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HARVARD MEDICAL SCHOOL

Impact of the Midlife and Menopause on Bone Health: What We Know, What We Need to Learn

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Boston/MGH Site PI, SWAN Study

Middle-Life Health of Women and the Menopause

60th Meeting of the National Institutes of Health Advisory Committee on Research on Women's Health

April 9, 2024

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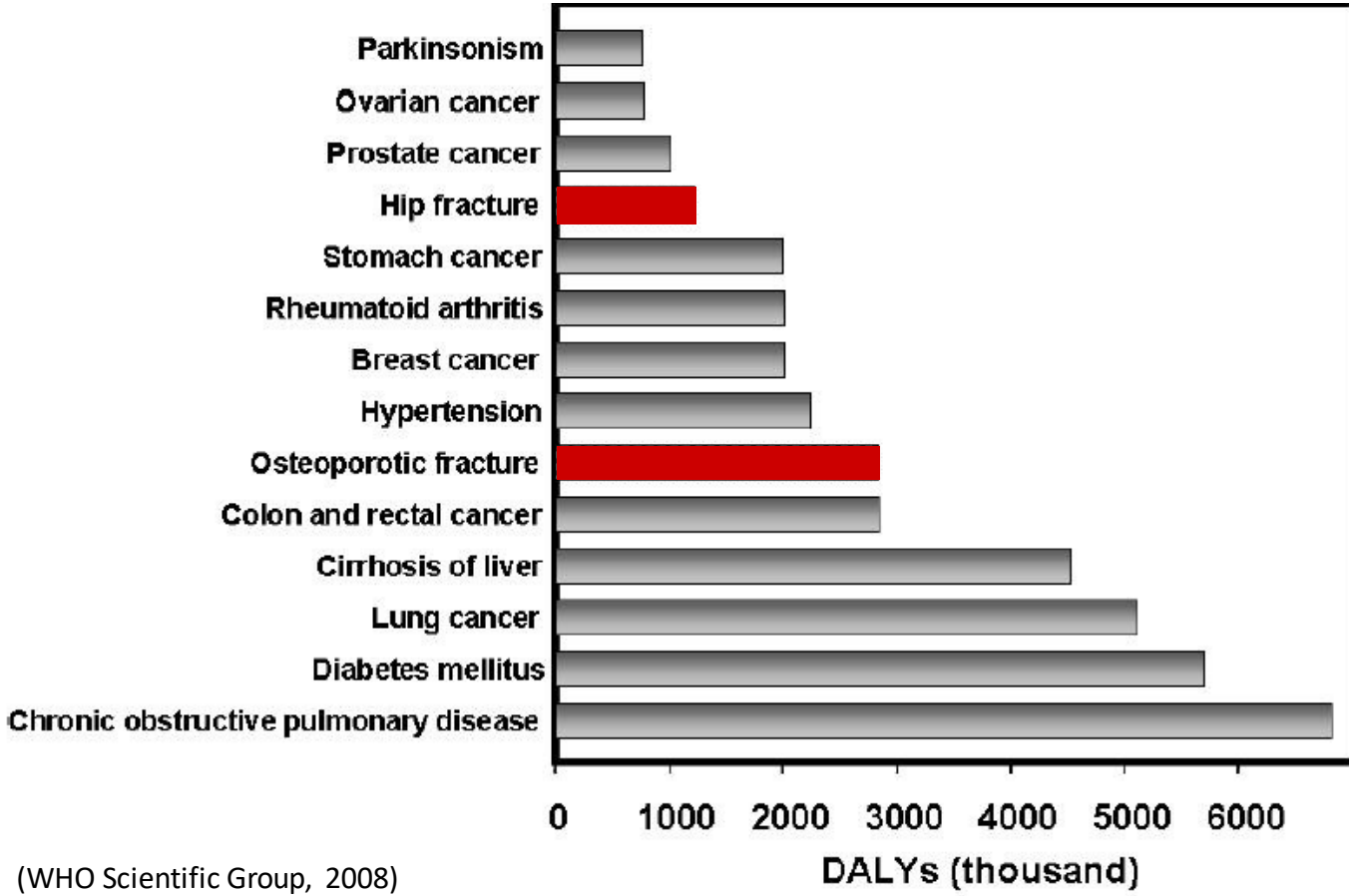
Disclosures

