.90, 3.83) | none |
| Castano-Betancourt, 2013 | nonvertebral | osteoarthritis, hip | atrophic type vs subjects without OA | HR | 1.44 (1.08, 1.92) | age, height, weight, and femoral neck bone mineral density |
| Lee, 2010 | hip, wrist, humerus, rib, pelvis | osteoarthritis, / | Y vs N | RR | 1.73 (1.17, 2.58) | Age, body mass index, menopausal state, history of previous fracture, hip circumference, weekly dairy product consumption, regular exercise duration, alcohol intake, and history of RA and OA, SoSR, SoST |

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|---|---|---|---|---|---|---|
| Dennison, 2012 | any | osteoarthritis, / | Y vs N | HR | 1.2 (1.1, 1.3) | FRAX risk factors, comorbidities (hypertension, heart disease, high cholesterol, asthma, chronic obstructive pulmonary disease [COPD], arthritis [reported osteoarthritis or rheumatoid arthritis], stroke, inflammatory bowel disease, celiac disease, Parkinson's disease, multiple sclerosis, cancer, and type I diabetes) |
| FitzGerald, 2012 | major | osteoarthritis, / | ever vs N | HR | 1.9 (NR, NR) | age, weight, BMI, any baseline fracture, maternal hip fracture, paternal hip fracture, current smoker, weight loss in 12 months, falls in past year, comorbidities, general health, physical activity, drinks/week) |
| Gregson, 2014 | any | osteoarthritis, / | Y vs without any morbidities | HR | 1.63 (1.44, 1.85) | none |
| Prieto-Alhambra, 2013 | any | osteoarthritis, / | Y vs N | HR | 1.16 (1.08, 1.25) | age, body mass index, antiosteoporosis medication use, chronic obstructive pulmonary disease or emphysema, Parkinson's disease, fracture history, parental hip fracture history, baseline oral corticosteroid use, and secondary osteoporosis (as defined by use of aromatase inhibitors, diagnosis of inflammatory bowel disease, type 1 diabetes, and menopause before age 45 years). |

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|---|---|---|---|---|---|---|
| Dennison, 2012 | any | Parkinson's disease, / | Y vs N | HR | 1.9 (1.3, 2.8) | FRAX risk factors, comorbidities (hypertension, heart disease, high cholesterol, asthma, chronic obstructive pulmonary disease [COPD], arthritis [reported osteoarthritis or rheumatoid arthritis], stroke, inflammatory bowel disease, celiac disease, Parkinson's disease, multiple sclerosis, cancer, and type I diabetes) |
| Gregson, 2014 | any | Parkinson's disease, / | Y vs without any morbidities | HR | 3.89 (2.78, 5.44) | none |
| Paskins, 2018 | MOF | polymyalgia rheumatica, / | Y vs N | HR | 1.85 (1.56, 2.10) | age, sex, BMI, alcohol consumption, smoking status, Charlson comorbidity index and PPI use |
| Paskins, 2018 | MOF | polymyalgia rheumatica, / | Y vs N | HR | 1.51 (1.38, 1.64) | age, sex, BMI, alcohol consumption, smoking status, Charlson comorbidity index and PPI use |
| Paskins, 2018 | MOF | polymyalgia rheumatica, / | Y vs N | HR | 1.61 (1.43, 1.81) | age, sex, BMI, alcohol consumption, smoking status, Charlson comorbidity index and PPI use |
| Paskins, 2018 | fragility | psoriasis, / | Y vs N | HR | 1.15 (1.03, 1.29) | age, gender, BMI, alcohol consumption, smoking status, Charlson comorbidity, bisphosphonate, glucocorticoid, and PPI use |
| Paskins, 2018 | fragility | psoriasis, / | Y vs N | HR | 1.21 (1.09, 1.35) | age, gender, BMI, alcohol consumption, smoking status, Charlson comorbidity, bisphosphonate, glucocorticoid, and PPI use |

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|---|---|---|---|---|---|---|
| Huopio, 2005 | any | pulmonary embolism, / | Y vs N | HR | 3.51 (1.12, 10.98) | age, weight, height, HRT-use, previous fracture history and femoral neck BMD |
| Yeh, 2016 | fragility | Respiratory tuberculosis, / | Y vs N | HR | 1.76 (1.12, 2.75) | age, sex, occupation, drug of oral steroid, bisphosphonates, hormone replacement therapy (HRT), vitamin D supplements, and aromatase inhibitors and each comorbidity [including hyperlipidemia, hypertension, diabetes, pneumonia, live cirrhosis, ischemia heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), alcohol-related illness, hyperparathyroidism, celiac disease, Chron's disease, and lower body weight]; |
| Yeh, 2016 | fragility | Respiratory tuberculosis, / | Y vs N | HR | 1.94 (1.18, 3.19) | age, sex, occupation, drug of oral steroid, bisphosphonates, hormone replacement therapy (HRT), vitamin D supplements, and aromatase inhibitors and each comorbidity [including hyperlipidemia, hypertension, diabetes, pneumonia, live cirrhosis, ischemia heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), alcohol-related illness, hyperparathyroidism, celiac disease, Chron's disease, and lower body weight]; |

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|---|---|---|---|---|---|---|
| Gregson, 2014 | any | rheumatoid arthritis, / | Y vs without any morbidities | HR | 2.15 (1.53, 3.04) | none |
| Tsai, 2014 | MOF | schizophrenia, / | Y vs N | HR | 1.852 (1.638, 2.095) | demographic data and osteoporotic fracture-related illness |
| Axelsson, 2022 | any | seasonal influenza, hospitalization | Y vs N | HR | 1.24 (1.12, 1.38) | age, sex, CCI, length of admission, number of admission last 5 years, rural residency, non-nordic citizenship at birth, osteoporosis, secondary osteoporosis, osteoporosis medication last year, calcium or VD last year, prednisolone use, previous alcohol-related disease 5 years, previous RA 5 years, previous fracture, previous fall injury, PD, knee replacement, hip replacement, fall-related medications last year |
| Huopio, 2005 | any | thrombocytopenia, / | Y vs N | HR | 5.25 (1.30, 21.19) | age, weight, height, HRT-use, previous fracture history and femoral neck BMD |

