2024

The Association Between Cardiovascular Disease Risk And Fractures In Postmenopausal Women

Rafeka Hossain
University of Alabama at Birmingham

THE ASSOCIATION BETWEEN CARDIOVASCULAR DISEASE RISK AND FRACTURES IN POSTMENOPAUSAL WOMEN

by

RAFEKA HOSSAIN

NICOLE C. WRIGHT, COMMITTEE CHAIR

SUZANNE E. PERUMEAN-CHANEY

KELLEY PETTEE GABRIEL

SHAKIA T. HARDY

A THESIS

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Master of Science in Public Health

BIRMINGHAM, ALABAMA

2024

THE ASSOCIATION BETWEEN CARDIOVASCULAR DISEASE RISK AND FRACTURES IN POSTMENOPAUSAL WOMEN

RAFEKA HOSSAIN

MASTER OF SCIENCE IN PUBLIC HEALTH

ABSTRACT

Background: Fragility fractures pose a significant healthcare and economic burden in the United States. While age and bone mineral density (BMD) are the primary established risk factors for fragility fractures, the relationship between cardiovascular disease (CVD) and fractures remains underexplored. The primary objective of this analysis was to estimate the association of CVD risk with fractures in postmenopausal women.

Methods: Utilizing 30 years of data from the WHI, Atherosclerotic Cardiovascular Disease (ASCVD) risk scores were computed using baseline age, race, systolic blood pressure, total cholesterol, high-density lipoprotein, diabetes, anti-hypertension medications, and smoking. Fracture outcomes encompassed any clinical fracture, major osteoporotic fractures (MOF), and hip. Cox proportional hazard models accounting for the WHI study component were used to assess the association between ASCVD and fracture risk, adjusting for sociodemographic, lifestyle, nutrition, and health variables. Effect modification by obesity status was explored.

Results: Among the 161,808 women in the WHI, 5,519 had complete data for ASCVD score calculation. Of these, 40.3%, 15.1%, 32.5%, and 12.1% of participants fell into low, borderline, intermediate, and high CVD risk categories respectively based on ASCVD

thresholds. Compared to those with a low ASCVD score, a high ASCVD score was associated with significant elevated fracture risk (Any clinical - HR: 1.48, 95% CI: 1.28–1.72; MOF- HR: 2.35; 95% CI: 1.93–2.87; hip - HR: 4.97; 95% CI: 3.34–7.40). The associations attenuated after adjustment, but compared to the low ASCVD score group, significantly higher fracture risk was still observed in the fully adjusted model for MOF in the intermediate group (HR: 1.31, 95% CI: 1.07–1.60), and for MOF (HR: 1.38, 95% CI: 1.02–1.86) and hip fracture (HR: 1.88, 95% CI: 1.03–3.43) in the high ASCVD group. No evidence of heterogeneity by obesity status was observed in the association between ASCVD risk and fractures.

Conclusion: In this racially and ethnically diverse sample of postmenopausal women, a higher ASCVD score was significantly associated with higher MOF and hip fracture risk. Integrating CVD risk assessment could provide valuable insights for clinical practice regarding fracture prevention strategies.

Keywords: Fractures, Osteoporosis, Cardiovascular Disease, Race/Ethnicity, Postmenopausal women, Epidemiology.

ACKNOWLEDGEMENTS

WHI Bone SIG: Dr. Carolyn J. Crandall, Dr. Kristine E. Ensrud, Dr. Jane A. Cauley, Dr. Meryl S. LeBoff, Dr. Ann V. Schwartz

Statistical Support: Dr. Russell Griffin from the Department of Epidemiology, Joseph Larson from WHI

WHI Coordinating Center

TABLE OF CONTENTS

Page

ABSTRACT ……...……...iii

ACKNOWLEDGEMENT ……..……....v

LIST OF TABLES …….……...vii

LIST OF FIGURES …….……viii

LIST OF ABBREVIATIONS ……ix

CHAPTER

1 INTRODUCTION ……..1
2 METHODS ……3

Study Design and Setting ……...3
Participants ……....3
Primary Exposure: CVD Risk ……....4
Primary Outcome: Fracture ……5
Potential Covariates ……....6
Statistical Analysis ……7

3 RESULTS ……....9

The Association Between ASCVD Score and Fracture ……....13
Any Clinical Fracture ……..13
Major Osteoporotic Fracture …….…..15
Hip Fracture ……....18
Effect Modification ……21
Sensitivity Analysis …….....21

4 DISCUSSION ……23
5 CONCLUSION ……..28

LIST OF REFERENCES ……. 29

APPENDIX: IRB APPROVAL ……..... 53

LIST OF TABLES

Tables *Page*

1 Baseline Characteristics of the WHI Participants Overall and by ASCVD Risk Score ……11

2a Any Clinical Fracture Incidence Rates Overall and by ASCVD Risk Level ……....13

3a The Association between CVD Risk Score and Any Clinical Fracture (n = 2,097) ……..…..15

2b MOF Incidence Rates Overall and by ASCVD Risk Level ……...16

3b The Association between CVD Risk Score and MOF (n = 1,067) ……17

2c Hip Fracture Incidence Rates Overall and by ASCVD Risk Level ……19

3c The Association between CVD Risk Score and Hip Fracture (n = 261) ……20

4 Evaluating model fit on the Association between CVD Risk Score and Fracture ……..…..22

LIST OF FIGURES

Figures *Page*

1 Participant Selection Flowchart ……..10

2a Kaplan-Meier plots by ASCVD Category for Any Clinical Fracture …….....14

2b Kaplan-Meier plots by ASCVD Category for MOF ……..…..16

2c Kaplan-Meier plots by ASCVD Category for Hip fracture ……19

LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
ASCVD	Atherosclerotic Cardiovascular Disease
BMD	Bone Mineral Density
BMI	Body Mass Index
CI	Confidence Interval
CT	Clinical Trial
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DXA	Dual Energy X-ray Absorptiometry
FX	Fracture
HDL	High–Density Lipoprotein
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
IR	Incidence Rate
KM	Kaplan–Meier
LDL	Low–Density Lipoprotein
MOF	Major Osteoporotic Fracture
SBP	Systolic Blood Pressure
T2DM	Type–2 Diabetes Mellitus
OP	Osteoporosis

OR	Odds Ratio
OS	Observational Study
PPI	Proton Pump Inhibitors
PPV	Positive Predictive Value
RR	Relative Risk
SAS	Statistical Analysis System
SERMs	Selective Estrogen Receptor Modulators
WHI	Women's Health Initiative

INTRODUCTION

Over two million fragility fractures occur each year in the United States (U.S.) with estimated costs ranging from $13.7 billion to $20.3 billion in direct medical costs in 2005 (1, 2). As the older adult population in the U.S. increases, so will the number of fractures and their related costs. Estimates show that when considering both direct medical and indirect societal costs by 2040, fracture-related annual costs will rise to $95.2 billion (3). Fragility fractures are associated with higher mortality rates (4 - 14) and lower quality of life outcomes (15), including losses in ambulation (16), increases in long-term nursing home care (17-19), and becoming Medicaid dependent (18-19), with these outcomes being worse in communities of color (19). Factors associated with fractures have not only been identified to aid in the understanding of fractures but also in the development of pharmaceutical and non-pharmaceutical interventions to reduce fractures and their subsequent adverse outcomes (20).

The primary risk factors for fragility fractures are age and bone mineral density (4), but several health conditions are found to be associated with fractures (21-22), including cardiovascular diseases (CVD) (23). CVD and fragility fractures share pathogenetic mechanisms, with disruptions in bone mineral and bone metabolism implicated in both conditions (24). Studies have shown bidirectional relationships with individual CVDs and fractures. For example, an increased risk for hip and vertebral fractures was shown in those with myocardial infarction (MI), hypertension (HTN) (25-

26), and aortic and arterial calcification (27-28), while other studies have shown that low BMD and fractures are associated with increased risk of CVD (29). Similarly, medications used in the treatment of CVDs (e.g., loop diuretics) are also linked to an increased risk of fractures, particularly in women (30).

CVD risk prediction equations such as the American College of Cardiology's Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator (31-32) have been used widely in research to evaluate individual and population-level risk for CVD. Clinical thresholds have been developed to identify individuals at higher risk to ultimately trigger clinical intervention (33). Given the association between CVD and bone health, CVD risk prediction equations could also provide an avenue to prompt fracture prevention interventions; however, as far as is known, the association between ASCVD score and fractures has not been previously evaluated, particularly in a racial and ethnic diverse cohort. Thus, this study will leverage 30 years of longitudinal CVD and bone health data collected in the Women's Health Initiative (WHI) to address this research gap. The objective of this study is to estimate the association between CVD risk, based on the ASCVD risk estimator, and fractures, and evaluate if obesity status modifies the association between CVD risk and fracture.

METHODS

Study Design and Setting

This study utilized data from the WHI, a comprehensive investigation aimed at addressing major health concerns in postmenopausal women, such as heart disease, cancer, and osteoporotic fractures. Enrolling 161,808 women between the ages of 50-79 from 1993-1998, the primary objectives of the WHI were to 1) understand the etiology of these conditions, 2) evaluate preventive strategies to attenuate risk, and 3) apply findings to inform public health policy and clinical guidelines. The WHI study design included three randomized controlled trials (WHI-CT) and an observational study (WHI-OS) component, to provide evidence-based recommendations for improving the health and quality of life of postmenopausal women (34).

Participants

This study was limited to participants who were selected for measurements of core analytes (e.g., Total cholesterol, HDL, and LDL), which included the WHI-CT 6% subsample and the OS Measurement Precision Study (1% of WHI-OS participants). Women missing data necessary to calculate the ASCVD scores and those reporting bone cancer at baseline were further excluded. The University of Alabama at Birmingham

Institutional Review Board designated this analysis as non-human subjects' research given all data were coded using a unique identifier.

Primary Exposure: CVD Risk

The 10-year ASCVD risk score includes the following characteristics: age, sex, race (White, Black, Other), systolic blood pressure (SBP), total cholesterol, high-density lipoprotein (HDL), history of diabetes, use of antihypertensive medication, and smoking status (current or non-smoker) (35). The ASCVD score was calculated using only baseline data. SBP was measured using a standardized protocol at each of the 40 WHI centers. Cholesterol levels (total cholesterol, and HDL) were determined using a 12-hour fasting serum sample obtained (36). Diabetes status was based on self-report of Type 2 Diabetes Mellitus (T2DM) and the presence of T2DM medication (Insulin, Sulfonylureas, Antidiabetic amino acid derivatives, Biguanides, Meglitinide analogs, Aldose reductase inhibitors, Alpha-glucosidase inhibitors, insulin-sensitizing agents, and other antidiabetic combinations) in the WHI medication inventory that included pill bottle review at baseline clinical visit. Antihypertensive medication use was based on the self-report of HTN medications or recording of antihypertensive medications (e.g., Diuretics, Beta-blockers, ACE inhibitors, Angiotensin II receptor blockers, Calcium channel blockers, Alpha blockers, Alpha-2 receptor agonists, combined alpha and beta-blockers, Vasodilators) from WHI medication inventory data. The personal habit questionnaire was used to determine smoking status. ASCVD scores were utilized as a categorical variable based on clinical thresholds [Low risk (<5.0%), Borderline risk (5.0% - 7.4%), Intermediate risk (7.5% - 19.9%), and High risk (≥20.0%)].

Primary Outcome: Fracture

The fracture outcomes included: 1) any clinical fractures, 2) major osteoporotic fractures (MOF) (hip, clinical spine, forearm, or shoulder), and 3) hip fractures. The women reported fractures at each annual medical history follow-up questionnaire based on the following questions: "Since the date on this form, 1) have you been admitted to a hospital overnight?; 2) have you been treated in an emergency room, had a day surgery, or been seen on an outpatient basis; 3) has a doctor told you for the first time that you have a new broken, crushed, or fracture bone?" Medical records were obtained for those selecting "broken, crushed, or fractured bone" for questions 1 and 2 to identify fracture site. Women answering yes to question 3 were then asked "which bone did you break" with response options including 1) jaw, nose, face, and/or skull, finger and/or toe, 3) ribs and/or chest or breastbone, 4) other broken bone, to which they specified. During the first phase of the WHI (1993-2005), all hip fractures were centrally adjudicated at the WHI Coordinating Center using medical records, and all fractures reported in the DXA sub-cohort were locally adjudicated at the respective WHI Center. During Extension 1 (2005-2010), hip fractures continued to be adjudicated, whereas all other fractures were based on self-report only. In Extension 2 and Beyond (2010 – present), all fractures were based on self-reported data (36-37). Studies, including one from the WHI, have shown that the self-report of fragility fractures is highly valid with positive predictive values (PPV) ranging from 85% – 97% for hip and other non-vertebral fractures (38), with lower validity for clinical spine fractures (PPV: 50 – 70%) (39-43). Those reporting a pathologic fracture during follow-up were excluded, as these fractures are typically related to cancer and are not considered fragility fractures (44-47).