I am a member of the Clinical Advisory Board for Upliv Health

Burden of Diseases in US & Europe

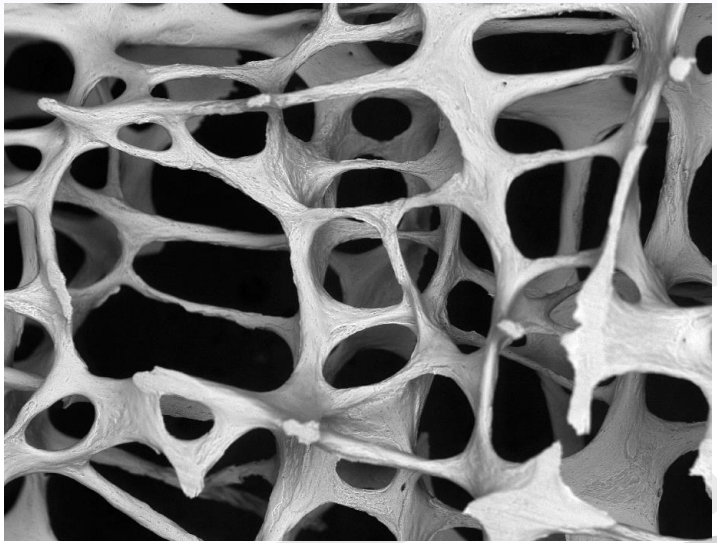
(in disability-adjusted life yrs - # of yrs lost to ill-health, disability, or early death)



(WHO Scientific Group, 2008)

Osteoporosis is a public health problem

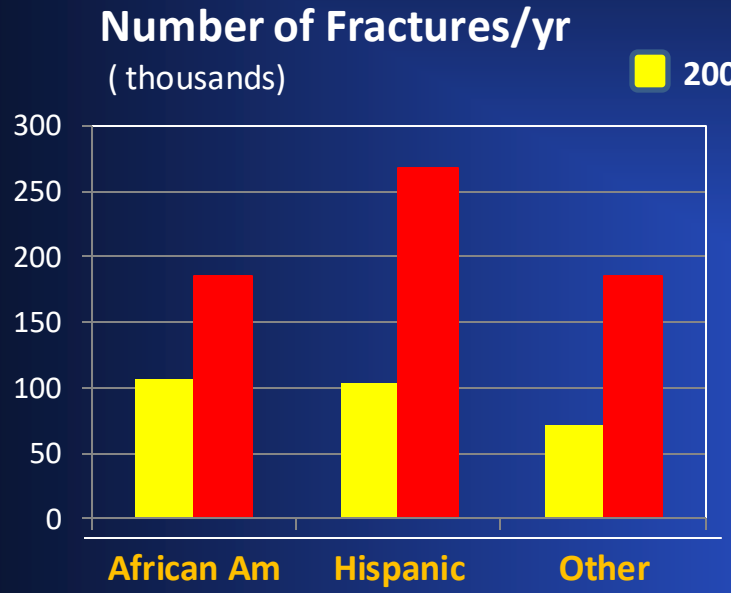
- 2005, 2 million osteoporotic fractures, costing $17 billion
  - 70% women, 30% men
  - 72% cost is related to hip fractures, which constituted 14% of all fractures
- 2025, 3 million fractures anticipated, costing $25 billion/year
  - Greatest rise in fractures anticipated in Hispanic individuals

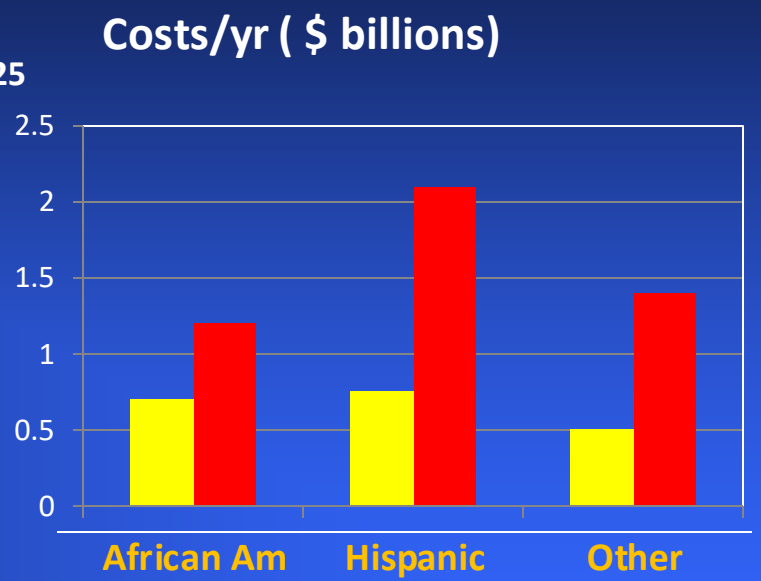


Burge et al, JBMR 2007

(Courtesy of The Bone Research Society)

Numbers of fractures and associated costs are expected to rise dramatically in minoritized groups