**Appendix 8** Genetic Factors and Fractures

| first author | fracture site | factor, detail | comparison (exposed vs unexposed) | effect measure | effect size | adjusted for |
|---|---|---|---|---|---|---|
| Yazdan panah, 2007 | fragility | collagen type Ia1 (COLIA1)_haplotype (promoter - intron): 1997G/T_rs1107946 - Sp1 G/T_rs1800012 | G promoter-T intron vs G promoter- G intron | OR | 2.12 (1.23, 2.12) | age, BMI |
| Uitterlinden, 2001 | nonvertebral | vitamin D receptor (VDR)_haplotype computed from BsmI_rs1544410, ApaI_rs7975232, TaqI_rs731236 | homozygetes 11 vs reference 22, 23 and 33 | OR | 2.4 (1.2, 2.4) | age, weight, and femoral neck BMD |
| Uitterlinden, 2001 | nonvertebral | collagen type Ia1 (COLIA1)_rs1800012 (Sp1 site) | TT vs GG | OR | 3.3 (1.3, 3.3) | age, weight, and femoral neck BMD |
| Yazdan panah, 2007 | fragility | collagen type Ia1 (COLIA1)_rs1800012 (Sp1 site) | TTvs GG | RR | 2.33 (1.39, 2.33) | age, BMI |
| Swanberg, 2012 | osteoporotic | C-type lectin domain 16A (CLEC16A)_rs725613 | TG/GG vs TT | OR | 0.705 (0.522, 0.705) | weight, TB BMD |
| Torekov, 2014 | nonvertebral | Glucose Dependent Insulinotropic Polypeptide Receptor (GIPR)_rs1800437 | CC vs GG | HR | 1.6 (1.0, 1.6) | age, HT and BMI. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Swanberg, 2012 | osteoporotic | Major Histocompatibility Complex class II transactivator (MHC2TA, CIITA)_rs3087456 | AG/GG vs AA | OR | 0.732 (0.538, 0.732) | weight, TB BMD |
| Abrahamsen, 2003 | any excluding finger and toe | methylenetetrahydrofolate reductase (MTHFR)_ rs1801133(C677T) | TTvs (CC+CT) | HR | 2.4 (1.1, 2.4) | lumbar spine BMD |
| Harslof, 2013 | osteoporotic | Myostatin (MSTN)_ rs7570532 | GG vs (AG+AA) | HR | 1.82 (1.15, 1.82) | Adjusting the analyses for changes in LBM did not change the results |
| Tranah, 2008 | nonvertebral nonhip | prolactin PRL_T228C_ rs7739889 | TC vs TT | HR | 0.81 (0.68, 0.81) | age, clinic site, and self-reported ethnicity (northern, central, and southern European) |
| Tranah, 2008 | nonvertebral nonhip | prolactin PRL_T228C_ rs7739889 | CC vs TT | HR | 0.80 (0.67, 0.80) | age, clinic site, and self-reported ethnicity (northern, central, and southern European) |

**Appendix 9** Lifestyle Factors and Fractures

| first author | fracture site | factor, detail | comparison (exposed vs unexposed) | effect measure | effect size | adjusted for |
|---|---|---|---|---|---|---|
| Feart, 2013 | hip, vertebral and wrist | alcohol, / | >=4 vs 1-4 glasses (1.4-5.7g/d) per week | HR | 0.61 (0.42, 0.88) | each individual food group component of the Mediterranean diet score, age, gender, physical activity, total energy intake, educational level, marital status, BMI, self-reported osteoporosis, osteoporosis treatment, calcium and/or vitamin D treatment |
| Hansen, 2000 | any | alcohol, / | beer >=2 glasses/ day vs <1 /month | RR | 1.55 (1.25, 1.92) | age |
| Hansen, 2000 | any | alcohol, / | liquor >=2 glasses/ day vs <1 /month | RR | 1.25 (1.03, 1.54) | age |
| Lee, 2010 | hip, wrist, humerus, rib, pelvis | alcohol, / | >=1.82 unit/week vs <1.82 | RR | 2.07 (1.22, 3.51) | Age, body mass index, menopausal state, history of previous fracture, hip circumference, weekly dairy product consumption, regular exercise duration, alcohol intake, and history of RA and OA, SoSR, SoST |
| Tuppurainen, 1995 | low energy | alcohol, / | Y vs N | OR | 1.45 (1.05, 2.02) | age |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ostbye, 2004 | any | alcohol, used regularly | Y vs N | OR | 1.72 (1.23, 2.40) | multivariable |
| Appleby, 2008 | any excluding fingers, thumb, toes, or ribs | physical activity, bicycling | 2-4.5 vs 0 h/week | IRR | 1.50 (1.16, 1.93) | method of recruitment and adjusted for age, energy and calcium intake, smoking, alcohol consumption, body mass index, marital status, use of HRT, and number of children, and further adjusted for each other |
| Appleby, 2008 | any excluding fingers, thumb, toes, or ribs | physical activity, bicycling | >=5 vs 0 h/week | IRR | 1.45 (1.04, 2.03) | method of recruitment and adjusted for age, energy and calcium intake, smoking, alcohol consumption, body mass index, marital status, use of HRT, and number of children, and further adjusted for each other |
| Nikander, 2011 | low trauma | physical activity, frequency | times/ week | OR | 1.03 (1.01, 1.06) | age, BMI, QOL (total score of physical component), history of CVD, previous history of fractures, smoking status, calcium intake and serum 25(OH)D |
| Morseth, 2012 | weight bearing | physical activity, leisure time | moderate/ high (at least 3 hrs) vs sedentary (0h/wk) | HR | 0.77 (0.62, 0.95) | age, smoking, body mass index, height, and previous fracture |
| Heesch, 2008 | any in the previous 12 months | physical activity, / | very high vs none/ very low | OR | 0.53 (0.34, 0.83) | country of birth, number of chronic conditions, eyesight problems, body mass index, and previous fall, injury from fall or fractured bone at S2 |

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| Rouzi, 2012 | osteoporotic | physical activity, / | 7 day PAR score <=12.61 vs >12.61 | RR | 2.87 (1.88, 4.38) | Binary logistic regression with forward stepwise analysis for multiple factors was used to assess relationships with incident of ORFs |
| Appleby, 2008 | any excluding fingers, thumb, toes, or ribs | physical activity, at work | standing vs not working or sedentary | IRR | 0.78 (0.63, 0.98) | method of recruitment and adjusted for age, energy and calcium intake, smoking, alcohol consumption, body mass index, marital status, use of HRT, and number of children, and further adjusted for each other |
| LaMonte, 2019 | any | physical activity, recreational | >0 to 7.5 MET h/wk vs 0 | HR | 0.94 (0.90, 0.98) | age, race/ethnicity, education, smoking status, alcohol use, height, weight, history of fracture after age 55 years, bone drug use, corticosteroid use, calcium intake, vitamin D intake, lifetime hormone therapy use (years), falls in the past year, physical function construct, thiazide use, diabetes, age at menopause, history of osteoporosis, and sedentary time. |
| LaMonte, 2019 | any | physical activity, recreational | >7.5 to 17.7 MET h/wk vs 0 | HR | 0.95 (0.91, 0.99) | age, race/ethnicity, education, smoking status, alcohol use, height, weight, history of fracture after age 55 years, bone drug use, corticosteroid use, calcium intake, vitamin D intake, lifetime hormone therapy use (years), falls in the past year, physical function construct, thiazide use, diabetes, age at menopause, history of osteoporosis, and sedentary time. |