Potential Covariates

Based on previous literature and/or underlying biological plausibility, baseline, self-reported variables from the following domains were identified as covariates of interest: sociodemographic (48-53), lifestyle (54-58), anthropometric (58-60), nutritional (61-63), health conditions (57, 64-65), and medications (66-79). Sociodemographic variables included Hispanic ethnicity (Hispanic vs. non-Hispanic), education (<high school, high school graduate, some college or vocational degree, college graduate, and professional degree), and income (<$35,000, $35,000 - $75,000, >$75,000). Lifestyle factors included alcohol consumption (non, past, and current drinkers) and physical activity (total energy expenditure from recreational physical activities). Anthropometric factors included body mass index (BMI), which was calculated based on height and weight measurements from baseline clinic visits. Nutritional factors included total calcium (mg/d) and vitamin D (IU/d) intake as a combination of dietary, ascertained from the food frequency questionnaire, and supplemental, ascertained from medication inventory data. Health conditions of interest included parental history of fracture (yes vs. no) and falls in the last year (yes vs. no). Lastly, medications that have positive or negative effects on bone health and CVD were also included, and those were hormone replacement therapy (i.e., estrogen or estrogen + progestin), anti-osteoporosis medications (bisphosphonates, selective estrogen receptor modulators/SERMs, calcitonin), glucocorticoids, antidepressants, and proton pump inhibitors (PPI). The ASCVD risk estimator plus (ASCVD Risk Estimator + (acc.org)) also considers statin and aspirin use; however, these variables were not included in the original ASCVD risk estimator equation (80). To account for these variables, statin and aspirin were included

to use as covariates in the models. All medications were ascertained from medical inventory data.

Statistical Analysis

The baseline characteristics of the sample overall and by ASCVD risk category were described, with means and standard deviations reported for continuous variables and frequencies and proportions for categorical variables. Normality assumptions were tested with histogram, normal quantile plot, and Shapiro-Wilk tests. Chi-square tests and analysis of variance (ANOVA) were used, with appropriate post-hoc tests, to evaluate differences in the distribution of participant characteristics by CVD risk thresholds for categorical and continuous variables, respectively. Crude and age- and race-adjusted fracture incidence rates (number of fractures/10,000 person-years) were calculated for each fracture outcome overall and by ASCVD score and used the Kaplan-Meier (KM) method to evaluate the cumulative incidence rate of fractures by CVD risk. Cox proportional hazard models were also used to evaluate the association between CVD risk and fracture. The time from baseline to fracture served as the event time, and the time from baseline to last follow-up or end of the study was used for those not sustaining a fracture, while also accounting for the WHI phase (main, extension 1, extension 2). The base model included the WHI design variable (CT vs OS). Then the models were adjusted hierarchically, including sociodemographic factors (model 2); lifestyle, anthropometric, and nutritional variables (model 3); and health and medication variables (model 4). Given that age and race are variables in the ASCVD score, the correlation between age and ASCVD score was assessed, and additional sensitivity analyses were

completed where the fully adjusted (model 4) model was run first without age and again without age and race. Akaike Information Criterion (AIC) was used to evaluate model fit. Lastly, a stepwise model was used for building methods to identify all significant variables identified with an entry p-value of 0.2 and exit p-value of 0.1. Given that obesity is associated with more cardiovascular events (81-85) but fewer fracture events (86-90), interest was directed toward examining whether obesity modified the association between CVD risk and fracture. Effect modification was tested using an ASCVD score*obesity (BMI < or ≥ 30 kg/m2) status interaction term. If significant, models were stratified by obesity status. All statistical analyses were performed using SAS 9.4 with an alpha level of 0.05.

RESULTS

The WHI enrolled 161,808 women at baseline (Figure 1). Participants not selected for the baseline core analyte study (N=156,097) and those reporting bone cancer (N=85) were excluded. From the remaining 5,625 participants, 100 participants were subsequently excluded due to missing one or more elements needed to calculate the ASCVD score. Of the participants with ASCVD data, an additional seven women were excluded for reporting a pathologic fracture. The final analytic sample included 5,519 women (Figure 1), who were on average 62.6 ± 7.1 years of age with the majority enrolled in WHI-CT (80.7%), identified as White (61.8%) and non-Hispanic (86.9%), had some college or vocational degrees (39.3%), and had an annual family income of <$35,000 (47.6%) (Table 1).

The mean (SD) ASCVD risk score was 9.8 (10.4), with 2,224 (40.3%), 837 (15.2%), 1,791 (32.5%), and 667 (12.1%) in the low, borderline, intermediate, and high categories, respectively (Table 1). Compared to women with low CVD risk, women with high CVD risk were significantly older (71.3 ± 5.7 vs. 56.9 ± 4.4 years, $p<0.0001$), and more likely to identify as Black (Black: 36.7% vs. 14.4%, $p<0.0001$), non-Hispanic (95.0% vs. 82.1%, $p<0.0001$), have less than a high school-level education (13.0% vs. 7.4%, $p<0.0001$), have an annual family income <$35,000 (70.9% vs. 34.3%, $p<0.0001$), be a past drinker (32% vs. 17.5%, $p<0.0001$), a current smoker (13.8% vs. 3.8%, $p<0.0001$), use anti-hypertension treatments (71.2% vs. 15.3%, $p <0.0001$) and have a

history of diabetes (33.6% vs. 1.8%, p<0.0001), but were less likely to report hormone replacement therapy use (37.6% vs. 56.1%, p <0.0001) (Table 1).

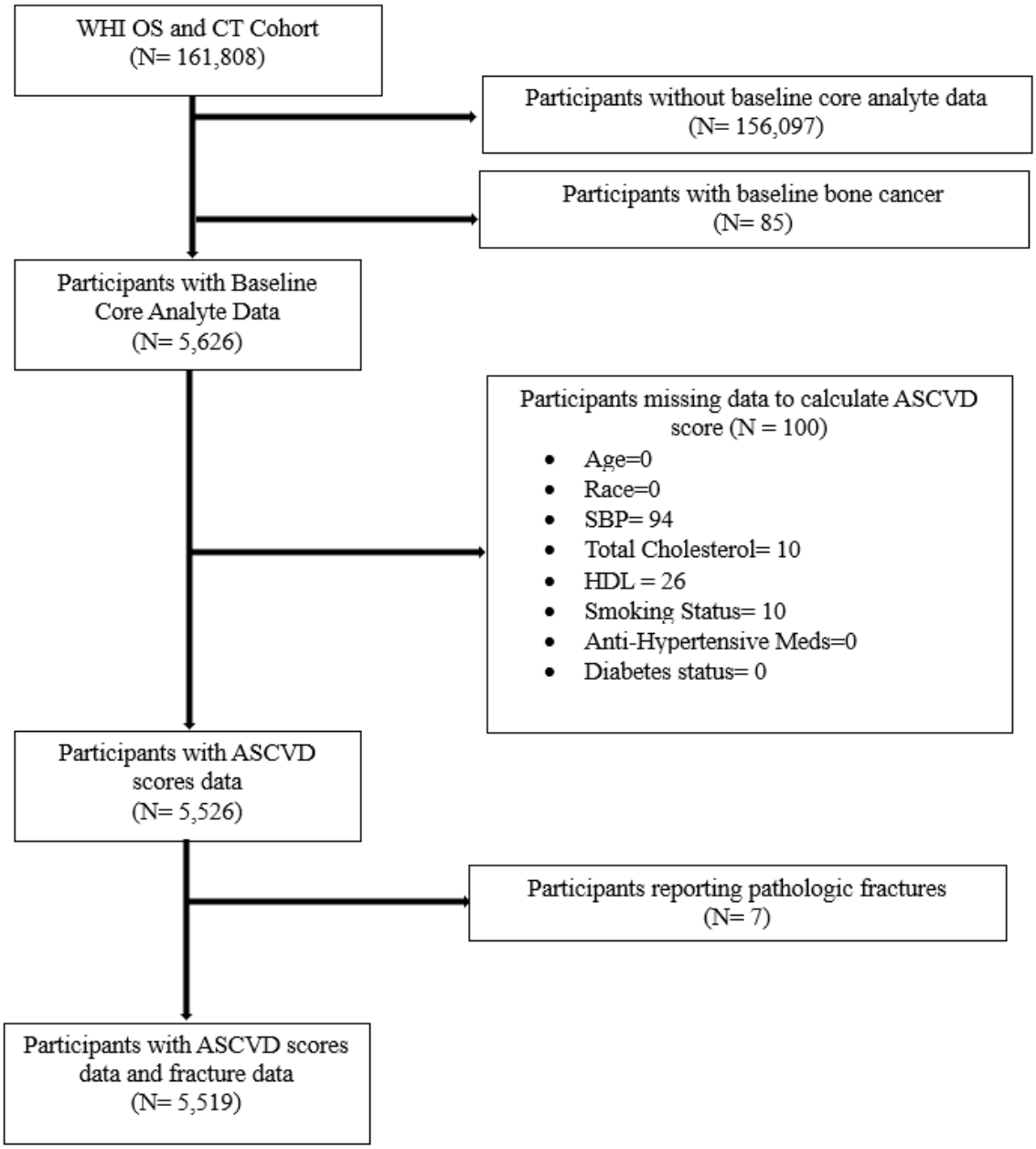

Figure 1. Participant Selection Flowchart

Table 1.

Baseline Characteristics of the WHI Participants Overall and by ASCVD Risk Score

	Total N =5,519	**Low (<5%) N= 2,224**	**Borderline (5% - 7.4%) N= 837**	**Intermediate (7.5% - 19.9%) N= 1,791**	**High (≥20%) N=667**	**p-value**
WHI Specific, N (%)						0.370
Observational Study (OS)	1066 (19.3%)	434 (19.5%)	147 (17.6%)	344 (19.2%)	141 (21.1%)	
Clinical Trial (CT)	4453 (80.7%)	1790 (80.5%)	690 (82.4%)	1447 (80.8%)	526 (78.9%)	
Sociodemographic, N (%)						
Age (years), mean (SD)	62.6 ± 7.1	56.9 ± 4.3	62.3 ± 4.4	66.6 ± 5.3	71.3 ± 5.7	**<0.001**
Race						**<0.001**
White	3408 (61.8%)	1505 (67.7%)	517 (61.8%)	1043 (58.2%)	343 (51.4%)	
Black	1260 (22.8%)	321 (14.4%)	187 (22.3%)	507 (28.3%)	245 (36.7%)	
Other	851 (15.4%)	398 (17.9%)	133 (15.9%)	241 (13.5%)	79 (11.9%)	
Ethnicity*						**<0.001**
Hispanic	711 (13.1%)	393 (17.9%)	110 (13.3%)	175 (9.9%)	33 (5.0%)	
Non-Hispanic	4735 (86.9%)	1803 (82.1%)	716 (86.7%)	1592 (90.1%)	624 (95.0%)	
Education*						**<0.001**
<High School	483 (8.8%)	164 (7.4%)	62 (7.5%)	171 (9.6%)	86 (13.0%)	
High School Graduate	992 (18.1%)	354 (16.1%)	156 (18.8%)	355 (20.0%)	127 (19.2%)	
Some College or Vocational School	2153 (39.3%)	833 (37.8%)	321 (38.6%)	722 (40.6%)	277 (41.8%)	
College Graduate	534 (9.8%)	238 (10.7%)	82 (9.9%)	164 (9.2%)	50 (7.6%)	
Post-Graduate	1316 (24.0%)	617 (28.0%)	210 (25.2%)	367 (20.6%)	122 (18.4%)	
Income level*						**<0.001**
<$35,000	2466 (47.6%)	717 (34.3%)	356 (45.2%)	954 (56.8%)	439 (70.9%)	
$35,000 – $75,000	1990 (38.4%)	902 (43.1%)	345 (43.8%)	588 (35.0%)	155 (25.0%)	
>$75,000	722 (14.0%)	473 (22.6%)	86 (11.0%)	138 (8.2%)	25 (4.1%)	
Lifestyle, N (%)						
Physical Activity, METS/Day, mean (SD)*	10.6 ± 13.0	11.0 ± 13.2	10.7 ± 13.3	10.6 ± 13.2	9.7 ± 11.5	0.062
Alcohol consumption*						**<0.001**
Non-Drinker	766 (14.0%)	286 (13.0%)	91 (10.9%)	274 (15.5%)	115 (17.5%)	
Past Drinker	1192 (21.8%)	387 (17.5%)	179 (21.5%)	416 (23.5%)	210 (32.0%)	
Current Drinker	3510 (64.2%)	1534 (69.5%)	563 (67.6%)	1081 (61.0%)	332 (50.5%)	
Current Smoker						**<0.001**
Yes	462 (8.4%)	84 (3.8%)	91 (10.9%)	195 (10.9%)	92 (13.8%)	