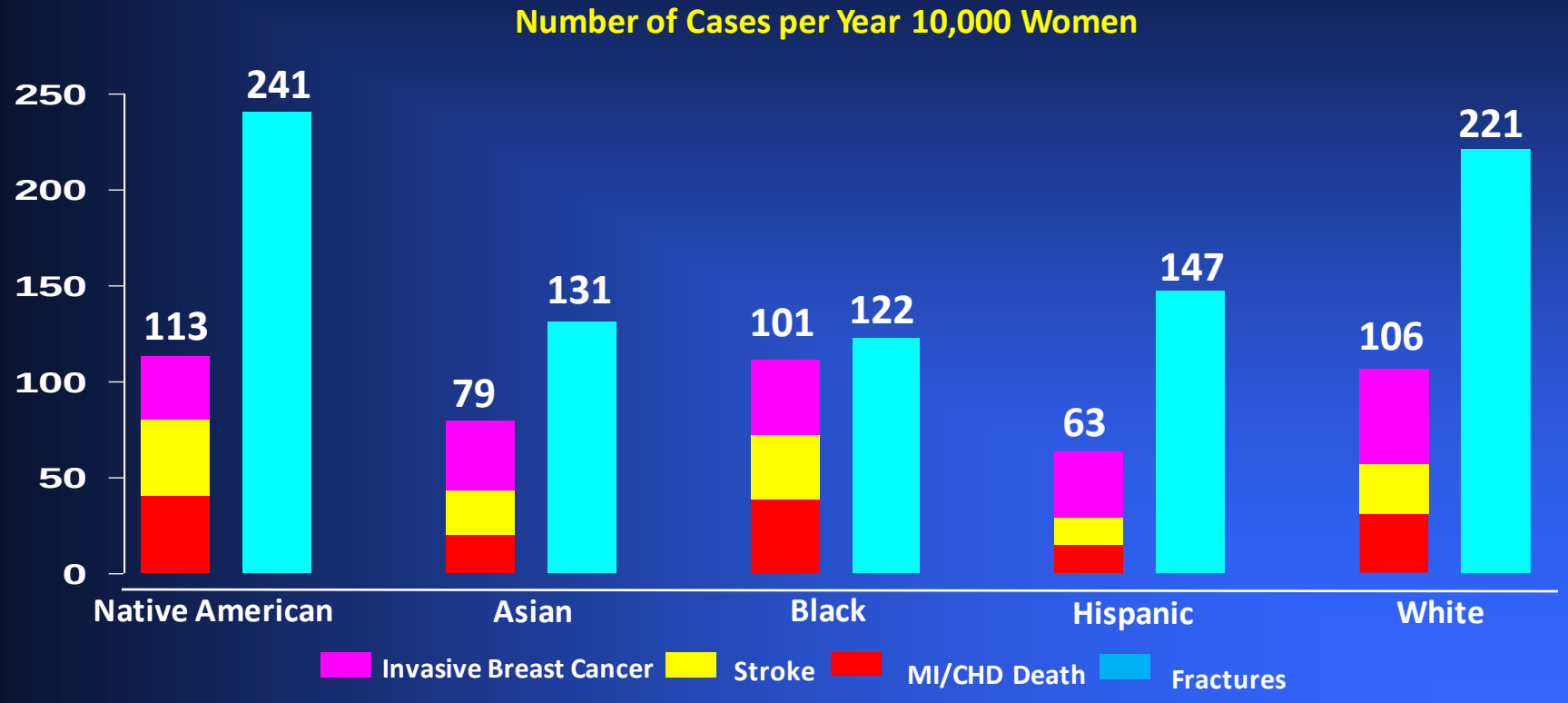


Other = Asian, Pacific Islander, Native American

In 2025, 21% of fractures will occur in BIPOC compared to 12% in 2005

(Burge R, et al. *J Bone Miner Res*. 2007 Mar;22(3):465-75)