| | | | | | | |
|---|---|---|---|---|---|---|
| LaMonte, 2019 | any | physical activity, recreational | >17.7 MET h/wk vs 0 | HR | 0.94 (0.90, 0.98) | age, race/ethnicity, education, smoking status, alcohol use, height, weight, history of fracture after age 55 years, bone drug use, corticosteroid use, calcium intake, vitamin D intake, lifetime hormone therapy use (years), falls in the past year, physical function construct, thiazide use, diabetes, age at menopause, history of osteoporosis, and sedentary time. |
| Lee, 2010 | hip, wrist, humerus, rib, pelvis | physical activity, regular exercise | >=30min per day vs <30 | RR | 0.58 (0.34, 0.98) | Age, body mass index, menopausal state, history of previous fracture, hip circumference, weekly dairy product consumption, regular exercise duration, alcohol intake, and history of RA and OA, SoSR, SoST |
| LaMonte, 2019 | any | physical activity, sedentary behavior | >9.5 h/d vs <6.5 | HR | 1.04 (1.01, 1.07) | age, race/ethnicity, education, smoking status, alcohol use, height, weight, history of fracture after age 55 years, bone drug use, corticosteroid use, calcium intake, vitamin D intake, lifetime hormone therapy use (years), falls in the past year, physical function construct, thiazide use, diabetes, age at menopause, history of osteoporosis, and total recreational physical activity |
| FitzGerald, 2012 | major | physical activity, walking | not at all vs very active | HR | 1.6 (NR, NR) | age, weight, BMI, any baseline fracture, maternal hip fracture, paternal hip fracture, current smoker, weight loss in 12 months, falls in past year, comorbidities, general health, physical activity, drinks/week) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Nikander, 2011 | low trauma | physical activity, walking | times/ week | OR | 1.06 (1.02, 1.09) | in the multivariate model independent of moderate to vigorous physical activity |
| Nikander, 2011 | low trauma | physical activity, walking | >3 hours per week vs no walking | OR | 1.51 (1.01, 2.24) | independent of moderate to vigorous physical activity |
| LaMonte, 2019 | any | physical activity, yard work | >6 MET h/wk vs 0 | HR | 0.95 (0.82, 0.98) | age, race/ethnicity, education, smoking status, alcohol use, height, weight, history of fracture after age 55 years, bone drug use, corticosteroid use, calcium intake, vitamin D intake, lifetime hormone therapy use (years), falls in the past year, physical function construct, thiazide use, diabetes, age at menopause, history of osteoporosis, recreational physical activity, and sedentary time |
| Otonari, 2021 | any | skipping breakfast, / | seldom vs almost everyday | OR | 2.30 (1.41, 3.74) | multiple |
| Jacqmin-Gadda, 1998 | nonhip | smoking, / | current vs nonsmoker | OR | 1.68 (1.08, 2.60) | none |
| Jorgensen, 2011 | nonvertebral | smoking, / | current >=20 cigarettes per day vs never | HR | 1.93 (1.30, 2.84) | age, body mass index, physical inactivity, alcohol consumption habits, prevalent cardiovascular disease, and present use of hormone replacement therapy |

**Appendix 10** Medical Conditions and Fractures

| first author | fracture site | factor, detail | comparison (exposed vs unexposed) | effect measure | effect size | adjusted for |
|---|---|---|---|---|---|---|
| Tolea, 2007 | any | depressive symptoms, CESD score | >=16 vs <16 | OR | 1.39 (1.01, 1.95) | controlling for other independent variables |
| Mober g, 2014 | any | family history of diabetes, / | Yes vs No | OR | 0.66 (0.44, 0.98) | age, BMI, current smoking status, marital status, number of falls, fractures after age 40, family history of diabetes, SSRIs, PPIs, p.o. corticosteroids, previous use of oral contraceptives, age at menopause, amenorrhea for 6 months or more |
| Naves, 2005 | osteoporotic | family history of fracture, hip | Y vs N | OR | 3.59 (1.01, 12.79) | age, handgrip strength, femoral neck BMD, prevalent vertebral fracture and the history of falls in the follow-up |
| Torger son, 1996 | any | family history of fracture, hip by maternal grandmother | Y vs N | OR | 3.70 (1.50, 8.85) | stepwise logistic regression analysis was undertaken for all the variables |
| FitzGe rald, 2012 | major | family history of fracture, maternal hip | Y vs N | HR | 1.4 (NR, NR) | age, weight, BMI, any baseline fracture, maternal hip fracture, paternal hip fracture, current smoker, weight loss in 12 months, |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | falls in past year, comorbidities, general health, physical activity, drinks/week) |
| Otonari, 2021 | any | family history of fracture, parental | Y vs N | OR | 1.42 (1.04, 1.94) | multiple |
| Ahn, 2014 | fragility | family history of osteoporosis, parental | Y vs N | HR | 2.03 (1.18, 3.49) | age, body mass index, previous fracture history, parental history of osteoporosis, dietary calcium intake, menopausal status, duration of total breast-feeding, and bone mineral density |
| Nguyen, 2007 | osteoporotic | personal history of fall, the last 12 months | Y vs N | HR | 1.89 (1.52, 2.34) | age, postural sway, quadriceps strength, FNBMD, fall, and prior fracture |
| FitzGerald, 2012 | major | personal history of fall, in past year | 1 vs 0 | HR | 1.1 (NR, NR) | age, weight, BMI, any baseline fracture, maternal hip fracture, paternal hip fracture, current smoker, weight loss in 12 months, falls in past year, comorbidities, general health, physical activity, drinks/week) |
| FitzGerald, 2012 | major | personal history of fall, in past year | >=2 vs 0 | HR | 1.6 (NR, NR) | age, weight, BMI, any baseline fracture, maternal hip fracture, paternal hip fracture, current smoker, weight loss in 12 months, |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | falls in past year, comorbidities, general health, physical activity, drinks/week) |
| Afrin, 2020 | any | personal history of fall, in the 12 months prior to baseline | any fall vs no fall | OR | 1.38 (1.14, 1.66) | age, BMI, dairy calcium intake, number of prescribed medications, number of chronic health disorders, use of estrogen hormone therapy during follow up, current smoking, alcohol use, leisure physical activity, and restricted mobility |
| Portho use, 2004 | nonvertebral excluding fingers, toes, ribs | personal history of fall, in the last 12 months | Y vs N | OR | 2.06 (1.63, 2.59) | NR |
| Thong, 2021 | any | personal history of fall, in the past 12 months | Y vs N | OR | 2.16 (1.81, 2.59) | diabetes, age, BMI, MHT use, reproductive lifespan, falls |
| Rouzi, 2012 | osteoporotic | personal history of fall, fall in the past year | Y vs N | RR | 1.61 (1.06, 2.48) | Binary logistic regression with forward stepwise analysis for multiple factors was used to assess relationships with incident of ORFs |
| Kim, 2022 | nonvertebral | personal history of fall, in the previous 4 months | at least one fall but no fracture vs no fall no fracture | OR | 2.4 (2.3, 2.5) | The multivariate model for fractures included a fall history and any adjudicated fracture in the preceding 4 months, age, BMI and total hip BMD to evaluate the |