No	5057 (91.6%)	2140 (96.2%)	746 (89.1%)	1596 (89.1%)	575 (86.2%)	
Nutritional, mean (SD)						
Calcium intake (mg/d)*	1295.3 ± 690.9	1355.8 ± 683.0	1318.4 ± 648.3	1246.3 ± 717.7	1178.5 ± 672.2	**<0.001**
Vitamin D intake (mcg/d)*	14.2 ± 5.8	14.2 ± 5.9	14.4 ± 6.7	14.1 ± 5.3	13.7 ± 5.2	0.268
Anthropometric, mean (SD)						
BMI (kg/m^2)*	29.1 ± 6.1	28.4 ± 5.9	29.4 ± 6.4	29.6 ± 6.1	29.5 ± 6.2	**<0.001**
Health-related, N (%)						
Parental history of fracture*						**0.002**
Yes	1723 (34.5%)	753 (36.9%)	265 (34.6%)	540 (33.7%)	165 (28.3%)	
No	3273 (65.5%)	1290 (63.1%)	501 (65.4%)	1064 (66.3%)	418 (71.7%)	
Falls*						0.555
Yes	1629 (31.4%)	650 (31.5%)	260 (33.4%)	524 (30.8%)	195 (30.3%)	
No	3556 (68.6%)	1411 (68.5%)	519 (66.6%)	1177 (69.2%)	449 (69.7%)	
SBP (mmHg), mean (SD)	128.6 ± 17.8	118.9 ± 13.9	127.4 ± 14.7	134.5 ± 15.5	146.8 ± 18.4	**<0.001**
DPB (mmHg), mean (SD)*	76.1 ± 9.3	74.8 ± 8.7	76.4 ± 9.2	77.0 ± 9.3	77.6 ± 10.6	**<0.001**
Hypertension Treatment						**<0.001**
Yes	1952 (35.4%)	341 (15.3%)	270 (32.3%)	866 (48.4%)	475 (71.2%)	
No	3567 (64.6%)	1883 (84.7%)	567 (67.7%)	925 (51.6%)	192 (28.8%)	
Type-2 Diabetes						**<0.001**
Yes	461 (8.4%)	40 (1.8%)	27 (3.2%)	170 (9.5%)	224 (33.6%)	
No	5058 (91.6%)	2184 (98.2%)	810 (96.8%)	1621 (90.5%)	443 (66.4%)	
Total Cholesterol (mg/dL), mean (SD)	222.4 ± 38.4	215.7 ± 35.1	223.2 ± 39.5	226.7 ± 38.8	231.8 ± 42.5	**<0.001**
HDL (mg/dL), mean (SD)	58.9 ± 15.6	61.6 ± 15.7	57.8 ± 15.5	56.9 ± 15.2	56.5 ± 15.3	**<0.001**
LDL (mg/dL), mean (SD)*	133.7 ± 35.6	126.8 ± 32.7	134.8 ± 37.0	138.0 ± 35.4	143.7 ± 39.6	**<0.001**
Medications, N (%)						
Hormone Replacement Therapy						**<0.001**
Yes	2633 (47.7%)	1247 (56.1%)	390 (46.6%)	745 (41.6%)	251 (37.6%)	
No	2886 (52.3%)	977 (43.9%)	447 (53.4%)	1046 (58.4%)	416 (62.4%)	
Anti-Osteoporosis Medications						0.254

Yes	77 (1.4%)	36 (1.6%)	13 (1.5%)	24 (1.3%)	4 (0.6%)	
No	5442 (98.6%)	2188 (98.4%)	824 (98.5%)	1767 (98.7%)	552 (99.4%)	
Statins						0.061
Yes	169 (3.1%)	58 (2.6%)	26 (3.1%)	70 (3.9%)	15 (2.3%)	
No	5350 (96.9%)	2166 (97.4%)	811 (96.9%)	1721 (96.1%)	652 (97.7%)	
Aspirin						0.0634
Yes	460 (8.3%)	180 (8.1%)	74 (8.8%)	166 (9.3%)	40 (6.0%)	
No	5059 (91.7%)	2044 (91.9%)	763 (91.2%)	1625 (90.7%)	627 (94.0%)	

***** Number of missing participants in different baseline characteristic categories: Ethnicity = 73 (1.3%), Education = 41 (0.7%), Income level = 341 (6.2%), Physical activity = 376 (6.8%), Alcohol consumption = 51 (0.9%), Calcium intake = 1714 (31.1%), Vitamin D intake = 1714 (31.1%), BMI = 37 (0.7%), Parents history of fracture = 523 (9.5%), Falls = 334 (6.1%), Diastolic BP = 1 (0.02%), and LDL = 89 (1.6%).

The Association Between ASCVD Score and Fracture

Any Clinical Fracture

Over an average of 13.2 (8.1) mean years of follow-up, 2,097 (38.0%) of the women reported a clinical fracture, with a crude IR of 287.80 per 10,000-woman years (Table 2a). After adjusting for age and race, the overall any clinical fracture IR attenuated

Table 2a.

Any Clinical Fracture Incidence Rates Overall and by ASCVD Risk Level

	Any Clinical		
	Events N	**Crude IR[a] (95% CI)**	**Adjusted[b] IR[a] (95% CI)**
Overall	2,097	287.80 (275.75 – 300.39)	266.72 (251.35 – 283.03)
Low (<5%)	869	259.38 (242.70–277.22)	261.94 (236.17 –290.54)
Borderline (5% - 7.4%)	318	280.10 (250.95–312.64)	269.16 (237.27– 305.32)
Intermediate (7.5% - 19.9%)	680	315.06 (292.25–339.65)	268.08 (245.60– 292.62)
High (≥20%)	230	358.07 (314.66–407.47)	271.07 (233.33– 314.91)

IR = Incidence Rate; CI = Confidence Interval

[a]IR per 10,000 Person-Years; [b]Age- and Race- Adjusted

(266.72 per 10,000 person-years), with the greatest IR attenuation in the intermediate and high ASCVD groups (Intermediate: -14.9%; High: -24.3%) (Table 2a). Given the overlapping confidence intervals, there were no differences in the IR by ASCVD score (Table 2a); however, the Kaplan-Meier analysis showed significant differences ($p < 0.0001$) in time to any clinical fracture by ASCVD score, with the median time (95% CI) to fracture was longest in the low CVD risk group [9.97 (8.99 – 10.87)] and shortest in the high CVD risk group [6.01 (5.04 – 7.07)] (Fig. 2a).

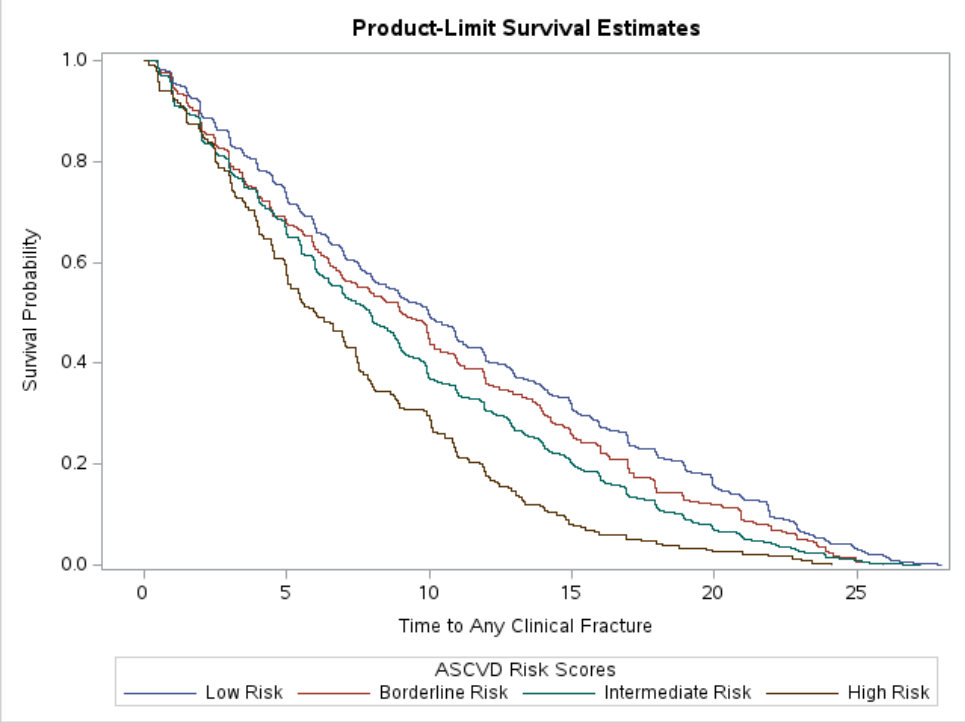

Figure 2a: Kaplan-Meier plots by ASCVD Category for Any Clinical Fracture

The base Cox proportional hazards model showed that after accounting for WHI study group, compared to women in the low ASCVD group, women in the intermediate and high ASCVD groups had 29% (HR: 1.29; 95% CI: 1.16, 1.42) and 48% (HR: 1.48; 95% CI: 1.28, 1.72) higher risk of any clinical fracture (Table 3a – Model 1), which became

statistically null after adjusting for the sociodemographic factors (age, race, ethnicity, education, income) (Table 3a – Model 2), lifestyle, nutrition, anthropometric variables (Table 3a - Model 3), and health-related, medication variables (Table 3a – Model 4).

Table 3a.

The Association between CVD Risk Score and Any Clinical Fracture (n = 2,097)

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)	Model 5 HR (95% CI)
ASCVD Risk					
Low (<5%)	Ref	Ref	Ref	Ref	Ref
Borderline (5% to 7.4%)	1.12 (0.99 – 1.29)	1.03 (0.89 – 1.19)	1.12 (0.94 – 1.34)	1.09 (0.91 – 1.32)	1.07 (0.92 – 1.25)
Intermediate (7.5% to 19.9%)	1.29 (1.16 – 1.42)	1.04 (0.91 – 1.20)	1.14 (0.95 – 1.35)	1.16 (0.96 – 1.39)	1.09 (0.94 – 1.27)
High (≥20%)	1.48 (1.28 – 1.72)	1.04 (0.84 – 1.29)	0.98 (0.75 – 1.29)	0.95 (0.71 – 1.27)	1.03 (0.82 – 1.30)

Model 1: WHI Component (OS vs. CT)
Model 2: Model 1 + Sociodemographic (Age, Race, Ethnicity, Education, Income)
Model 3: Model 2 + Lifestyle, Nutrition, and Anthropometric (Physical Activity, Alcohol, Calcium Intake, vitamin D Intake, BMI)
Model 4: Model 3 + Health-related and Medication variables (Parental fx, Falls, HRT, Anti-Osteoporotic Meds, Statins, Aspirin)
Model 5: Stepwise (OS vs. CT, Age, Race, Income, Falls, Parental fx)

When using stepwise modeling techniques, again there was no association between ASCVD risk score and fracture after adjusting for OS vs. CT, age, race, income, falls, and parental fracture (Table 3a – Model 5).

Major Osteoporotic Fracture

Over an average of 15.4 (8.1) mean years of follow-up, 1,067 (19.3%) of the women experienced a MOF, with a crude IR of 125.79 per 10,000 person-years (Table 2b). After adjusting for age and race, the overall MOF IR attenuated to 104.61 per 10,000 person-years, with the greatest attenuation of the IRs in the intermediate and high ASCVD groups (Intermediate: -27.4%; High: -75.4%) (Table 2b). The crude or adjusted

Table 2b.