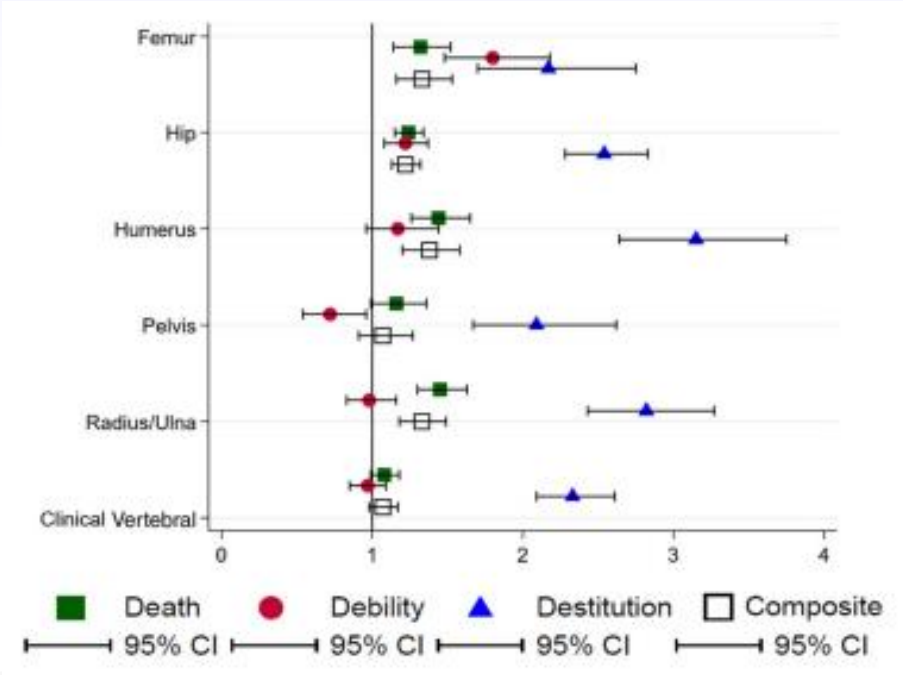
Fractures are more common in ALL women than MI, stroke or breast cancer combined: WHI-OS



Cauley et al OI 2008

Black women are more likely to experience mortality, debility, or destitution 1y after fracture than White women

- US Medicare data 2010-2016
- Observational cohort study
- ~ 4.5 M NHB & NHW women with PMO (2000-2015)
  - ~ 400K (2.8% NHB) w fragility fracture (~ 81 yo)
- Outcomes:
  - Mortality, debility (new placement in long-term nursing facility), destitution (newly eligible for Medicaid)



Wright et al, JAGS 2020

If the goal is to prevent osteoporosis or fractures:

How does the midlife/menopause transition impact bone loss?

Are there racial/ethnic differences in fractures and/or bone loss?

Investigating Health for Mid-Life and Older Women

The Study of Women's Health Across the Nation (SWAN) is a multi-site longitudinal, epidemiologic study designed to examine the health of women during their middle years. The study examines the physical, biological, psychological and social changes during this transitional period.

SWAN is an active study with engaged investigators and participants.

SWAN examines the physical, biological, psychological and social changes during this transitional period. The goal of SWAN's research is to help scientists, health care providers and women learn how mid-life experiences affect health and quality of life during aging.

The study is co-sponsored by the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), the National Institutes of Health (NIH), Office of Research on Women's Health, and the National Center for Complementary and Alternative Medicine.

The SWAN Study: Study of Women's Health Across the nation

- Multi-center longitudinal, epidemiologic study of 3,302 community-based women:
  - Michigan
  - MGH, Boston
  - Chicago
  - UC Davis (Davis, CA)
  - UCLA (Los Angeles, CA)
  - New Jersey
  - Pittsburgh
- Enrollment: 1996-1997
- Each site recruited White & Black, Chinese, Japanese, Hispanic premenopausal women
- Visits: screening, baseline, up to 16 follow-up visits
- 75% retention at Visit 15 (n=2366); just concluded Visit 17!
- 2024: SWAN now has more than 640 publications

Sites	Black	Chinese	Hispanic	Japanese	White
Michigan	325				218
MGH	199				253
Chicago	249				208
UC Davis		250			209
UCLA				281	215
New Jersey			286		146
Pittsburgh	162				301

SWAN study: Inclusion criteria

- Age between 42 and 52 years
- Intact uterus and at least one intact ovary
- Not currently using hormone therapy
- At least one menses in the last 3 months
- Self-identification as a member eligible ethnic/racial groups:
  - Black
  - Chinese
  - Hispanic
  - Japanese
  - White