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|---|---|---|---|---|---|---|
| | | | | | | independent predictive values |
| Edwards, 2013 | any | personal history of fall, since age 45 | Y vs N | HR | 2.64 (1.21, 5.78) | age, weight, height, fracture after aged 45 but before baseline, parent or sibling having a fracture after aged 45, smoker status, diagnosis of rheumatoid arthritis since baseline, number of comorbidities, and alcohol consumption |
| Charles, 2023 | fragility excluding toes, fingers or nose | personal history of fall, / | Y vs N | OR | 1.28 (1.06, 1.55) | Age, history of fall, history of fracture, corticoids use, osteoporosis treatment and BMD |
| Piirtola, 2008 | any | personal history of fracture, compression fracture/s in thoracic or upper lumbar vertebrae at baseline | Y vs N | RR | 2.0 (1.3, 3.0) | Age, handgrip strength, BMI, occurrence of a previous fracture after 45 years of age and compression of thoracic or upper lumbar vertebrae |
| Huopio, 2000 | osteoporotic | personal history of fracture, after age 15 | Y vs N | RR | 1.9 (1.3, 2.9) | independent risk factor but did not specify confounders adjusted for |
| Tuppurainen, 1995 | low energy | personal history of fracture, in the previous 10 years | Y vs N | OR | 2.83 (1.95, 4.10) | age |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ostbye, 2004 | any | personal history of fracture, in the previous 12 months | Y vs N | OR | 2.00 (1.19, 3.35) | multivariable |
| Ojo, 2007 | any | personal history of fracture, after age 50 | Y vs N | HR | 2.52 (1.22, 5.20) | age, gender, marital status, smoking status, medical conditions, any ADL limitation, MMSE, CES-D, near vision impairment, distant vision impairment, BMI, summary performance score of lower body function |
| Ojo, 2007 | any | personal history of fracture, hip after age 50 | Y vs N | HR | 3.03 (1.77, 5.19) | age, gender, marital status, smoking status, medical conditions, any ADL limitation, MMSE, CES-D, near vision impairment, distant vision impairment, BMI, summary performance score of lower body function |
| Lee, 2010 | hip, wrist, humerus, rib, pelvis | personal history of fracture, after 40 | Y vs N | RR | 1.93 (1.17, 3.18) | Age, body mass index, menopausal state, history of previous fracture, hip circumference, weekly dairy product consumption, regular exercise duration, alcohol intake, and history of RA and OA, SoSR, SoST |

| | | | | | | |
|---|---|---|---|---|---|---|
| Mobergg, 2014 | any | personal history of fracture, after 40 | Yes vs No | OR | 1.70 (1.24, 2.32) | age, BMI, current smoking status, marital status, number of falls, fractures after age 40, family history of diabetes, SSRIs, PPIs, p.o. corticosteroids, previous use of oral contraceptives, age at menopause, amenorrhea for 6 months or more |
| Charles, 2023 | fragility excluding toes, fingers or nose | personal history of fracture, after 50 | Y vs N | OR | 1.48 (1.25, 1.76) | Age, history of fall, history of fracture, corticoids use, osteoporosis treatment and BMD |
| Domiciano, 2021 | nonvertebral | personal history of fracture, osteoporotic nonvertebral | Y vs N | RR | 3.08 (1.36, 6.95) | age, weight, BMI, prevalence of any osteoporotic fracture, prevalence of non-vertebral fracture, eGFR, BMD at lumbar spine, BMD at femoral neck, BMD at total hip |
| Ojo, 2007 | any | personal history of fracture, nonhip after age 50 | Y vs N | HR | 2.58 (1.97, 3.38) | age, gender, marital status, smoking status, medical conditions, any ADL limitation, MMSE, CES-D, near vision impairment, distant vision impairment, BMI, summary performance score of lower body function |
| Porthouse, 2004 | nonvertebral excluding fingers, | personal history of fracture, / | Y vs N | OR | 2.67 (2.1, 3.4) | NR |

| | | | | | | |
|---|---|---|---|---|---|---|
| | toes, ribs | | | | | |
| vanGeel, 2007 | any | personal history of fracture, / | Y vs N | HR | 2.9 (2.3, 3.6) | none |
| Torgerson, 1996 | any | personal history of fracture, / | One vs None | OR | 2.10 (1.03, 4.26) | stepwise logistic regression analysis was undertaken for all the variables |
| Torgerson, 1996 | any | personal history of fracture, / | Two or more vs none | OR | 4.04 (1.72, 9.50) | stepwise logistic regression analysis was undertaken for all the variables |
| Torgerson, 1996 | any | personal history of fracture, / | Y vs N | OR | 2.00 (1.31, 3.03) | after adjustment for other covariates |
| Lauppe, 2019 | any | personal history of fracture, hip | Y vs N | HR | 1.3 (1.1, 1.6) | NR |
| Holloway, 2015 | any at age 71+ | personal history of fracture, at age 51-70 | Y vs N | HR | 1.15 (1.06, 1.23) | none |
| Gregson, 2014 | any | self-perceived fracture risk, / | about the same vs much or a little lower | HR | 1.20 (1.10, 1.31) | none |
| Gregson, 2014 | any | self-perceived fracture risk, / | much or a little higher vs much or a | HR | 2.27 (2.06, 2.50) | none |

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|---|---|---|---|---|---|---|
| | | | little lower | | | |

**Appendix 11** Medications and Fractures

| first author | fracture site | factor, detail | comparison (exposed vs unexposed) | effect measure | effect size | adjusted for |
|---|---|---|---|---|---|---|
| Spangler, 2008 | any | antidepressants, / | Y vs N | HR | 1.22 (1.15, 1.30) | age, weight, height, ethnicity, years since menopause, physical function, exercise, current smoking, CVD, analgesic or narcotics, and previous fracture, depressive symptoms |
| Carriere, 2016 | any | antidepressants, fluoxetine | user vs no antidepressant | HR | 2.07 (1.28, 3.32) | age, center, sex, smoking, benzodiazepines, other CNS drugs, osteo-articular pains, time since first MDE, anti-osteoporosis drugs, and oral corticosteroids |
| Diem, 2011 | nonvertebral | antidepressants, SSRIs | current vs nonuser | HR | 1.30 (1.04, 1.62) | age, health status, IADLs, ability to risk from chair, m-MMSE, smoking, alcohol use, estrogen use, bisphosphonate use, benzodiazepine use, thiazide use, proton pump inhibitor use, oral steroid use, weight, GDS score, walks for exercise, history of prior fracture, total hip BMD at Year 6, updating total hip BMD, history of falls in the previous year |

| | | | | | | |
|---|---|---|---|---|---|---|
| Carbone, 2010 | any | Antiepileptic drugs, / | current user (any duration, any type) vs nonuser | HR | 1.44 (1.30, 1.61) | age, race/ethnicity, BMI, smoking, alcohol, calcium and vitamin D intake, history of fractures (fracture at age 55þ), history of falls (two or more in the year prior to enrollment), bisphosphonates, past/current use of HT, SERMs, calcitonin, age of menopause, physical activity levels, physical function construct, diabetes, stroke, parental history of hip fractures, study site region, self-reported health, multiple sclerosis, Parkinson's, WHI trial participation and intervention |
| Colon-Emeric, 2002 | any | Antiepileptic drugs, / | ever vs never | HR | 2.21 (1.27, 3.04) | multivariable analysis identified correlations and interactions among the significant variables. |
| Gafoor, 2019 | all | Antipsychotic drugs, first generation | ever vs never | RR | 1.24 (1.07, 1.43) | age, age-squared, sex, dementia, frailty category, number of deficits, and clustering by patient |
| Gafoor, 2019 | all | Antipsychotic drugs, second generation | ever vs never | RR | 1.12 (1.01, 1.24) | age, age-squared, sex, dementia, frailty category, number of deficits, and clustering by patient |
| Meisinger, 2007 | any | beta blockers, / | Y vs nonusers | HR | 0.60 (0.37, 0.96) | age, sex, survey, BMI, alcohol intake, physical activity, smoking status, hypertension, education, history of diabetes mellitus, thiazide use, and |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | glucocorticosteroid use |
| Rejnmark, 2004 | any | beta blockers, / | Y vs N | OR | 3.3 (1.1, 9.4) | age, years postmenopausal, previous fracture, weight, physical activity, medicine, BMD, biochemistry |
| Papaioannou, 2005 | nonvertebral | diuretics, / | Y vs N | RR | 0.550 (0.304, 0.994) | age, urbanization, charlson index |
| Lauppe, 2019 | any | drugs that increase fall risk, / | Y vs N | HR | 1.3 (1.2, 1.5) | NR |
| Viniol, 2016 | any | levothyroxine, / | current vs nonusers | HR | 1.063 (1.046, 1.080) | age |
| Vestergaard, 2012 | any | NSAIDs, / | Y vs N | HR | 1.44 (1.07, 1.93) | age, HT, BMI, baseline spine BMD, family fracture, prior fracture, serum 25-hydroxy-vitamin, and smoking |
| Steinbuch, 2004 | any | oral glucocorticoids, / | Y vs N | RR | 2.05 (1.67, 2.52) | prior fracture, and prior exposure to oral GCs. |
| Pan, 2014 | any | polypharmacy, fall related medications | use of 1 category vs 0 | OR | 1.26 (1.05, 1.52) | age, urbanization, charlson index |