MOF Incidence Rates Overall and by ASCVD Risk Level

	MOF		
	Events N	**Crude IR[a] (95% CI)**	**Adjusted[b] IR[a] (95% CI)**
Overall	1,067	125.79 (118.46 – 133.57)	104.61 (95.45 – 114.65)
Low (<5%)	406	102.72 (93.20–113.22)	94.74 (81.36–110.31)
Borderline (5% - 7.4%)	150	112.58 (95.93–132.12)	94.49 (78.34–113.98)
Intermediate (7.5% - 19.9%)	374	150.57 (136.06–166.63)	109.27 (96.23–124.09)
High (≥20%)	137	191.92 (162.33–226.91)	122.60 (100.13–150.12)

IR = Incidence Rate; CI = Confidence Interval

[a]IR per 10,000 Person-Years; [b]Age- and Race- Adjusted

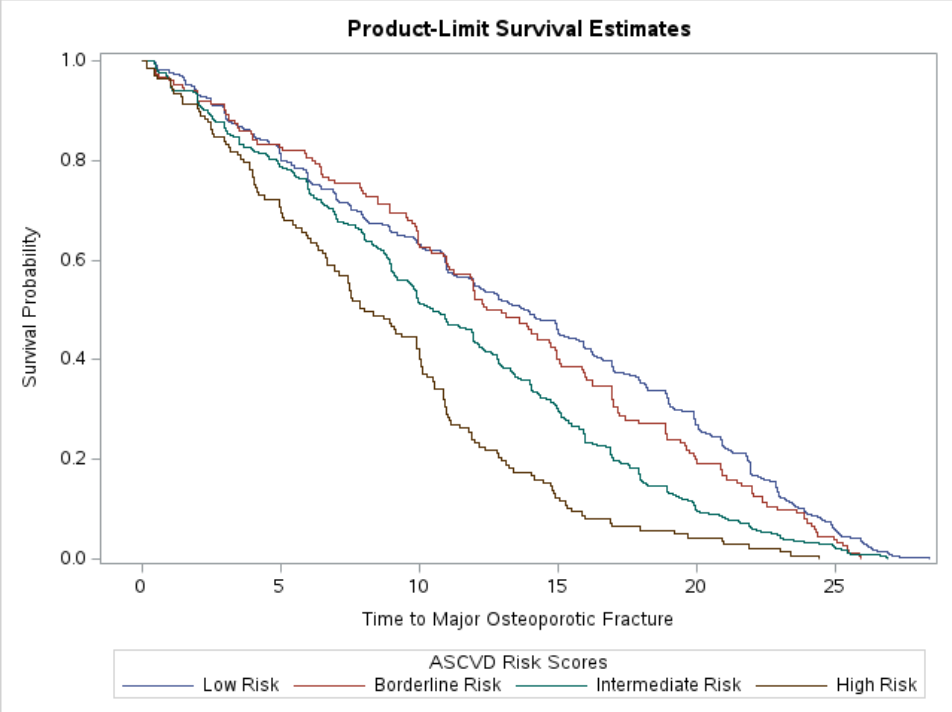

Figure 2b: Kaplan-Meier plots by ASCVD Category for Major Osteoporotic Fracture (MOF)

IR confidence intervals by ASCVD status overlapped, indicating no significant difference by group (Table 2b). However, a similar trend was also observed in the Kaplan-Meier analysis showing significant differences ($p < 0.0001$) in time to fracture by ASCVD score, with the median time (95% CI) to fracture being longest in the low CVD group [13.83 (12.00 – 15.04)] and shortest in the high CVD risk groups [8.00 (6.95 – 10.00)] in case of MOF (Fig. 2b).

When compared to the low ASCVD group, the crude model showed that women in the intermediate and high ASCVD groups had 67% (HR: 1.67; 95% CI: 1.45, 1.93) and 2.4-fold (HR: 2.35; 95% CI: 1.93, 2.87) higher risk of MOF in the base model, respectively (Table 3b – Model 1). The association attenuated downward slightly after the various adjustments, but compared to women with a low ASCVD score, women with an intermediate ASCVD score had 37% and 31% higher risk of MOF in the fully adjusted

Table 3b.

The Association between CVD Risk Score and MOF (n = 1,067)

	Model 1 HR (95% CI)	**Model 2 HR (95% CI)**	**Model 3 HR (95% CI)**	**Model 4 HR (95% CI)**	**Model 5 HR (95% CI)**
ASCVD Risk					
Low (<5%)	Ref	Ref	Ref	Ref	Ref
Borderline (5% to 7.4%)	1.18 (0.97 – 1.42)	1.03 (0.83 – 1.27)	1.18 (0.91 – 1.52)	1.11 (0.85 – 1.45)	1.07 (0.86 – 1.33)
Intermediate (7.5% to 19.9%)	1.67 (1.45 – 1.93)	1.24 (1.02 – 1.52)	1.41 (1.11 – 1.80)	1.37 (1.06 – 1.77)	1.31 (1.07 – 1.60)
High (≥20%)	2.35 (1.93 – 2.87)	1.52 (1.14 – 2.03)	1.37 (0.95 – 1.97)	1.17 (0.79 – 1.74)	1.38 (1.02 – 1.86)

Model 1: WHI Component (OS vs. CT)
Model 2: Model 1 + Sociodemographic (Age, Race, Ethnicity, Education, Income)

Model 3: Model 2 + Lifestyle, Nutrition, and Anthropometric (Physical Activity, Alcohol, Calcium Intake, vitamin D Intake, BMI)
Model 4: Model 3 + Health-related and Medication variables (Parental fx, Falls, HRT, Anti-Osteoporotic Meds, Statins, Aspirin)
Model 5: Stepwise (Age, Race, Falls, Parental fx)

(HR: 1.37, 95% CI: 1.06, 1.77) and final stepwise (HR: 1.31, 95% CI: 1.07, 1.60) models (Table 3b – Model 4 & 5). Likewise, the association between ASCVD score and MOF risk attenuated downward for women with a high ASCVD score, with no association observed in the fully adjusted model (Table 3b – Model 4). However, in the final model based on stepwise procedures, women with a high ASCVD score had 38% higher risk (HR: 1.38, 95% CI: 1.02, 1.86) of MOF risk compared to women in the low ASCVD score group after adjusting for age, race, falls, and parental fracture (Table 3b – Model 5).

Hip Fracture

Over an average of 16.7 (8.0) mean years of follow-up, 261 (4.7%) hip fractures were reported, with a crude IR of 28.33 per 10,000 person-years (Table 2c). After adjusting for age and race, the overall hip fracture IR attenuated to 17.38 per 10,000 person-years, again with the greatest IR attenuation in the intermediate and high ASCVD groups (Intermediate: -53.5%; High: -60.8%) (Table 2c). The Kaplan-Meier analysis showed significant differences ($p < 0.0001$) in time to fracture by ASCVD score, with the median time (95% CI) to fracture being longest in the low CVD group [20.07 (17.62 – 22.22)] and shortest in the high CVD risk groups [9.92 (6.69 – 10.54)] in case of hip fracture (Fig. 2c).

Table 2c.

Hip Fracture Incidence Rates Overall and by ASCVD Risk Level

	Hip		
	Events N	Crude IR[a] (95% CI)	Adjusted[b] IR[a] (95% CI)
Overall	261	28.33 (25.09–31.98)	17.38 (13.76–21.94)
Low (<5%)	79	18.45 (14.79 – 23.00)	16.21 (11.58–22.68)
Borderline (5% - 7.4%)	42	29.26 (21.63–39.60)	17.66 (11.95–26.08)
Intermediate (7.5% - 19.9%)	101	37.08 (30.51–45.06)	17.24 (12.86–23.12)
High (≥20%)	39	50.61 (36.98– 69.30)	19.86 (13.13–30.05)

IR = Incidence Rate; CI = Confidence Interval
[a]IR per 10,000 Person-Years;
[b]Age- and Race- Adjusted

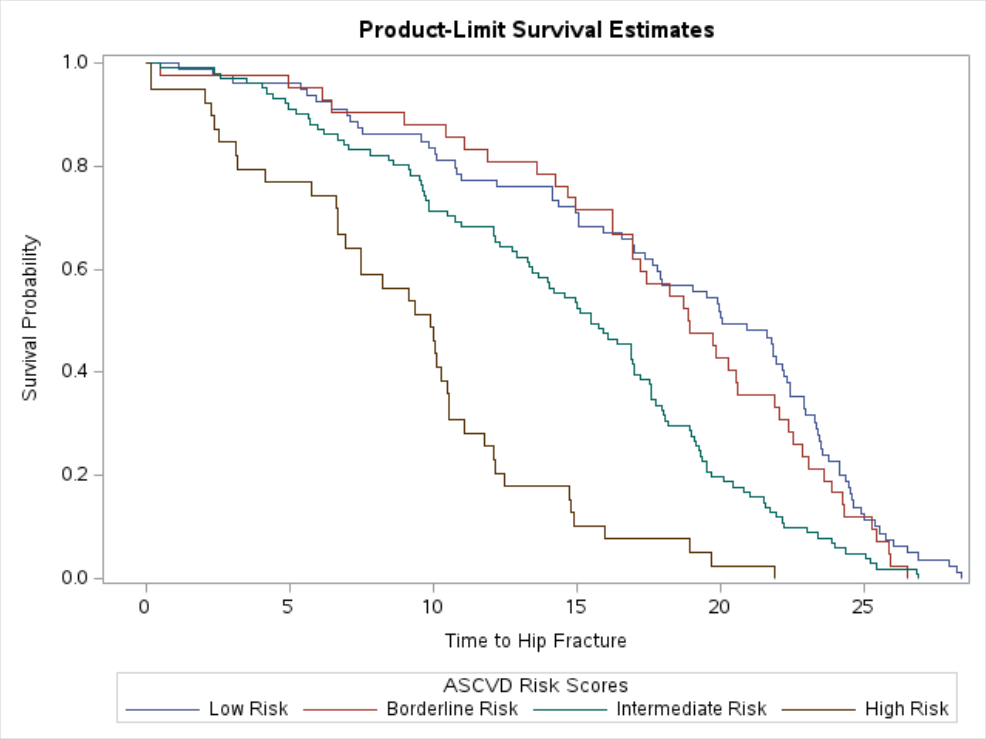

Figure 2c: Kaplan-Meier plots by ASCVD Category for Hip fracture

The base Cox proportional hazards model showed that after accounting for the WHI study group, compared to women in the low ASCVD group, women in the borderline, intermediate, and high ASCVD groups had 83% (HR: 1.83; 95% CI: 1.26, 2.68), 2.7-fold (HR: 2.68; 95% CI: 1.98, 3.62) and 5-fold (HR: 4.97; 95% CI: 3.34, 7.40) higher risk of hip fractures, respectively (Table 3c – Model 1). The association significantly attenuated, but the point estimates indicated a higher risk for fracture in the high ASCVD group after adjusting for sociodemographic factors (age, race, ethnicity, education, income), with a significant 81% higher risk for hip fracture in the high ASCVD score group (Table 3c – Model 2). Similarly, after further adjustment for lifestyle, nutrition, anthropometric, health-related, and medication there was no

Table 3c.
The Association between CVD Risk Score and Hip Fracture (n = 261)

	Model 1 HR (95% CI)	**Model 2 HR (95% CI)**	**Model 3 HR (95% CI)**	**Model 4 HR (95% CI)**	**Model 5 HR (95% CI)**
ASCVD Risk					
Low (<5%)	Ref	Ref	Ref	Ref	Ref
Borderline (5% to 7.4%)	1.83 (1.26 – 2.68)	1.16 (0.76 – 1.76)	1.28 (0.77 – 2.12)	1.24 (0.75 – 2.06)	1.27 (0.82 – 1.96)
Intermediate (7.5% to 19.9%)	2.68 (1.98 – 3.62)	1.28 (0.86 – 1.90)	1.38 (0.84 – 2.27)	1.29 (0.78 – 2.12)	1.43 (0.94 – 2.18)
High (≥20%)	4.97 (3.34 – 7.40)	1.81 (1.02 – 3.18)	1.64 (0.79 – 3.41)	1.45 (0.67 – 3.14)	1.88 (1.03 – 3.43)

Model 1: WHI Component (OS vs. CT)
Model 2: Model 1 + Sociodemographic (Age, Race, Ethnicity, Education, Income)
Model 3: Model 2 + Lifestyle, Nutrition, and Anthropometric (Physical Activity, Alcohol, Calcium Intake, vitamin D Intake, BMI)
Model 4: Model 3 + Health-related and Medication variables (Parental fx, Falls, HRT, Anti-Osteoporotic Meds, Statins, Aspirin)
Model 5: Stepwise (Age, Race, Ethnicity, Physical Activity, BMI, Parental fx, HRT)

significant association between ASCVD score and hip fracture risk despite point estimates showing indicating higher risk (Table 3c – Hip: Models 3, 4). In the final model, the high ASCVD group had a significantly 88% higher risk (HR: 1.88, 95% CI: 1.03, 3.43) of hip fracture compared to women in the low group after adjusting for age, race, ethnicity, physical activity, BMI, parental fracture, and HRT (Table 3c – Hip: Model 5).