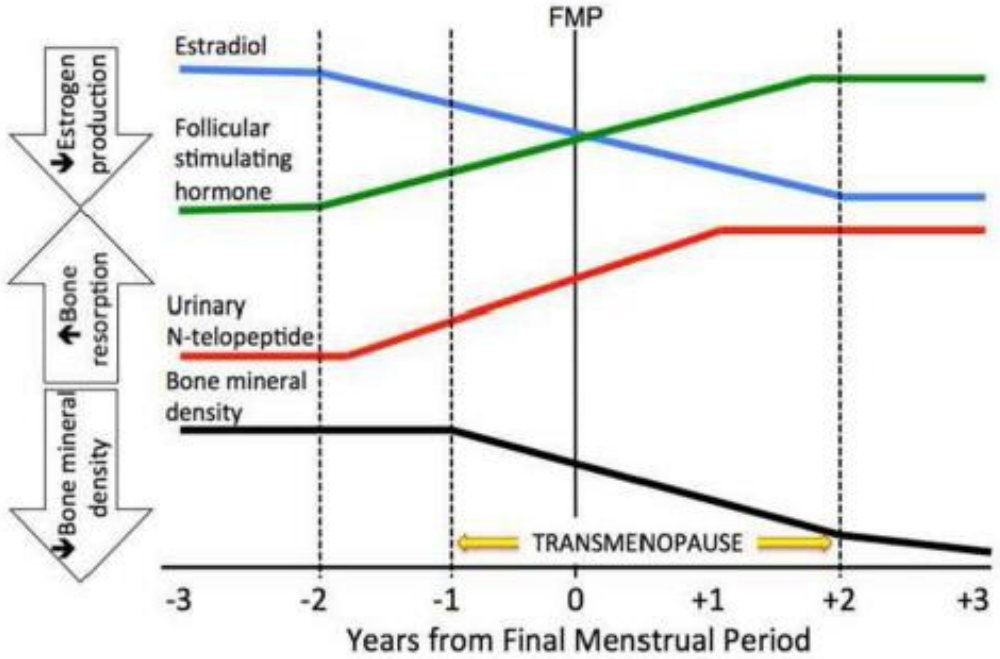


Figure 1:
Schematic depiction of the trajectories of sex steroid hormones (estradiol (blue) and follicular stimulating hormone (green)), bone resorption marker urinary N-telopeptide (U-NTX) (red), and bone mineral density (black) over the menopause transition. Rapid bone loss occurs during transmenopause, a period that lasts from 1 year before to 2 years after the final menstrual period (FMP). Changes in hormone levels and in U-NTX start about 1 year before the transmenopause. *Courtesy of* A. Shieh, MD, Los Angeles, CA.

Karlamangla et al Ob Gyn Clin North Am 2018

ORIGINAL ARTICLE

JBMR

2012

Bone Mineral Density Loss in Relation to the Final Menstrual Period in a Multiethnic Cohort: Results From the Study of Women's Health Across the Nation (SWAN)

Gail A Greendale,[1] MaryFran Sowers,[2] Weijuan Han,[1] Mei-Hua Huang,[1] Joel S Finkelstein,[3] Carolyn J Crandall,[4] Jennifer S Lee,[5] and Arun S Karlamangla[1]

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[5]Division of Endocrinology, Department of Internal Medicine, University of California-Davis, Davis, CA, USA

- SWAN Bone: 5 sites (excluding Chicago & New Jersey)
- Hologic QDR 2000 or Hologic QDR 4500A
- N = 862, age 47(±3) y, age at FMP 52(±2) y, BMI 27
- Pre-transmenopause (5 years to 1 year before FMP)
- Transmenopause (1 year before to 2 years after FMP)
- Postmenopause (2 to 5 years after FMP)
- BMI associated with less loss
- Racial & ethnic variation noted (differs from 5 year data)

Annualized & 10-year cumulative rates of lumbar spine bone loss with menopause showing BMI independent racial/ethnic variation in bone loss

	Pretrans-menopause	Trans-menopause	Post-menopause	10 year cumulative
White (n=384)	-0.02%	-2.46%	-1.06%	- 10.6%
Japanese (n=119)	-0.01%	-2.26%	-1.1%	-10.1%
Chinese (n=117)	**-0.16%**	-2.69%	-1.28%	**-12.6%**
Black (n=242)	-0.09%	**-2.19%**	-0.93%	-9.7%

Bold = statistically significant between group differences w White referent group
Greendale et al, JBMR 2012