| | | | | | | |
|---|---|---|---|---|---|---|
| Pan, 2014 | any | polypharmacy, fall related medications | use of 2 category vs 0 | OR | 1.48 (1.24, 1.77) | age, urbanization, charlson index |
| Pan, 2014 | any | polypharmacy, fall related medications | use of 3 category vs 0 | OR | 1.47 (1.24, 1.75) | age, urbanization, charlson index |
| Pan, 2014 | any | polypharmacy, fall related medications | use of >=4 category vs 0 | OR | 2.23 (1.90, 2.62) | age, urbanization, charlson index |
| Lauppe, 2019 | any | polypharmacy, pre-packaged drug dispensing (ApoDos) | Y vs N | HR | 1.4 (1.1, 1.7) | NR |
| Jacqmin-Gadda, 1998 | nonhip | polypharmacy, use of >3 nonpsychotropic drugs | Y vs N | OR | 1.36 (1.04, 1.78) | none |
| Ding, 2014 | any excluding skull | PPIs, / | current users vs nonusers | HR | 1.27 (1.12, 1.43) | gender, race, age, BMI, comorbidity, smoking status, and medication usage status of antidepressants, anxiolytics/sedatives/ hypnotics, antipsychotics, anticonvulsants, loop diuretics, thiazide diuretics, cardiac glycosides, hypotensive agents, vasodilators, antiarrhythmic agents, |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | ARB/ACE inhibitors, calcium channel blockers, b-blockers, statins, osteoporosis drugs, NSAIDs/COX-2 inhibitors, corticosteroids, antidiabetic agents, narcotic analgesics, and thyroid agents |
| Kim, 2020 | osteoporotic | PPIs, / | current users vs nonusers | OR | 1.15 (1.11, 1.20) | CCI, comorbidity, medication |
| Lauppe, 2019 | any | PPIs, / | Y vs N | HR | 1.2 (1.1, 1.3) | NR |
| Lewis, 2014 | MOF | PPIs, / | >=1 year use vs not on long term use | OR | 2.07 (1.14, 3.77) | age, low BMI, physical activity, smoked ever, diabetes, CNS medication use, g total hip bone mineral density, bisphosphonate and corticosteroid use |
| Moberg, 2014 | any | PPIs, / | Yes vs No | OR | 2.53 (1.28, 4.99) | age, BMI, current smoking status, marital status, number of falls, fractures after age 40, family history of diabetes, SSRIs, PPIs, p.o. corticosteroids, previous use of oral contraceptives, age at menopause, amenorrhea for 6 months or more |
| vanderHoorn, 2015 | any | PPIs, / | current or past vs N | HR | 1.29 (1.08, 1.55) | area of residence, age, body mass index, number of chronic conditions, physical functioning, and use of each of |

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|---|---|---|---|---|---|---|
| | | | | | | the following medicines: thyroid hormones, high dose glucocorticoids, aromatase inhibitors, and selective serotonin receptor inhibitors |
| Yu, 2008 | nonvertebral | PPIs, / | current vs never PPI or H2RA | HR | 1.34 (1.10, 1.64) | age, clinic, race, BMI, alcohol use, exercise, oral or inhaled corticosteroid use, NSAID use, calcium supplement use, osteoporosis medication use, self-reported health, initial total hip BMD, and concurrent weight change, caffeine intake, estrogen use |
| Nordstrom, 2019 | any | propiomazine, / | users vs nonusers | OR | 1.51 (1.31, 1.75) | civil status, education, early retirement pension receipt, diagnoses, and drug use |
| Nordstrom, 2019 | any | propiomazine, / | users vs nonusers | OR | 1.27 (1.04, 1.55) | civil status, education, early retirement pension receipt, diagnoses, and drug use |
| Nordstrom, 2019 | any | propiomazine, / | users vs nonusers | OR | 1.44 (1.22, 1.69) | civil status, education, early retirement pension receipt, diagnoses, and drug use |
| Nordstrom, 2019 | any | propiomazine, / | users vs nonusers | OR | 1.57 (1.38, 1.78) | none |
| Nordstrom, 2019 | any | propiomazine, / | users vs nonusers | OR | 1.69 (1.37, 2.08) | none |

| | | | | | | |
|---|---|---|---|---|---|---|
| Nordstrom, 2019 | any | propiomazine, / | users vs nonusers | OR | 1.41 (1.20, 1.64) | none |
| Chan, 2000 | MOF+distal tibia | statins, during the 2 years prior to event | >=1 year use vs never | OR | 0.52 (0.29, 0.91) | age, hospital admissions during the previous year, use of antipsychotic, long-acting hypnotic, or antidepressant drugs during the previous 30 days, and use of thiazide diuretics, hypoglycaemic agents, and systemic steroids during the previous 2 years in conditional logistic regression model. Use of statins and non-statin lipid lowering drugs included in the same model |
| Meier, 2000 | any | statins, / | current use vs nonusers | OR | 0.52 (0.34, 0.79) | BMI, smoking, number of general practitioner visits, steroid or estrogen use |
| Nordstrom, 2019 | any | z-drugs, zolpidem/zopiclone/zaleplon | users vs nonusers | OR | 1.76 (1.61, 1.93) | civil status, education, early retirement pension receipt, diagnoses, and drug use |
| Nordstrom, 2019 | any | z-drugs, zolpidem/zopiclone/zaleplon | users vs nonusers | OR | 1.41 (1.26, 1.59) | civil status, education, early retirement pension receipt, diagnoses, and drug use |
| Nordstrom, 2019 | any | z-drugs, zolpidem/zopiclone/zaleplon | users vs nonusers | OR | 1.43 (1.32, 1.56) | civil status, education, early retirement pension receipt, diagnoses, and drug use |

| | | | | | | |
|---|---|---|---|---|---|---|
| Nordstrom, 2019 | any | z-drugs, zolpidem/zopiclone/zaleplon | users vs nonusers | OR | 2.27 (1.75, 2.95) | civil status, education, early retirement pension receipt, diagnoses, and drug use |
| Nordstrom, 2019 | any | z-drugs, zolpidem/zopiclone/zaleplon | users vs nonusers | OR | 2.40 (1.52, 3.77) | civil status, education, early retirement pension receipt, diagnoses, and drug use |