Effect Modification

There was no evidence of heterogeneity by obesity status in the association of ASCVD score with 1) any clinical fractures (p-value= 0.9905), 2) MOF (p-value= 0.5710), or 3) hip fractures (p-value= 0.0650) by obesity status.

Sensitivity Analysis

When age was excluded, all the ASCVD groups had a significantly higher risk of fracture for any clinical, MOF, and hip fracture sites when compared to the low ASCVD group (Table 4), with magnitudes similar to our crude findings. Similarly, after excluding both age and race, all the ASCVD groups showed a significantly higher risk of fracture for all fracture sites when compared to the low ASCVD group (Table 4). The correlation between age and ASCVD score was 0.68, indicating a moderate positive correlation (91) between age and ASCVD score. However, the AIC showed that the model with age and race had the lowest score, indicating better model fit in terms of balancing model

complexity and goodness of fit, and is more likely to be closer to the true underlying model (Table 4).

Table 4.

Evaluating model fit on the Association between CVD Risk Score and Fracture

	Model 5 HR (95% CI)	AIC	Model 5 w/o age HR (95% CI)	AIC	Model 5 w/o age and race HR (95% CI)	AIC
Any Clinical Fracture						
ASCVD Score		25395.76		25435.97		25533.79
Low (<5%)	Ref		Ref		Ref	
Borderline (5% to 7.4%)	1.07 (0.92 – 1.25)		1.26 (1.09 – 1.45)		1.19 (1.03 – 1.37)	
Intermediate (7.5% to 19.9%)	1.09 (0.94 – 1.27)		1.49 (1.33 – 1.68)		1.38 (1.23 – 1.55)	
High (≥20%)	1.03 (0.82 – 1.30)		1.68 (1.41 – 1.99)		1.48 (1.25 – 1.76)	
MOF						
ASCVD Score		13669.13		13715.04		13856.93
Low (<5%)	Ref		Ref		Ref	
Borderline (5% to 7.4%)	1.07 (0.86 – 1.33)		1.35 (1.10 – 1.65)		1.25 (1.02 – 1.53)	
Intermediate (7.5% to 19.9%)	1.31 (1.07 – 1.60)		2.07 (1.77 – 2.42)		1.81 (1.55 – 2.11)	
High (≥20%)	1.38 (1.02 – 1.86)		2.80 (2.23 – 3.50)		2.27 (1.81 – 2.83)	
Hip Fracture						
ASCVD Score		3112.31		3140.36		3202.46
Low (<5%)	Ref		Ref		Ref	
Borderline (5% to 7.4%)	1.27 (0.82 – 1.96)		2.06 (1.37 – 3.09)		1.94 (1.30 – 2.92)	
Intermediate (7.5% to 19.9%)	1.43 (0.94 – 2.18)		3.13 (2.24 – 4.36)		2.79 (2.00 – 3.89)	
High (≥20%)	1.88 (1.03 – 3.43)		5.34 (3.38 – 8.43)		4.32 (2.74 – 6.81)	

Model 5: All Significant variables associated with fx
(Any clinical fracture: OS vs. CT, Age, Race, Income, Falls, Parental fx
MOF: Age, Race, Falls, Parental fx
Hip fracture: Age, Race, Ethnicity, Physical Activity, BMI, Parental fx, HRT)

DISCUSSION

Over the last 30 years, the WHI has provided valuable insights into a myriad of women's health issues including fragility fractures. This study found that CVD risk, based on the ASCVD score, was associated with higher fracture risk, with women in the intermediate risk group (ASCVD score 7.5% – 19.9%) having a higher risk for MOF and women in the high risk group (ASCVD score ≥20%) having a higher risk for both MOF and hip fractures, even after adjusting for age, race, and other covariates. Further, there was no evidence of effect measure modification by obesity status.

To our knowledge, this was one of the first analyses applying the ASCVD risk score to evaluate the association of CVD and fracture outcomes in postmenopausal women. Previous studies looking at CVD conditions as a composite exposure have shown CVD to be associated with higher fracture risk. For example, a study of adults aged 50 – 85 years found different types of CVD conditions, including heart failure, stroke, peripheral atherosclerosis, and ischemic heart disease, to be associated with increased hip fracture risk ranging from 2.32-fold to 5.09-fold, with comparable levels in both men and women (92). Similarly, a study in China showed that compared to other older hospitalized patients, males with CVDs (hypertensive diseases, ischemic heart disease, cerebrovascular disease, and other circulatory diseases) had 48% higher (RR: 1.48; 95% CI:1.40, 1.56) and women had 63% (RR: 1.63, 95% CI: 1.52, 1.76) higher risk of hip fracture with cerebrovascular disease patients being the highest risk group (93).

Likewise, a study of adults aged 50 to 84 years evaluating the effect of CVD on MOF, showed that compared to their non-CVD counterparts, men and women with CVD had 24% (HR: 1.24 95% CI: 1.13, 1.36) and 18% (HR: 1.18, 95% CI: 1.11, 1.25) higher risk of MOF respectively (94). The findings of this study of postmenopausal women are consistent with the previous studies, showing a higher risk for MOF and hip fractures.

Similarly, investigations into specific cardiovascular conditions have revealed noteworthy associations with fracture outcomes. A meta-analysis on the association between HTN and fracture showed that the association between HTN and fracture risk was slightly stronger in women (pooled OR: 1.52, 95% CI: 1.30-1.79) than in men (pooled OR: 1.35, 95% CI: 1.26-1.44) (95). More specifically, high systolic blood pressure (SBP) was found to be associated with increased fracture risk (HR: 1.22; 95% CI: 1.00, 1.47) in women even after adjusting for confounders and medications (96). Similarly, meta-analyses have shown that heart failure (HF) was associated with a higher risk of all fracture incidents (HR: 1.67; 95% CI: 1.30, 2.16) and hip fractures (HR: 2.20; 95% CI: 1.28, 3.77), with studies showing higher risk in different age, sample size, sex, and follow-up duration subgroups (97). Likewise, studies looking specifically at coronary heart disease (CHD), cerebral vascular disease, and peripheral arterial disease (PAD) found these conditions to be associated with an increased risk for fracture including the fracture outcomes in this study. The magnitude of the findings utilizing a score comprised of individual CVD conditions was again consistent with these studies looking individually at one CVD condition.

Concerning the individual components of the ASCVD score, studies have found higher total cholesterol levels were associated with an increased risk of osteoporotic

fractures as there was a 17% higher risk of fracture due to elevated total cholesterol (HR: 1.17; 95% CI: 1.02, 1.34), and this relationship became more pronounced over time (98). Another study found a significant association between HDL level and an increased risk of osteoporotic fracture in participants [OR 1.20, 95% CI 1.03, 1.40]. Though women who participated in this study had normal levels of HDL cholesterol, they showed an increased risk of fracture (OR 1.37, 95% CI 1.12, 1.68) due to HDL levels, whereas men who participated in this study had lower HDL levels, but no association was observed (OR 1.01, 95% CI 0.73, 1.40) between HDL level and fracture (99). Another study that analyzed HDL levels in quintiles found that higher rates of fractures occurred in the highest quintile of HDL cholesterol level compared to those in the lowest quintile (HR: 1.33; 95% CI: 1.14, 1.54) (100).

Lastly, the ASCVD risk score includes diabetes, smoking, and alcohol, all of which are found to be associated with fracture risk (101-102). For example, previous studies in the WHI have shown that diabetes (103), smoking status (104), and alcohol consumption (105) were associated with fractures, especially hip fractures. These studies collectively reinforce the notion that individuals with CVD either based on individual conditions or at high CVD risk based on risk factors have increased susceptibility to fractures.

As previously mentioned, this study also evaluated if obesity status modified the association between CVD risk and fracture. The causal relationship between obesity and CVD has been well documented (106-107), but obesity was once thought of as a protective factor against fragility fractures(108-110). However, in recent years, studies have shown that obesity is associated with an increased vertebral (111), wrist, and ankle

fracture risk (112), and accounting for factors like bone mineral density showed a reversal in the protective factor of obesity on hip (113-114) and other long-bone fractures (115-118). While it was initially hypothesized that the association between CVD risk and hip fractures may vary by obesity status, the interaction term was not statistically significant.

This study has several limitations that warrant consideration when interpreting the results. First, the study's sample was restricted to those with baseline biomarker data. Studies with larger sample sizes are warranted to validate the findings. Reliance on self-reported data to calculate ASCVD score, covariates, and fracture outcomes could have led to misclassification due to information bias. The self-report of factors in the ASCVD score and covariates has been shown to be valid in various epidemiological studies (119-120). To minimize misclassification, this study used multiple methods (e.g., self-report and medication data) to identify different variables of the ASCVD score. With respect to the fracture outcomes, all the hip fractures were centrally adjudicated for the first 17 years of the WHI. The self-report of fractures has been shown to vary in accuracy depending on the fracture site (39). Clinical spine fractures have the lowest self-reported validity and were included in any clinical and MOF fracture outcomes. Misclassification of clinical spine fractures would bias the associations between ASCVD risk and fracture outcomes towards the null. However, while still observing significant associations in MOF, the results could be a conservative estimate of the true association between CVD risk and MOF. Model overfit could have affected the findings given that the ASCVD score included variables that were also considered as covariates (i.e., age and race). Despite the strong correlation between age and ASCVD score, our model fit statistics

indicated better performance when age and race were included, emphasizing that without age (one of the primary risk factors for fracture) and race, the association between CVD risk and fractures would be biased. Lastly, despite comprehensive adjustment for potential confounders, the study could be biased by residual confounding.

CONCLUSION

Utilizing data from the Women's Health Initiative and incorporating the atherosclerotic cardiovascular disease (ASCVD) risk estimator tool, this study identified that elevated CVD risk was associated with increased fracture risk, particularly major osteoporotic fractures (MOF) and hip fractures. While this study benefited from the well-characterized WHI dataset with 30 years of data comprehensive adjustment for potential confounders, and rigorous statistical analyses, limitations such as sample size restrictions and potential biases necessitate cautious interpretation of the findings. Nevertheless, the findings indicate the potential clinical utility of considering CVD risk in fracture prevention strategies, aimed at reducing fracture burden in postmenopausal women. Continued investigation into this complex association is warranted to further elucidate underlying mechanisms and inform targeted interventions.

LIST OF REFERENCES

1. Burge, Dawson-Hughes, B., Solomon, D. H., Wong, J. B., King, A., & Tosteson, A. (2007). Incidence and Economic Burden of Osteoporosis-Related Fractures in the United States, 2005–2025. Journal of Bone and Mineral Research, 22(3), 465–475. https://doi.org/10.1359/jbmr.061113

2. Sambrook, & Cooper, C. (2006). Osteoporosis. The Lancet (British Edition), 367(9527), 2010–. https://doi.org/10.1016/S0140-6736(06)68891-0

3. Lewiecki, Ortendahl, J. D., Vanderpuye-Orgle, J., Grauer, A., Arellano, J., Lemay, J., Harmon, A. L., Broder, M. S., & Singer, A. J. (2019). Healthcare Policy Changes in Osteoporosis Can Improve Outcomes and Reduce Costs in the United States. JBMR Plus, 3(9), e10192–n/a. https://doi.org/10.1002/jbm4.10192

4. Sànchez-Riera, L., Wilson, N., Kamalaraj, N., Nolla, J. M., Kok, C., Li, Y., ... & March, L. (2010). Osteoporosis and fragility fractures. *Best practice & research Clinical rheumatology*, *24*(6), 793-810.