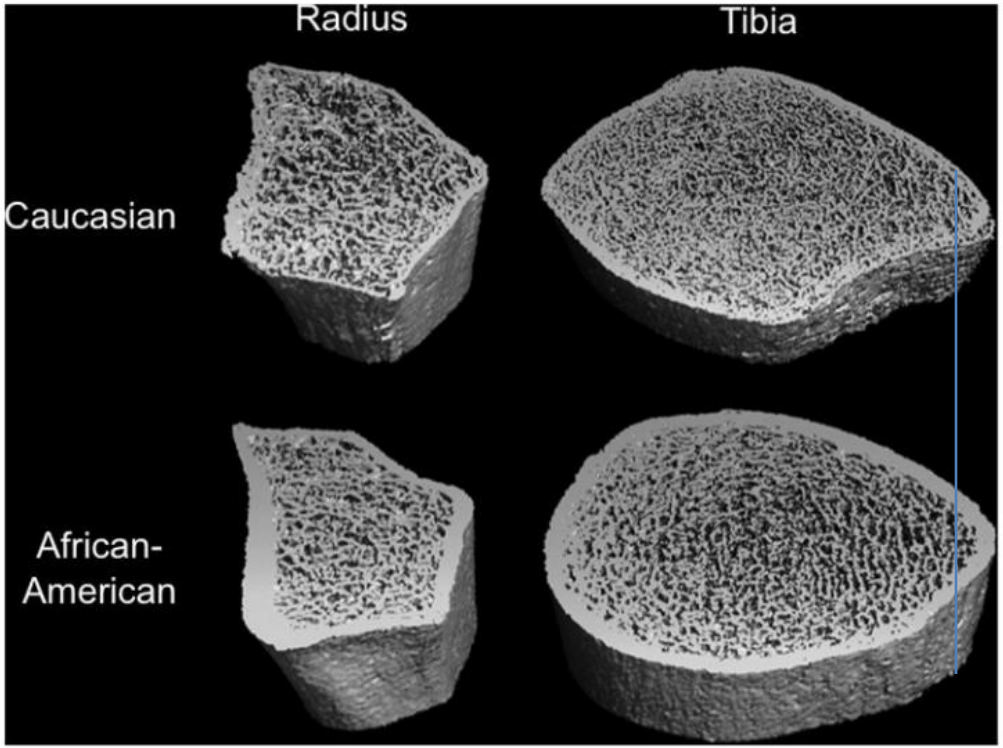


Figure 1. HR-pQCT scans of the radius (left) and tibia (right) in a representative Caucasian subject (top) and African-American subject (bottom)

ORIGINAL ARTICLE

JBMR®

2022

Age-Related Changes in Bone Density, Microarchitecture, and Strength in Postmenopausal Black and White Women: The SWAN Longitudinal HR-pQCT Study

Fjola Johannesdottir,[1,2] Melissa S Putman,[2,3,4] Sherri-Ann M Burnett-Bowie,[2,3] Joel S Finkelstein,[2,3] Elaine W Yu,[2,3†] and Mary L Bouxsein[1,2,3†]