**Appendix 12** Physical Capability and Fractures

| first author | fracture site | factor, detail | comparison (exposed vs unexposed) | effect measure | effect size | adjusted for |
|---|---|---|---|---|---|---|
| Wagner, 2009 | osteoporotic | balance, impaired | Y vs N | OR | 4.45 (1.50, 13.20) | age (continuous), weight (continuous), height (continuous), body mass index (continuous), physical activity (low, medium, high), difficulty rising from a chair (yes/no), smoking (never, former, current), alcohol use (abstainer, normal consumption, suspected dependence), systemic corticosteroid use (yes/no), a fall within the past 10 years (yes/no), any fracture after the age of 50 years before study entry (yes/no), diabetes mellitus (yes/no), and index for activities of daily living (continuous) |
| Nguyen, 1993 | atraumatic | body sway, / | based on natural logarithmic transformation of mm2. Per SD | OR | 1.90 (1.63, 2.21) | femoral neck BMD, quadriceps strength, body sway |
| Nguyen, 2007 | osteoporotic | body sway, / | per 40 cm2 | HR | 1.08 (1.02, 1.15) | age, postural sway, quadriceps strength, FNBMD, fall, and prior fracture |

| | | | | | | |
|---|---|---|---|---|---|---|
| Colon-Emeric, 2002 | any | daily living activities, Katz | one or more impairments vs none | HR | 1.54 (1.13, 1.92) | multivariable analysis identified correlations and interactions among the significant variables. |
| Stel, 2004 | any excluding toes, fingers, head and those caused by a motor vehicle accident | daily living activities, number of functional limitations | 2-6 vs 0-1 | HR | 3.2 (1.8, 5.5) | age, sex, handgrip strength, physical activity |
| Kamiya, 2019 | osteoporotic | hand grip strength, / | per 5 kg reduction | HR | 1.33 (1.11, 1.60) | age, BMD at total hip, BMI, history of diabetes and log-transformed calcium intake |
| Piirtola, 2008 | any | hand grip strength, / | 48-75 kPa vs 76+ | RR | 1.6 (1.1, 2.3) | Age, handgrip strength, BMI, occurrence of a previous fracture after 45 years of age and compression of thoracic or upper lumbar vertebrae |
| Piirtola, 2008 | any | hand grip strength, / | <=47 kPa vs 76+ | RR | 2.2 (1.4, 3.5) | Age, handgrip strength, BMI, occurrence of a previous fracture after 45 years of age and compression of thoracic or upper lumbar vertebrae |
| Rouzi, 2012 | osteoporotic | hand grip strength, / | <=13.88 kg vs >13.88 | RR | 1.88 (1.15, 3.05) | Binary logistic regression with forward stepwise analysis for multiple factors was used to assess relationships with incident of ORFs |

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|---|---|---|---|---|---|---|
| Sirola, 2008 | low trauma | hand grip strength, / | <54 kPa vs >74 | HR | 1.96 (1.22, 2.13) | fracture history, body mass index, age, years since menopause, use of HRT (yes/no), alcohol intake, smoking, nutritional calcium intake, and bone-affecting diseases/medications |
| Stel , 2004 | any excluding toes, fingers, head and those caused by a motor vehicle accident | hand grip strength, / | <=15 vs >15 | HR | 2.0 (1.1, 3.6) | age, sex, physical activity |
| Karkkainen, 2008 | low energy trauma | quadriceps strength, / | per 1 kg decrease | HR | 1.018 (1.004, 1.033) | age, BMI, current smoking, years since menopause, years of HT and history of fracture |
| Nguyen, 1993 | atraumatic | quadriceps strength, / | based on natural logarithmic transformation of kg. Per SD decrease | OR | 1.83 (1.49, 2.24) | femoral neck BMD, quadriceps strength, body sway |
| Papaioannou, 2005 | nonvertebral | quality of life, SF-36 PCS physical component | per 5-unit decrease | RR | 1.185 (1.108, 1.268) | age, current height, height loss, current weight, weight loss, BMI, lumbar spine and femoral neck BMD, SF-36 PCS, and prevalent vertebral fracture status |

| | | | | | | |
|---|---|---|---|---|---|---|
| Coleman, 2009 | nonvertebral/ nonhip | vision, binocular visual field loss | severe (20+) vs none (0) | HR | 1.46 (1.13, 1.89) | age, race (black vs. white), study sites (four sites), cognitive function (MMSE), current smoker (yes vs. no), alcohol use (yes vs. no), self-reported health status (good/excellent vs. poor/fair), self-reported diabetes (yes vs. no), self-reported hyperthyroidism (yes vs. no), self-reported osteoporosis (yes vs. no), depression (yes vs. no), current use of anticonvulsant drugs (yes vs. no), current use of long-acting benzodiazepines (yes vs. no), body mass index, walking speed, average grip strength, use arms to stand up (yes vs. no), at least one fall in last year (yes vs. no), history of any fractures (yes vs. no) |
| deBoer, 2004 | any excluding head, neck, foot, toes, hand, fingers | vision, recognizing faces from a distance of 4 meters | much difficulty or cannot see vs no difficulty or little difficulty | HR | 3.10 (1.65, 5.82) | age. No additional confounders changed the beta of recognizing faces with >10% |

**Appendix 13** Other Radiographic Parameters and Fractures

| first author | fracture site | factor, detail | comparison (exposed vs unexposed) | effect measure | effect size | adjusted for |
|---|---|---|---|---|---|---|
| Lewis, 2019 | low trauma | ACS, / | >=2 vs 0 or 1 | HR | 1.40 (1.08, 1.81) | age, treatment, hip BMD |
| Zhou, 2014 | nonvertebral | ACS, / | >6 vs 0 | HR | 1.93 (1.54, 3.26) | age, BMI, BMD, history of two or more falls, current smoking, current drinking, previous fracture, hypertension, diabetes, total cholesterol, myocardial infarction, stroke, adiponectin, osteocalcin, leptin and 25(OH)D |
| Sornay-Rendu, 2017 | fragility | ASMI, / | per SD increase | HR | 0.77 (0.62, 0.96) | age, prior Fx, FN BMD, physical activity, incident falls and accounting for competing risk of death |
| Diez-Perez, 2007 | nonvertebral | BUA, central calcaneal zone | per SD decrease | HR | 1.33 (1.17, 1.51) | age, history of falls, prevalent fractures, family history of fractures and calcium intake from dairy products |
| Huang, 1998 | any | BUA, calcaneal | per SD decrease | OR | 1.72 (1.30, 2.31) | age |
| Huopio, 2004 | low energy | | per SD decrease | HR | 1.53 (1.01, 2.33) | age, weight, height, HRT use, previous fracture history and femoral neck BMD |