5. Center, J. R., Nguyen, T. V., Schneider, D., Sambrook, P. N., & Eisman, J. A. (1999). Mortality after all major types of osteoporotic fracture in men and women: an observational study. *The Lancet (British Edition)*, *353*(9156), 878–882. https://doi.org/10.1016/S0140-6736(98)09075-8

6. Empana, J.-P., Dargent-Molina, P., & Bréart, G. (2004). Effect of Hip Fracture on Mortality in Elderly Women: The EPIDOS Prospective Study. *Journal of the American Geriatrics Society (JAGS)*, *52*(5), 685–690. https://doi.org/10.1111/j.1532-5415.2004.52203.x

7. Bliuc, D., Nguyen, N. D., Milch, V. E., Nguyen, T. V., Eisman, J. A., & Center, J. R. (2009). Mortality Risk Associated With Low-Trauma Osteoporotic Fracture and Subsequent Fracture in Men and Women. *JAMA : The Journal of the American Medical Association*, *301*(5), 513–521. https://doi.org/10.1001/jama.2009.50

8. Huntjens, K. M. B., Kosar, S., van Geel, T. A. C. M., Geusens, P. P., Willems, P., Kessels, A., Winkens, B., Brink, P., & van Helden, S. (2010). Risk of subsequent fracture and mortality within 5 years after a non-vertebral fracture. *Osteoporosis International*, *21*(12), 2075–2082. https://doi.org/10.1007/s00198-010-1178-5

9. Cauley, J. A., Thompson, D. E., Ensrud, K. C., Scott, J. C., & Black, D. (2000). Risk of mortality following clinical fractures. *Osteoporosis International*, *11*(7), 556–561. https://doi.org/10.1007/s001980070075

10. ISMAIL, A. A., O'NEILL, T. W., JOHNELL, O., DIAZ-LOPEZ, J. B., LOPES VAZ, A., MARCHAND, F., RASPE, H., REID, D. M., TODD, C., WEBER, K., WOOLF, A., REEVE, J., COOPER, C., SILMAN, A. J., FINN, J. D., BHALLA, A. K., CANNATA, J. B., DELMAS, P., FALCH, J. A., … HOSZOWSKI, K. (1998). Mortality associated with vertebral deformity in men and women : Results

from the European Prospective Osteoporosis Study (EPOS). *Osteoporosis International*, *8*(3), 291–297. https://doi.org/10.1007/s001980050067

11. JOHNELL, O., KANIS, J. A., ODEN, A., SERNBO, I., REDLUND-JOHNELL, I., PETTERSON, C., DE LAET, C., & JÖNSSON, B. (2004). Mortality after osteoporotic fractures. *Osteoporosis International*, *15*(1), 38–42. https://doi.org/10.1007/s00198-003-1490-4

12. KADO, D. M., DUONG, T., STONE, K. L., ENSRUD, K. E., NEVITT, M. C., GREENDALE, G. A., & CUMMINGS, S. R. (2003). Incident vertebral fractures and mortality in older women: a prospective study. *Osteoporosis International*, *14*(7), 589–594. https://doi.org/10.1007/s00198-003-1412-5

13. Ong, T., Kantachuvesiri, P., Sahota, O., & Gladman, J. R. F. (2018). Characteristics and outcomes of hospitalised patients with vertebral fragility fractures: a systematic review. *Age and Ageing*, *47*(1), 17–25. https://doi.org/10.1093/ageing/afx079

14. Shortt, N. L., & Robinson, C. M. (2005). Mortality After Low-Energy Fractures in Patients Aged at Least 45 Years Old. *Journal of Orthopaedic Trauma*, *19*(6), 396–403. https://doi.org/10.1097/01.bot.0000155311.04886.7e

15. Dy, C. J., Lane, J. M., Pan, T. J., Parks, M. L., & Lyman, S. (2016). Racial and Socioeconomic Disparities in Hip Fracture Care. *Journal of Bone and Joint Surgery. American Volume, 98(10), 858–865.* *https://doi.org/10.2106/JBJS.15.00676*

16. Harada, N. D., Chun, A., Chiu, V., & Pakalniskis, A. (2000). Patterns of Rehabilitation Utilization after Hip Fracture in Acute Hospitals and Skilled Nursing Facilities. *Medical Care, 38(11), 1119–1130.* *https://doi.org/10.1097/00005650-200011000-00006*

17. Berry, S. D., & Miller, R. R. (2008). Falls: Epidemiology, pathophysiology, and relationship to fracture. *Current Osteoporosis Reports, 6(4), 149–154.* *https://doi.org/10.1007/s11914-008-0026-4*

18. Tajeu, G. S., Delzell, E., Smith, W., Arora, T., Curtis, J. R., Saag, K. G., Morrisey, M. A., Yun, H., & Kilgore, M. L. (2014). Death, debility, and destitution following hip fracture. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *69*(3), 346–353. https://doi.org/10.1093/gerona/glt105

19. Wright, Chen, L., Saag, K. G., Brown, C. J., Shikany, J. M., & Curtis, J. R. (2020). Racial Disparities Exist in Outcomes After Major Fragility Fractures. Journal of the American Geriatrics Society (JAGS), 68(8), 1803–1810. https://doi.org/10.1111/jgs.16455

20. Jacobsen, S. J., Goldberg, J., Miles, T. P., Brody, J. A., Stiers, W., & Rimm, A. A. (1992). Race and sex differences in mortality following fracture of the hip. *American Journal of Public Health (1971), 82(8), 1147–1150.* *https://doi.org/10.2105/AJPH.82.8.1147*

21. Camacho, P. M., Petak, S. M., Binkley, N., Diab, D. L., Eldeiry, L. S., Farooki, A., Harris, S. T., Hurley, D. L., Kelly, J., Lewiecki, E. M., Pessah-Pollack, R., McClung, M., Wimalawansa, S. J., & Watts, N. B. (2020). American Association

of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis—2020 Update. Endocrine Practice, 26(Suppl 1), 1–46. https://doi.org/10.4158/GL-2020-0524SUPPL

22. Cosman, F., de Beur, S. J., LeBoff, M. S., Lewiecki, E. M., Tanner, B., Randall, S., Lindsay, R., & National Osteoporosis Foundation (2014). Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 25(10), 2359–2381. https://doi.org/10.1007/s00198-014-2794-2

23. den Uyl, D., Nurmohamed, M. T., van Tuyl, L. H., Raterman, H. G., & Lems, W. F. (2011). (Sub)clinical cardiovascular disease is associated with increased bone loss and fracture risk; a systematic review of the association between cardiovascular disease and osteoporosis. *Arthritis Research & Therapy, 13(1), R5–R5. https://doi.org/10.1186/ar3224*

24. Fisher, Srikusalanukul, W., Davis, M., & Smith, P. (2013). Cardiovascular diseases in older patients with osteoporotic hip fracture: prevalence, disturbances in mineral and bone metabolism, and bidirectional links. Clinical Interventions in Aging, 8, 239–256. https://doi.org/10.2147/CIA.S38856

25. Gerber, Melton, L. J., McNallan, S. M., Jiang, R., Weston, S. A., & Roger, V. L. (2013). Cardiovascular and Noncardiovascular Disease Associations with Hip

Fractures. The American Journal of Medicine, 126(2), 169.e19–169.e26. https://doi.org/10.1016/j.amjmed.2012.06.032

26. Wada, Hirano, F., Kuroda, T., & Shiraki, M. (2012). Breast arterial calcification and hypertension associated with vertebral fracture: Vascular calcification and fracture. Geriatrics & Gerontology International, 12(2), 330–335. https://doi.org/10.1111/j.1447-0594.2011.00775.x

27. Szulc, Samelson, E. J., Sornay-Rendu, E., Chapurlat, R., & Kiel, D. P. (2013). Severity of aortic calcification is positively associated with vertebral fracture in older men—a densitometry study in the STRAMBO cohort. Osteoporosis International, 24(4), 1177–1184. https://doi.org/10.1007/s00198-012-2101-z

28. den Uyl, Nurmohamed, M. ., van Tuyl, H. ., Raterman, H. ., & Lems, W. . (2011). (Sub) clinical cardiovascular disease is associated with increased bone loss and fracture risk; a systematic review of the association between cardiovascular disease and osteoporosis. Arthritis Research & Therapy, 13(1), R5–R5. https://doi.org/10.1186/ar3224

29. Veronese, N., Stubbs, B., Crepaldi, G., Solmi, M., Cooper, C., Harvey, N. C., ... & Lamb, S. E. (2017). Relationship between low bone mineral density and fractures with incident cardiovascular disease: a systematic review and meta-analysis. *Journal of Bone and Mineral Research*, *32*(5), 1126-1135.

30. Paik, Rosen, H. N., Gordon, C. M., & Curhan, G. C. (2016). Diuretic Use and Risk of Vertebral Fracture in Women. The American Journal of Medicine, 129(12), 1299–1306. https://doi.org/10.1016/j.amjmed.2016.07.013+

31. American College of Cardiology. ASCVD Risk Estimator Plus. Available at: https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/. Accessed October 16, 2018.

32. Gluckman, T. J., Kovacs, R. J., Stone, N. J., Damalas, D., Mullen, J. B., & Oetgen, W. J. (2016). The ASCVD Risk Estimator App. Journal of the American College of Cardiology, 67(3), 350–352. https://doi.org/10.1016/j.jacc.2015.10.068

33. Goff Jr, D. C., Lloyd-Jones, D. M., Bennett, G., Coady, S., D'agostino, R. B., Gibbons, R., ... & Wilson, P. W. (2014). 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation, 129(25_suppl_2), S49-S73. https://doi.org/10.1161/01.cir.0000437741.48606.98

34. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. (1998). *Controlled clinical trials*, *19*(1), 61–109. https://doi.org/10.1016/s0197-2456(97)00078-0

35. Goff, J., Lloyd-Jones, D. M., Bennett, G., Coady, S., D'Agostino, S., Gibbons, R., Greenland, P., Lackland, D. T., Levy, D., O'Donnell, C. J., Robinson, J. G., Schwartz, J. S., Shero, S. T., Smith, J., Sorlie, P., Stone, N. J., & Wilson, P. W. F. (2014). 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology, 63(25), 2935–2959. https://doi.org/10.1016/j.jacc.2013.11.005

36. Anderson, G. L., Manson, J., Wallace, R., Lund, B., Hall, D., Davis, S., Shumaker, S., Wang, C.-Y., Stein, E., & Prentice, R. L. (2003). Implementation of the women's health initiative study design. *Annals of Epidemiology*, *13*(9), S5–S17. https://doi.org/10.1016/S1047-2797(03)00043-7

37. The Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical Trial and Observational Study. Control Clin Trials. 1998;19:61–109.

38. Wright, N. C., Daigle, S. G., Melton, M. E., Delzell, E. S., Balasubramanian, A., & Curtis, J. R. (2019). The Design and Validation of a New Algorithm to Identify Incident Fractures in Administrative Claims Data. *Journal of Bone and Mineral Research, 34(10), 1798–1807. https://doi.org/10.1002/jbmr.3807*

39. Chen, Kooperberg, C., Pettinger, M. B., Bassford, T., Cauley, J. A., LaCroix, A. Z., Lewis, C. E., Kipersztok, S., Borne, C., & Jackson, R. D. (2004). Validity of self-report for fractures among a multiethnic cohort of postmenopausal women: results from the Women's Health Initiative observational study and clinical trials. Menopause (New York, N.Y.), 11(3), 264–274. https://doi.org/10.1097/01.GME.0000094210.15096.FD

40. Bush, Miller, S. R., Golden, A. L., & Hale, W. E. (1989). Self-report and medical record report agreement of selected medical conditions in the elderly. American Journal of Public Health (1971), 79(11), 1554–1556. https://doi.org/10.2105/AJPH.79.11.1554

41. Nevitt, Cummings, S. R., Browner, W. S., Seeley, D. G., Cauley, J. A., Vogt, T. M., & Black, D. M. (1992). 92172829 The accuracy of self-report of fractures in elderly women: Evidence from a prospective study. Maturitas, 15(3), 257–257. https://doi.org/10.1016/0378-5122(92)90225-S

42. ISMAIL, A. A., O'NEILL, T. W., REEVE, J., SILMAN, A. J., COCKERILL, W., FINN, J. D., CANNATA, J. B., HOSZOWSKI, K., JOHNELL, O., MATTHIS, C., RASPE, H., & RASPE, A. (2000). Validity of self-report of fractures : Results from a prospective study in men and women across Europe. Osteoporosis International, 11(3), 248–254. https://doi.org/10.1007/s001980050288

43. Honkanen, Honkanen, R., Heikkinen, L., Kröger, H., & Saarikoski, S. (1999). Validity of Self-Reports of Fractures in Perimenopausal Women. American Journal of Epidemiology, 150(5), 511–516. https://doi.org/10.1093/oxfordjournals.aje.a010040

44. Kanis, J. A. (1995). Bone and cancer: pathophysiology and treatment of metastases. *Bone (New York, N.Y.)*, *17*(2 Suppl), 101S-S105. https://doi.org/10.1016/8756-3282(95)00194-I