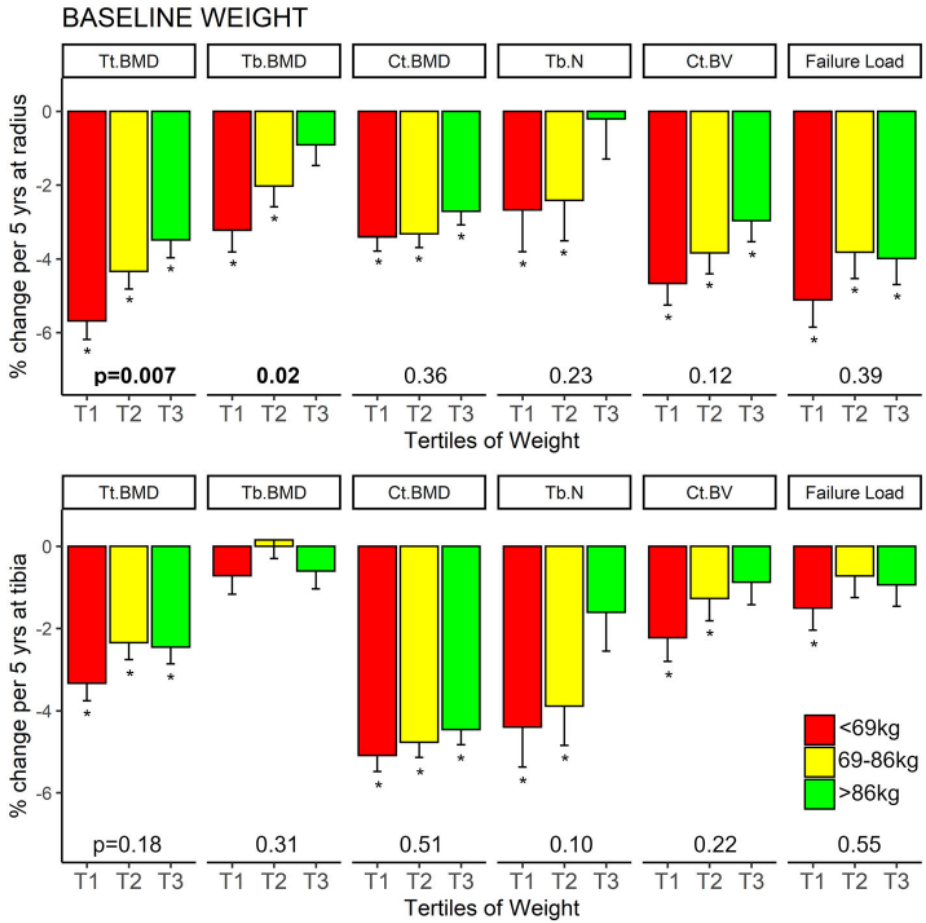


Fig 2. Average percent change (±SE) over 5 years for bone microarchitectural variables analyzed by tertiles of baseline body weight (tertile 1 [T1]: <69 kg; tertile 2 [T2]: 69–86 kg; tertile [T3]: >86 kg) at (*A*) distal radius, T1 $n = 60$, T2 $n = 61$, T3 $n = 61$; and (*B*) distal tibia, T1 $n = 69$, T2 $n = 69$, T3 $n = 69$. Models are adjusted for race/ethnicity, time since menopause and weight change over the follow-up time. Analysis of covariance *p* values comparing tertiles are shown. * indicates significant change from baseline within each tertile. BV = bone volume; Ct = cortical; N = number; Tb = trabecular; Tt = total.

Changes in body composition and weight during the menopause transition

Gail A. Greendale,[1] Barbara Sternfeld,[2] MeiHua Huang,[1] Weijuan Han,[1] Carrie Karvonen-Gutierrez,[3] Kristine Ruppert,[4] Jane A. Cauley,[5] Joel S. Finkelstein,[6] Sheng-Fang Jiang,[2] Arun S. Karlamangla[1]

Table 1. Characteristics of the analysis sample, overall and by race/ethnicity from the Study of Women's Health Across the Nation (SWAN)

Participant Characteristics[A,B]	Analysis Sample (*n* = 1246)	White Women (*n* = 559, 45%)	Black Women (*n* = 356, 29%)	Chinese Women (*n* = 153, 12%)	Japanese Women (*n* = 178, 14%)
Age					
At body composition baseline (y)	46.66 (2.64)	46.58 (2.67)	46.50 (2.69)	46.66 (2.51)	47.25 (2.50)
At final menstrual period (FMP) (y)	52.17 (2.77)	52.17 (2.85)	52.02 (2.85)	52.03 (2.62)	52.62 (2.49)
Anthropometrics at baseline					
Weight (kg)	72.77 (19.34)	74.82 (17.86)	84.01 (19.28)	57.44 (9.62)	56.99 (8.98)
BMI (kg/m2)	27.62 (6.79)	27.77 (6.39)	31.53 (7.16)	23.15 (3.75)	23.19 (3.61)
Body composition at baseline					
Fat mass (kg)	26.75 (11.35)	28.20 (11.15)	32.30 (11.75)	18.74 (5.76)	18.97 (5.56)
Proportion fat mass, times 100	39.44 (6.93)	40.14 (6.99)	42.11 (6.74)	35.68 (5.45)	35.62 (5.00)
Lean mass (kg)	38.71 (7.26)	39.84 (6.71)	42.37 (7.35)	32.96 (4.74)	33.43 (4.01)
Proportion lean mass × 100	60.56 (6.93)	59.86 (6.99)	57.89 (6.74)	64.32 (5.45)	64.38 (5.00)

[A]Percentages shown with race/ethnicity-specific *n*'s are the percent of analysis sample contributed by each racial group. All characteristics were measured at baseline except for age at FMP. Values provided in the table are means (SD). [B]SWAN enrolled 3302 women at baseline at 7 sites; 5 sites enrolled women into the SWAN Body Composition Cohort (*n* = 2349). Characteristics of the 1103 women who were ineligible for the present analysis (mainly, because they did not have ≥ 2 body composition measures or a date of FMP) were similar to those of the analysis sample (data not shown).

Changes in body weight over 15 years in midlife do not fully capture increase in fat mass and decrease in lean mass