| | | | | | | |
|---|---|---|---|---|---|---|
| Lasschuit, 2020 | low trauma | BUA, calcaneal | per SD reduction | HR | 1.47 (1.26, 1.71) | age, sex, BMI, fall count and previous fracture after age 50 |
| Dennison, 2014 | any | cortical area 66% slice, nondominant radius | per SD reduction | HR | 1.91 (1.04, 3.49) | total femur BMD, age, BMI, social class, smoker status, alcohol consumption, physical activity, dietary calcium, HRT use and years since menopause |
| Shieh, 2023 | any | fat mass, total percent gain during menopause transition | per SD | HR | 1.39 (1.07, 1.79) | lean mass and fat mass at the start of MT, race/ethnicity, study site, age, cigarette use, and exposure to bone-detrimental medication after the MT, lumbar spine BMD at the end of the MT |
| Hars, 2016 | low trauma excluding fingers, toes, skull | lean mass, appendicular | <=5.45 kg/m2 vs >5.45 | OR | 2.32 (1.04, 5.18) | gender, age, length of follow-up and FRAX probability with femoral neck BMD |
| Shieh, 2023 | any | lean mass, total percent loss during menopause transition | per SD | HR | 1.65 (1.24, 2.21) | lean mass and fat mass at the start of MT, race/ethnicity, study site, age, cigarette use, and exposure to bone-detrimental medication after the MT, lumbar spine BMD at the end of the MT |
| Sornay-Rendu, 2017 | fragility | lean mass, lean mass index | per SD increase | HR | 0.78 (0.62, 0.98) | age, prior fracture, FN BMD, physical activity, incident falls and accounting for competing risk of death |

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| Leslie, 2023 | MOF | lumbar spine TBS, / | per SD | HR | 1.19 (1.13, 1.26) | age, BMI, glucocorticoids, prior major fracture, RA, COPD, alcohol abuse, and osteoporosis therapy, diabetes, lumbar spine TBS and BMD |
| Popp, 2016 | fragility | lumbar spine TBS, / | per SD | HR | 1.87 (1.38, 2.54) | age, BMI, minimum BMD of LS FN or TH |
| Lee, 2018 | fragility | lumbar vertebra attenuation, L1 | 10 HU increase | HR | 0.63 (0.47, 0.85) | all collected confounders |
| Huopio, 2004 | low energy | SI, calcaneal | per SD decrease | HR | 1.90 (1.25, 2.91) | age, weight, height, HRT use, previous fracture history and femoral neck BMD |
| Diez-Perez, 2007 | nonvertebral | SOS, central calcaneal zone | per SD decrease | HR | 1.20 (1.08, 1.34) | age, history of falls, prevalent fractures, family history of fractures and calcium intake from dairy products |
| Huopio, 2004 | low energy | SOS, calcaneal | per SD decrease | HR | 1.95 (1.30, 2.94) | age, weight, height, HRT use, previous fracture history and femoral neck BMD |
| Lasschuit, 2020 | low trauma | SOS, calcaneal | per SD reduction | HR | 1.19 (1.06, 1.34) | age, sex, BMI, fall count and previous fracture after age 50 |
| Nguyen, 2004 | low trama | SOS, distal radius | per SD decrease | OR | 1.76 (1.29, 2.41) | age, weight, height, BMD, SOS |

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| Gnudi, 2000 | nonvertebral | SOS, distal radius | per SD decrease | RR | 3.69 (1.18, 11.49) | age, age at menopause, height, weight, treatment |
| Gnudi, 2000 | nonvertebral | SOS, patella | per SD decrease | RR | 3.89 (1.53, 9.90) | age, age at menopause, height, weight, treatment |
| Black, 1999 | nonvertebral | vertebral deformity, X-ray | Y vs N | RR | 1.6 (1.5, 1.8) | age, BMD |

**Appendix 14** Reproductive History and Fractures

| first author | fracture site | factor, detail | comparison (exposed vs unexposed) | effect measure | effect size | adjusted for |
|---|---|---|---|---|---|---|
| Naves, 2005 | osteoporotic | amenorrhea, at any age during the fertile period | Y vs N | OR | 6.30 (1.61, 24.70) | age, handgrip strength, femoral neck BMD, prevalent vertebral fracture and the history of falls in the follow-up |
| Yoo, 2021 | any | breastfeeding, / | <6 months vs never | HR | 0.97 (0.94, 0.99) | age, reproductive span, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Yoo, 2021 | any | breastfeeding, / | >=12 months vs never | HR | 1.06 (1.04, 1.09) | age, reproductive span, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Cooper, 1997 | wrist, hip, vertebrae | cycle length, mean cycle length at age 28-32 | >30.5 days vs 26.6-30.5 | OR | 2.27 (NR, NR) | age at last contact or death, age at menarche, mean cycle length, standard deviation of cycle length, mean bleeding duration |

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| Cauley, 1995 | nonvertebral | HRT, estrogen (plus progestin or alone) | current vs never | RR | 0.66 (0.54, 0.80) | age, physical activity (kcal/wk), total calcium intake, body mass index, surgical menopause (yes or no), health status (very good or good compared with fair, poor, or very poor), current use of thiazide diuretics, poor cognition (Mini-Mental Status examination score < 23), alcohol intake, fall in the last 12 months, current use of sedatives or anxiolytics, smoking (ever), and use of thyroid supplements (ever). |
| Engel, 2011 | osteoporotic excluding ribs, fingers, face | HRT, / | ever vs never | HR | 0.85 (0.81, 0.91) | body mass index (weight (kg)/height (m)2 (25); time-dependent), physical activity in 1990 (in metabolic equivalent-hours/week (54 years), parity (number of full-term pregnancies), previous use of oral contraceptives (ever/never), previous use of calcium supplements (yes/no; time-dependent), and educational level (high school graduate, college graduate, or postgraduate study) |
| Engel, 2011 | osteoporotic excluding ribs, fingers, face | HRT, / | current vs never | HR | 0.78 (0.73, 0.83) | body mass index (weight (kg)/height (m)2 (25); time-dependent), physical activity in 1990 (in metabolic equivalent-hours/week (54 years), parity (number of full-term pregnancies), previous use of oral contraceptives (ever/never), previous use of |

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| | | | | | | calcium supplements (yes/no; time-dependent), and educational level (high school graduate, college graduate, or postgraduate study) |
| Hundrup 2004 | hip, wrist, upper arm | HRT, / | current vs never | HR | 0.50 (0.35, 0.71) | Family history, BMI and Age at menopause |
| Hundrup 2004 | hip, wrist, upper arm | HRT, / | past 10 years ago or more vs never | HR | 2.03 (1.25, 3.29) | Family history, BMI and Age at menopause |
| Huopio, 2000 | osteoporotic | HRT, / | N vs Y | RR | 2.2 (1.3, 4.0) | independent risk factor but did not specify confounders adjusted for |
| Lafferty, 1994 | any | HRT, / | estrogen vs N | RR | 0.28 (0.09, 0.89) | age |
| Randell, 2002 | any | HRT, / | current part time user vs never | RR | 0.71 (0.56, 0.91) | age, time since menopause, BMI, number chronic health disorders, and history of previous fractures |
| Randell, 2002 | any | HRT, / | current continuous user vs never | RR | 0.62 (0.48, 0.79) | age, time since menopause, BMI, number chronic health disorders, and history of previous fractures |
| Tuppurainen, 1995 | low energy | HRT, / | past or current vs N | OR | 0.70 (0.50, 0.96) | age |