45. Guise, T. A. (2006). Bone Loss and Fracture Risk Associated with Cancer Therapy. *The Oncologist (Dayton, Ohio)*, *11*(10), 1121–1131. https://doi.org/10.1634/theoncologist.11-10-1121

46. Saad, F., Lipton, A., Cook, R., Chen, Y., Smith, M., & Coleman, R. (2007). Pathologic fractures correlate with reduced survival in patients with malignant bone disease. *Cancer*, *110*(8), 1860–1867. https://doi.org/10.1002/cncr.22991

47. Johnson, S. K., & Knobf, M. T. (2008). Surgical interventions for cancer patients with impending or actual pathologic fractures. *Orthopaedic Nursing*, *27*(3), 160–171. https://doi.org/10.1097/01.NOR.0000320543.90115.d5

48. Wickrama, K.A.S., O'Neal, C.W. & Lott, R.E. Early Community Contexts, Race/Ethnicity and Young Adult CVD Risk Factors: The Protective Role of Education. J Community Health 37, 781–790 (2012). https://doi.org/10.1007/s10900-011-9511-2

49. Lawlor, D. A., Batty, G. D., Morton, S. M. B., Clark, H., Macintyre, S., & Leon, D. A. (2005). Childhood Socioeconomic Position, Educational Attainment, and Adult Cardiovascular Risk Factors: The Aberdeen Children of the 1950s Cohort Study. American Journal of Public Health (1971), 95(7), 1245–1251. https://doi.org/10.2105/AJPH.2004.041129

50. Bell, C. N., Thorpe, R. J., Bowie, J. V., & LaVeist, T. A. (2018). Race disparities in cardiovascular disease risk factors within socioeconomic status strata. *Annals of Epidemiology*, *28*(3), 147–152. https://doi.org/10.1016/j.annepidem.2017.12.007

51. Curtis, J. R., McClure, L. A., Delzell, E., Howard, V. J., Orwoll, E., Saag, K. G., ... & Howard, G. (2009). Population-based fracture risk assessment and osteoporosis treatment disparities by race and gender. *Journal of general internal medicine*, *24*, 956-962.

52. ZINGMOND, D. S., SOOHOO, N. F., & SILVERMAN, S. L. (2006). The role of socioeconomic status on hip fracture. Osteoporosis International, 17(10), 1562–1568. https://doi.org/10.1007/s00198-006-0161-7

53. Crandall, C. J., Han, W., Greendale, G. A., Seeman, T., Tepper, P., Thurston, R., Karvonen-Gutierrez, C., & Karlamangla, A. S. (2014). Socioeconomic status in relation to incident fracture risk in the Study of Women's Health Across the Nation. *Osteoporosis International*, *25*(4), 1379–1388. https://doi.org/10.1007/s00198-013-2616-y

54. Felson, D. T., Kiel, D. P., ANDERSON, J. J., & KANNEL, W. B. (1988). Alcohol consumption and hip fractures: the Framingham Study. American journal of epidemiology, 128(5), 1102-1110.

55. Rehm J. The risks associated with alcohol use and alcoholism. Alcohol Res Health. 2011;34(2):135-143.

56. Hoek, van Oort, S., Mukamal, K. J., & Beulens, J. W. . (2022). Alcohol Consumption and Cardiovascular Disease Risk: Placing New Data in Context. Current Atherosclerosis Reports, 24(1), 51–59. https://doi.org/10.1007/s11883-022-00992-1

57. Slemenda, C. (1997). Prevention of hip fractures: risk factor modification. The American journal of medicine, 103(2), S65-S73.

58. Buttar, H. S., Li, T., & Ravi, N. (2005). Prevention of cardiovascular diseases: Role of exercise, dietary interventions, obesity and smoking cessation. Experimental & clinical cardiology, 10(4), 229.

59. Premaor, Compston, J. E., Fina Avilés, F., Pagès-Castellà, A., Nogués, X., Díez-Pérez, A., & Prieto-Alhambra, D. (2013). The association between fracture site and obesity in men: A population-Based cohort study. Journal of Bone and Mineral Research, 28(8), 1771–1777. https://doi.org/10.1002/jbmr.1878

60. Poirier, P., Giles, T. D., Bray, G. A., Hong, Y., Stern, J. S., Pi-Sunyer, F. X., & Eckel, R. H. (2006). Obesity and Cardiovascular Disease: Pathophysiology, Evaluation, and Effect of Weight Loss. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *26*(5), 968–976. https://doi.org/10.1161/01.ATV.0000216787.85457.f3

61. LIPS, P., BOUILLON, R., VAN SCHOOR, N. M., VANDERSCHUEREN, D., VERSCHUEREN, S., KUCHUK, N., MILISEN, K., & BOONEN, S. (2010). Reducing fracture risk with calcium and vitamin D. *Clinical Endocrinology (Oxford)*, *73*(3), 277–285. https://doi.org/10.1111/j.1365-2265.2009.03701.x

62. Judd, S. E., & Tangpricha, V. (2009). Vitamin D deficiency and risk for cardiovascular disease. The American journal of the medical sciences, 338(1), 40-44.

63. Chung, M., Tang, A. M., Fu, Z., Wang, D. D., & Newberry, S. J. (2016). Calcium intake and cardiovascular disease risk: an updated systematic review and meta-analysis. Annals of internal medicine, 165(12), 856-866.

64. Hsu, Sing, C.-W., Li, G. H. Y., Tan, K. C. B., Cheung, B. M. Y., Wong, J. S. H., Wong, I. C.-K., & Cheung, C.-L. (2022). Immediate Risk for Cardiovascular Events in Hip Fracture Patients: A Population-Based Cohort Study. The Journals

of Gerontology. Series A, Biological Sciences and Medical Sciences, 77(9), 1923–1929. https://doi.org/10.1093/gerona/glab336

65. Yang, Nguyen, N. D., Center, J. R., Eisman, J. A., & Nguyen, T. V. (2014). Association between hypertension and fragility fracture: a longitudinal study. Osteoporosis International, 25(1), 97–103. https://doi.org/10.1007/s00198-013-2457-8

66. Byun, J.-H., Jang, S., Lee, S., Park, S., Yoon, H. K., Yoon, B.-H., & Ha, Y.-C. (2017). The Efficacy of Bisphosphonates for Prevention of Osteoporotic Fracture: An Update Meta-analysis. *Journal of Bone Metabolism*, *24*(1), 37–49. https://doi.org/10.11005/jbm.2017.24.1.37

67. Torgerson, D. J., & Bell-Syer, S. E. M. (2001). Hormone Replacement Therapy and Prevention of Nonvertebral Fractures: A Meta-analysis of Randomized Trials. *JAMA : The Journal of the American Medical Association*, *285*(22), 2891–2897. https://doi.org/10.1001/jama.285.22.2891

68. Maxim, P., Ettinger, B., & Spitalny, G. M. (1995). Fracture protection provided by long-term estrogen treatment. *Osteoporosis international*, *5*, 23-29.

69. Kanis, J. A., & McCloskey, E. V. (1999). Effect of calcitonin on vertebral and other fractures. *QJM : Monthly Journal of the Association of Physicians*, *92*(3), 143–150. https://doi.org/10.1093/qjmed/92.3.143

70. Li, L., Bensing, S., & Falhammar, H. (2021). Rate of fracture in patients with glucocorticoid replacement therapy: a systematic review and meta-analysis. *Endocrine*, *74*, 29-37.

71. Van Den Brand, M. W. M., Samson, M. M., Pouwels, S., Van Staa, T. P., Thio, B., Cooper, C., ... & De Vries, F. (2009). Use of anti-depressants and the risk of fracture of the hip or femur. *Osteoporosis international*, *20*, 1705-1713.

72. Thong, B. K. S., Ima-Nirwana, S., & Chin, K. Y. (2019). Proton pump inhibitors and fracture risk: a review of current evidence and mechanisms involved. *International journal of environmental research and public health*, *16*(9), 1571.

73. Kranenburg, G., Bartstra, J. W., Weijmans, M., de Jong, P. A., Mali, W. P., Verhaar, H. J., ... & Spiering, W. (2016). Bisphosphonates for cardiovascular risk reduction: a systematic review and meta-analysis. Atherosclerosis, 252, 106-115.

74. Delli Poggi, C., Fusaro, M., Mereu, M. C., Brandi, M. L., & Cianferotti, L. (2022). Cardiovascular safety and effectiveness of bisphosphonates: from intervention trials to real-life data. Nutrients, 14(12), 2369.

75. Khaksari, M., Raji-Amirhasani, A., Bashiri, H., Ebrahimi, M. N., & Azizian, H. (2022). Protective effects of combining SERMs with estrogen on metabolic parameters in postmenopausal diabetic cardiovascular dysfunction: The role of cytokines and angiotensin II. Steroids, 183, 109023.

76. Bush, T. L., Blumenthal, R., Lobo, R., & Clarkson, T. B. (2001). SERMs and cardiovascular disease in women. How do these agents affect risk?. Postgraduate medicine, 17-24.

77. Chester, R. C., Kling, J. M., & Manson, J. E. (2018). What the Women's Health Initiative has taught us about menopausal hormone therapy. Clinical cardiology, 41(2), 247-252.

78. Rahman, I., Humphreys, K., Bennet, A. M., Ingelsson, E., Pedersen, N. L., & Magnusson, P. K. E. (2013). Clinical depression, antidepressant use and risk of future cardiovascular disease. European journal of epidemiology, 28, 589-595.

79. Charlot, M., Ahlehoff, O., Norgaard, M. L., Jørgensen, C. H., Sørensen, R., Abildstrøm, S. Z., ... & Gislason, G. (2010). Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. Annals of internal medicine, 153(6), 378-386.

80. Goff, J., Lloyd-Jones, D. M., Bennett, G., Coady, S., D'Agostino, S., Gibbons, R., Greenland, P., Lackland, D. T., Levy, D., O'Donnell, C. J., Robinson, J. G., Schwartz, J. S., Shero, S. T., Smith, J., Sorlie, P., Stone, N. J., & Wilson, P. W. F. (2014). 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*, *63*(25), 2935–2959. https://doi.org/10.1016/j.jacc.2013.11.005

81. Ndumele, C. E., Matsushita, K., Lazo, M., Bello, N., Blumenthal, R. S., Gerstenblith, G., ... & Coresh, J. (2016). Obesity and subtypes of incident cardiovascular disease. *Journal of the American Heart Association*, *5*(8), e003921. https://doi.org/10.1161/JAHA.116.003921

82. Dikaiou, P., Björck, L., Adiels, M., Lundberg, C. E., Mandalenakis, Z., Manhem, K., & Rosengren, A. (2021). Obesity, overweight and risk for cardiovascular disease and mortality in young women. European journal of preventive cardiology, 28(12), 1351–1359. https://doi.org/10.1177/2047487320908983

83. Powell-Wiley, T. M., Poirier, P., Burke, L. E., Després, J. P., Gordon-Larsen, P., Lavie, C. J., Lear, S. A., Ndumele, C. E., Neeland, I. J., Sanders, P., St-Onge, M. P., & American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council (2021). Obesity and Cardiovascular Disease: A Scientific Statement from the American Heart Association. Circulation, 143(21), e984–e1010. https://doi.org/10.1161/CIR.0000000000000973

84. Riaz, H., Khan, M. S., Siddiqi, T. J., Usman, M. S., Shah, N., Goyal, A., Khan, S. S., Mookadam, F., Krasuski, R. A., & Ahmed, H. (2018). Association Between Obesity and Cardiovascular Outcomes: A Systematic Review and Meta-analysis of Mendelian Randomization Studies. JAMA network open, 1(7), e183788. https://doi.org/10.1001/jamanetworkopen.2018.3788

85. Dwivedi, A. K., Dubey, P., Cistola, D. P., & Reddy, S. Y. (2020). Association Between Obesity and Cardiovascular Outcomes: Updated Evidence from Meta-analysis Studies. Current cardiology reports, 22(4), 25. https://doi.org/10.1007/s11886-020-1273-y

86. Prieto-Alhambra, D., Premaor, M. O., Fina Avilés, F., Hermosilla, E., Martinez-Laguna, D., Carbonell-Abella, C., ... & Díez-Pérez, A. (2012). The association between fracture and obesity is site-dependent: a population-based study in postmenopausal women. *Journal of Bone and Mineral Research*, *27*(2), 294-300. https://doi.org/10.1002/jbmr.1466

87. Tanaka, S., Kuroda, T., Saito, M., & Shiraki, M. (2013). Overweight/obesity and underweight are both risk factors for osteoporotic fractures at different sites in Japanese postmenopausal women. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 24(1), 69–76. https://doi.org/10.1007/s00198-012-2209-1

88. Poiana, C., Carsote, M., Radoi, V., Mihai, A., & Capatina, C. (2015). Prevalent osteoporotic fractures in 622 obese and non- obese menopausal women. Journal of medicine and life, 8(4), 462–466.