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| Tuppurainen, 1995 | low energy | HRT, / | years | OR | 0.94 (0.88, 0.99) | age |
| Vestergaard, 2006 | any | HRT, / | current or past 0.3-0.99 DDD/ day vs no use | OR | 0.75 (0.71, 0.80) | Charlson index (co-morbidity), ever use of corticosteroids, alcoholism or not, ever use of oral contraceptives, hysterectomy, working or not, number of bed days in hospital in 1999, number of contacts to general practitioner or specialist in 1999, income, living with someone or living alone, education level, and prior fracture. It did not change the results to include use of selective estrogen receptor modulators (SERM) or bisphosphonates |
| Vestergaard, 2006 | any | HRT, / | current or past >=1 DDD/ day vs no use | OR | 0.63 (0.57, 0.69) | Charlson index (co-morbidity), ever use of corticosteroids, alcoholism or not, ever use of oral contraceptives, hysterectomy, working or not, number of bed days in hospital in 1999, number of contacts to general practitioner or specialist in 1999, income, living with someone or living alone, education level, and prior fracture. It did not change the results to include use of selective estrogen receptor modulators (SERM) or bisphosphonates |

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| Vestergaard, 2006 | any | HRT, / | current or past <0.3 DDD/ day vs no use | OR | 1.12 (1.04, 1.19) | Charlson index (co-morbidity), ever use of corticosteroids, alcoholism or not, ever use of oral contraceptives, hysterectomy, working or not, number of bed days in hospital in 1999, number of contacts to general practitioner or specialist in 1999, income, living with someone or living alone, education level, and prior fracture. It did not change the results to include use of selective estrogen receptor modulators (SERM) or bisphosphonates |
| Yoo, 2021 | any | HRT, / | current or past 2-4 years vs never | HR | 0.93 (0.91, 0.95) | age, reproductive span, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Yoo, 2021 | any | HRT, / | current or past >=5 years vs never | HR | 0.85 (0.83, 0.88) | age, reproductive span, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Melton, 2007 | any | hysterectomy, / | Y vs N | HR | 1.21 (1.13, 1.29) | clinical characteristics at baseline, with oophorectomy and pelvic floor repair (which could have occurred before or after the |

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| | | | | | | hysterectomy) handled as time-dependent covariates. |
| Cooper, 1997 | wrist, hip, vertebrae | menarche age, / | 14-18 vs 12-13 | OR | 3.16 (NR, NR) | age at last contact or death, age at menarche, mean cycle length, standard deviation of cycle length, mean bleeding duration |
| Naves, 2005 | osteoporotic | menarche age, / | the increase in the age at menarche | OR | 1.57 (1.04, 2.37) | age, handgrip strength, femoral neck BMD, prevalent vertebral fracture and the history of falls in the follow-up |
| Yoo, 2021 | any | menarche age, / | 13-14 VS <=12 | HR | 1.10 (1.04, 1.16) | age, age at menarche, age at menopause, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Yoo, 2021 | any | menarche age, / | 15-16 VS <=12 | HR | 1.16 (1.10, 1.23) | age, age at menarche, age at menopause, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Yoo, 2021 | any | menarche age, / | >=17 VS <=12 | HR | 1.24 (1.17, 1.31) | age, age at menarche, age at menopause, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, |

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| | | | | | | income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Shieh, 2022 | any | menopause status, age | per 1 year | HR | 0.95 (0.91, 0.99) | race/ethnicity, BMI, history of fracture before age 40, cigarette use, alcohol intake, diabetes status, exposure to bone-beneficial or bone detrimental medications and/or vitamin D or calcium supplementation, and study site |
| Gardsell, 1991 | fragility | menopause status, age | 3 years earlier | OR | 1.4 (1.1, 1.7) | age |
| Gardsell, 1991 | fragility | menopause status, age | 5 years earlier | OR | 1.7 (1.2, 2.4) | age |
| Gardsell, 1991 | fragility | menopause status, age | 10 years earlier | OR | 2.9 (1.4, 5.7) | age |
| Yoo, 2021 | any | menopause status, age | 45-49 VS <40 | HR | 0.94 (0.91, 0.97) | age, age at menarche, age at menopause, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |

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|---|---|---|---|---|---|---|
| Yoo, 2021 | any | menopause status, age | 50-54 VS <40 | HR | 0.90 (0.88, 0.93) | age, age at menarche, age at menopause, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Yoo, 2021 | any | menopause status, age | >=55 VS <40 | HR | 0.89 (0.86, 0.93) | age, age at menarche, age at menopause, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Mobergg, 2022 | any excluding skull and face | menopause status, age | 40-44 vs 45-54 | HR | 1.14 (1.03, 1.27) | age, BMI, previous fracture and all variables with a signifcant impact (p<0.05) on fracture risk from the basic model analysis |
| Ahn, 2014 | fragility | menopause status, / | post vs pre | HR | 3.50 (1.05, 11.67) | age, body mass index, previous fracture history, parental history of osteoporosis, dietary calcium intake, menopausal status, duration of total breast-feeding, and bone mineral density |
| Lee, 2010 | nonvertebral | menopause status, / | Y vs N | RR | 3.59 (1.06, 12.19) | multivariate |

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| Torgerson, 1996 | any | menopause status, menstruating | N vs Y | OR | 1.98 (1.02, 3.56) | stepwise logistic regression analysis was undertaken for all the variables |
| Barad, 2005 | any | oral contraceptive use, / | ever vs never | HR | 1.07 (1.01, 1.15) | baseline age (1-year intervals), hormone therapy (HT) use (never, past, current), and duration (5-year intervals), follow-up time, calcium intake (mg), corticosteroid use, vitamin D use, thiazide use, thyroid hormone use, age, race/ethnicity, smoking, alcohol use, moderate/strenuous exercise (hours/ week) body mass index, parity, history of irregular menses for more than 1 year before menopause, hysterectomy, age at menopause, menopausal symptoms, prior fracture before age 55, length of OC use, age of last OC use, age of first OC use, HT use, and duration of HT use |
| Yoo, 2021 | any | oral contraceptive use, / | >=1 year vs never | HR | 1.03 (1.01, 1.05) | age, reproductive span, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Yoo, 2021 | any | parity, / | 1 vs nulliparity | HR | 0.96 (0.92, 0.99) | age, age at menarche, age at menopause, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol |

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| | | | | | | consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Thong, 2021 | any | reproductive lifespan, / | per 5 years | OR | 0.89 (0.80, 0.98) | diabetes, age, BMI, MHT use, reproductive lifespan, falls |
| Yoo, 2021 | any | reproductive lifespan, / | 30-34 VS <30 years | HR | 0.94 (0.93, 0.95) | age, reproductive span, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Yoo, 2021 | any | reproductive lifespan, / | 35-39 VS <30 years | HR | 0.89 (0.88, 0.90) | age, reproductive span, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |
| Yoo, 2021 | any | reproductive lifespan, / | >=40 VS <30 years | HR | 0.86 (0.84, 0.88) | age, reproductive span, parity, duration of breast feeding, duration of HT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes, dyslipidemia, and cancer |