89. Johansson, H., Kanis, J. A., Odén, A., McCloskey, E., Chapurlat, R. D., Christiansen, C., Cummings, S. R., Diez-Perez, A., Eisman, J. A., Fujiwara, S., Glüer, C. C., Goltzman, D., Hans, D., Khaw, K. T., Krieg, M. A., Kröger, H., LaCroix, A. Z., Lau, E., Leslie, W. D., Mellström, D., … Zillikens, M. C. (2014). A meta-analysis of the association of fracture risk and body mass index in women. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research, 29(1), 223–233. https://doi.org/10.1002/jbmr.2017

90. De Laet, C., Kanis, J. A., Odén, A., Johanson, H., Johnell, O., Delmas, P., Eisman, J. A., Kroger, H., Fujiwara, S., Garnero, P., McCloskey, E. V., Mellstrom, D., Melton, L. J., 3rd, Meunier, P. J., Pols, H. A., Reeve, J., Silman, A., & Tenenhouse, A. (2005). Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 16(11), 1330–1338. https://doi.org/10.1007/s00198-005-1863-y

91. Schober, P., Boer, C., & Schwarte, L. A. (2018). Correlation Coefficients: Appropriate Use and Interpretation. Anesthesia and Analgesia, 126(5), 1763–1768. https://doi.org/10.1213/ANE.0000000000002864

92. Sennerby, U., Melhus, H., Gedeborg, R., Byberg, L., Garmo, H., Ahlbom, A., Pedersen, N. L., & Michaëlsson, K. (2009). Cardiovascular Diseases and Risk of Hip Fracture. JAMA : The Journal of the American Medical Association, 302(15), 1666–1673. https://doi.org/10.1001/jama.2009.1463

93. Xu, B., Han, L., Liu, H., Wang, J., Bao, X.-Y., Xi, H.-X., Zhao, L., & Yu, G.-P. (2013). Cardiovascular Disease and Hip Fracture among Older Inpatients in Beijing, China. BioMed Research International, 2013, 493696–6. https://doi.org/10.1155/2013/493696

94. Lai, S.-W., Liao, K.-F., Lai, H.-C., Tsai, P.-Y., Lin, C.-L., Chen, P.-C., & Sung, F.-C. (2013). Risk of Major Osteoporotic Fracture After Cardiovascular Disease: A

Population-Based Cohort Study in Taiwan. Journal of Epidemiology, 23(2), 109–114. https://doi.org/10.2188/jea.JE20120071

95. Li, C., Zeng, Y., Tao, L., Liu, S., Ni, Z., Huang, Q., & Wang, Q. (2017). Meta-analysis of hypertension and osteoporotic fracture risk in women and men. Osteoporosis International, 28(8), 2309–2318. https://doi.org/10.1007/s00198-017-4050-z

96. Yang, S., Nguyen, N. D., Center, J. R., Eisman, J. A., & Nguyen, T. V. (2014). Association between hypertension and fragility fracture: a longitudinal study. Osteoporosis International, 25(1), 97–103. https://doi.org/10.1007/s00198-013-2457-8

97. Liu, X., Jian, X., Liang, D., Wen, J., Wei, Y., Wu, J., & Li, Y.-Q. (2022). The association between heart failure and risk of fractures: Pool analysis comprising 260,410 participants. Frontiers in Cardiovascular Medicine, 9, 977082–977082. https://doi.org/10.3389/fcvm.2022.977082

98. Trimpou, P., Odén, A., Simonsson, T., Wilhelmsen, L., & Landin-Wilhelmsen, K. (2011). High serum total cholesterol is a long-term cause of osteoporotic fracture. Osteoporosis International, 22(5), 1615–1620. https://doi.org/10.1007/s00198-010-1367-2

99. Wang, Y., Dai, J., Zhong, W., Hu, C., Lu, S., & Chai, Y. (2018). Association between Serum Cholesterol Level and Osteoporotic Fractures. Frontiers in Endocrinology (Lausanne), 9, 30–30. https://doi.org/10.3389/fendo.2018.00030

100. Hussain, S. M., Ebeling, P. R., Barker, A. L., Beilin, L. J., Tonkin, A. M., & McNeil, J. J. (2023). Association of Plasma High-Density Lipoprotein Cholesterol Level With Risk of Fractures in Healthy Older Adults. JAMA Cardiology, 8(3), 268–272. https://doi.org/10.1001/jamacardio.2022.5124

101. DAVID T. FELSON, DOUGLAS P. KIEL, JENNIFER J. ANDERSON, WILLIAM B. KANNEL, ALCOHOL CONSUMPTION AND HIP FRACTURES: THE FRAMINGHAM STUDY, American Journal of Epidemiology, Volume 128, Issue 5, November 1988, Pages 1102–1110, https://doi.org/10.1093/oxfordjournals.aje.a115052

102. Zhang, X., Yu, Z., Yu, M., & Qu, X. (2015). Alcohol consumption and hip fracture risk. Osteoporosis International, 26(2), 531–542. https://doi.org/10.1007/s00198-014-2879-y

103. Bonds, D. E., Larson, J. C., Schwartz, A. V., Strotmeyer, E. S., Robbins, J., Rodriguez, B. L., Johnson, K. C., & Margolis, K. L. (2006). Risk of Fracture in Women with Type 2 Diabetes: the Women's Health Initiative Observational Study. The Journal of Clinical Endocrinology and Metabolism, 91(9), 3404–3410. https://doi.org/10.1210/jc.2006-0614

104. Robbins, J., Aragaki, A. K., Kooperberg, C., Watts, N., Wactawski-Wende, J., Jackson, R. D., LeBoff, M. S., Lewis, C. E., Chen, Z., Stefanick, M. L., & Cauley, J. (2007). Factors Associated With 5-Year Risk of Hip Fracture in Postmenopausal Women. JAMA : The Journal of the American Medical Association, 298(20), 2389–2398. https://doi.org/10.1001/jama.298.20.2389

105. Kubo, J. T., Stefanick, M. L., Robbins, J., Wactawski-Wende, J., Cullen, M. R., Freiberg, M., & Desai, M. (2013). Preference for wine is associated with lower hip fracture incidence in post-menopausal women. BMC Women's Health, 13(1), 36–36. https://doi.org/10.1186/1472-6874-13-36

106. Dwivedi, A. K., Dubey, P., Cistola, D. P., & Reddy, S. Y. (2020). Association Between Obesity and Cardiovascular Outcomes: Updated Evidence from Meta-analysis Studies. Current Cardiology Reports, 22(4), 25–25. https://doi.org/10.1007/s11886-020-1273-y

107. Riaz, H., Khan, M. S., Siddiqi, T. J., Usman, M. S., Shah, N., Goyal, A., Khan, S. S., Mookadam, F., Krasuski, R. A., & Ahmed, H. (2018). Association Between Obesity and Cardiovascular Outcomes: A Systematic Review and Meta-analysis of Mendelian Randomization Studies. JAMA Network Open, 1(7), e183788–e183788. https://doi.org/10.1001/jamanetworkopen.2018.3788

108. Gnudi, S., Sitta, E., & Lisi, L. (2009). Relationship of body mass index with main limb fragility fractures in postmenopausal women. Journal of Bone and Mineral Metabolism, 27(4), 479–484. https://doi.org/10.1007/s00774-009-0056-8

109. BENER, A., HAMMOUDEH, M., ZIRIE, M., & HELLER, R. F. (2005). Is obesity a protective factor for osteoporosis? APLAR Journal of Rheumatology, 8(1), 32–38. https://doi.org/10.1111/j.1479-8077.2005.00119.x

110. Premaor, M. O., Pilbrow, L., Tonkin, C., Parker, R. A., & Compston, J. (2010). Obesity and fractures in postmenopausal women. Journal of Bone and Mineral Research, 25(2), 292–297. https://doi.org/10.1359/jbmr.091004

111. Tanaka, S., Kuroda, T., Saito, M., & Shiraki, M. (2013). Overweight/obesity and underweight are both risk factors for osteoporotic fractures at different sites in Japanese postmenopausal women. Osteoporosis International, 24(1), 69–76. https://doi.org/10.1007/s00198-012-2209-1

112. Court-Brown, C. M., Duckworth, A. D., Ralston, S., & McQueen, M. M. (2019). The relationship between obesity and fractures. Injury, 50(8), 1423–1428. https://doi.org/10.1016/j.injury.2019.06.016

113. Rikkonen, T., Sund, R., Sirola, J., Honkanen, R., Poole, K. E. S., & Kröger, H. (2021). Obesity is associated with early hip fracture risk in postmenopausal women: a 25-year follow-up. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 32(4), 769–777. https://doi.org/10.1007/s00198-020-05665-w

114. Sadeghi, O., Saneei, P., Nasiri, M., Larijani, B., & Esmaillzadeh, A. (2017). Abdominal Obesity and Risk of Hip Fracture: A Systematic Review and Meta-Analysis of Prospective Studies. Advances in nutrition (Bethesda, Md.), 8(5), 728–738. https://doi.org/10.3945/an.117.015545

115. Piñar-Gutierrez, A., García-Fontana, C., García-Fontana, B., & Muñoz-Torres, M. (2022). Obesity and Bone Health: A Complex Relationship. International Journal of Molecular Sciences, 23(15), 8303-. https://doi.org/10.3390/ijms23158303

116. Compston, J. E., Watts, N. B., Chapurlat, R., Cooper, C., Boonen, S., Greenspan, S., Pfeilschifter, J., Silverman, S., Díez-Pérez, A., Lindsay, R., Saag, K. G., Netelenbos, J. C., Gehlbach, S., Hooven, F. H., Flahive, J., Adachi, J. D., Rossini, M., LaCroix, A. Z., Roux, C., … Siris, E. S. (2011). Obesity Is Not Protective against Fracture in Postmenopausal Women: GLOW. The American Journal of Medicine, 124(11), 1043–1050. https://doi.org/10.1016/j.amjmed.2011.06.013

117. Gnudi, S., Sitta, E., & Lisi, L. (2009). Relationship of body mass index with main limb fragility fractures in postmenopausal women. Journal of Bone and Mineral Metabolism, 27(4), 479–484. https://doi.org/10.1007/s00774-009-0056-8

118. Prieto-Alhambra, D., Premaor, M. O., Fina Avilés, F., Hermosilla, E., Martinez-Laguna, D., Carbonell-Abella, C., Nogués, X., Compston, J. E., & Díez-Pérez, A. (2012). The association between fracture and obesity is site-dependent: A population-based study in postmenopausal women. Journal of Bone and Mineral Research, 27(2), 294–300. https://doi.org/10.1002/jbmr.1466

119. Mansoor, H., Jo, A., Beau De Rochars, V. M., Pepine, C. J., & Mainous, 3rd. (2019). Novel Self-Report Tool for Cardiovascular Risk Assessment. Journal of the American Heart Association, 8(24), e014123–e014123. https://doi.org/10.1161/JAHA.119.014123

120. Pandey, A., Mehta, A., Paluch, A., Ning, H., Carnethon, M. R., Allen, N. B., Michos, E. D., Berry, J. D., Lloyd-Jones, D. M., & Wilkins, J. T. (2021). Performance of the American Heart Association/American College of Cardiology

Pooled Cohort Equations to Estimate Atherosclerotic Cardiovascular Disease Risk by Self-reported Physical Activity Levels. JAMA Cardiology, 6(6), 690–696. https://doi.org/10.1001/jamacardio.2021.0948

APPENDIX

IRB APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

NHSR DETERMINATION

TO: Hossain, Rafeka

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 11-Dec-2023

RE: IRB-300011618
The Association between Cardiovascular Disease Risk and Fractures in Postmenopausal Women

---

The Office of the IRB has reviewed your Application for Not Human Subjects Research Designation for the above referenced project.

The reviewer has determined this project is not subject to FDA regulations and is not Human Subjects Research. Note that any changes to the project should be resubmitted to the Office of the IRB for determination.

if you have questions or concerns, please contact the Office of the IRB at 205-934-3789.