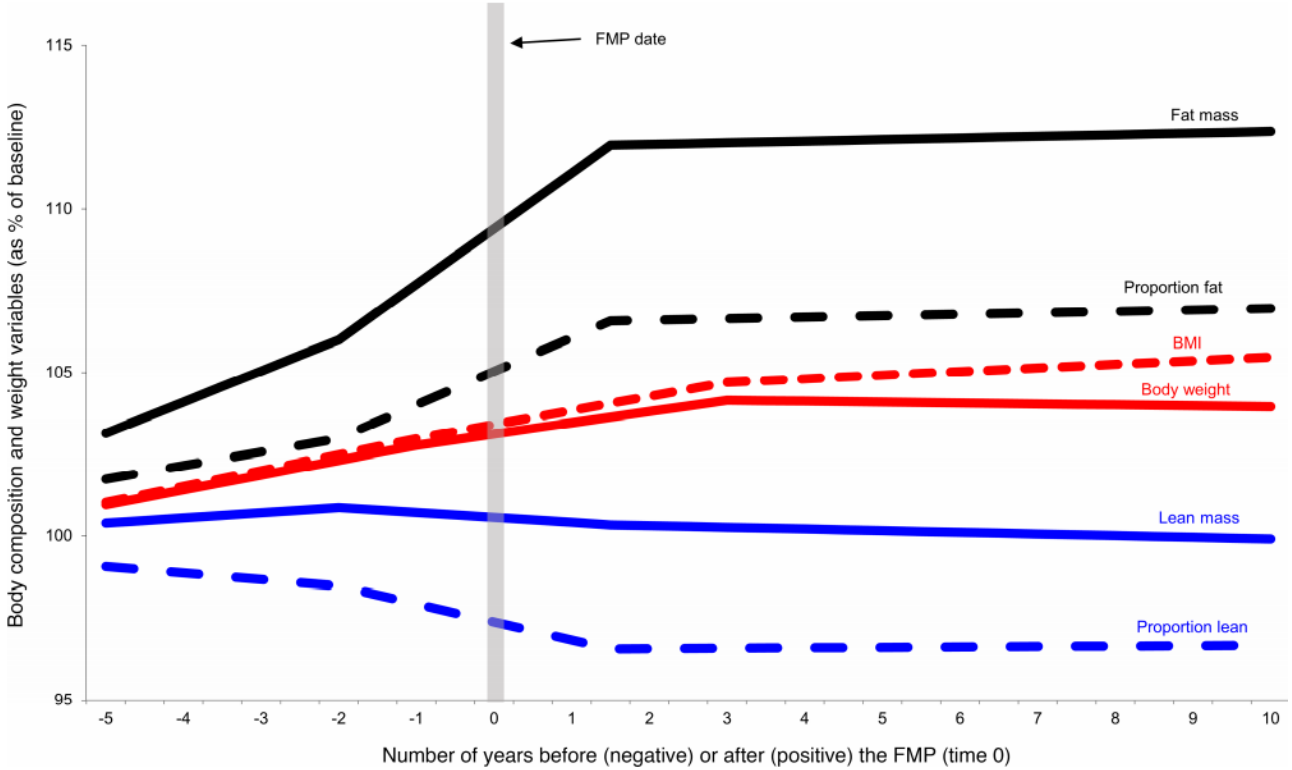


Figure 2. Model-predicted trajectories of body composition and body weight outcomes relative to the time prior to or after the FMP, SWAN. Values shown are for an average study participant (i.e., with each model covariate set at its analysis sample mean). Covariates were age at FMP, race, SWAN study site, and HT use.

Cumulative change in body composition & weight over 15 years

	Fat Mass Proportion	Lean Mass Proportion	Body Weight	BMI
White	**5.99%**	**-2.71%**	**3.85%**	**5.46%**
Japanese	**4.49%**	-1.68%	0.91%	2.42%
Chinese	-0.04%	1.13%	-0.38%	0.60%
Black	**6.68%**	**-3.76%**	**4.16%**	**5.52%**

Bold = statistically significant finding
Covariates = age at FMP, race, study site, and hormone therapy
Duration: 1996/1997 – 2013
Excluded BMI < 17 or > 49
Greendale et al, JCI 2019

Midlife/menopause related changes in body composition are associated with bone loss and increased fracture risk

Table 1. Characteristics of the analysis sample ($n = 539$)[a]

Characteristics	Value at the start of the MT[b,c]	Value at the end of the MT[b,d]
Age (years), mean ± SD	50.7 ± 2.8	55.7 ± 2.8
Body mass index (kg/m^2), mean ± SD	27.3 ± 6.9	27.7 ± 6.7
Cigarette use (Y/N), *n* (%)	86 (19)	79 (15)
Body composition, mean ± SD[e]		
Lean mass (kg)	38.5 ± 7.3	38.2 ± 7.5
Fat mass (kg)	27.2 ± 11.9	28.1 ± 11.8
Bone mineral density (g/cm^2), mean ± SD		
Lumbar spine	1.069 ± 0.146	0.983 ± 0.155
Femoral neck	0.833 ± 0.137	0.780 ± 0.134
Race/ethnicity, *n* (%)		
Black	142 (26.3)	
Chinese	75 (13.9)	
Japanese	90 (16.7)	
White	232 (43.0)	
Body composition changes during the MT, mean ± SD		
Lean mass loss (cumulative %)	0.70 (6.93)	
Fat mass gain (cumulative %)	6.0 (19.9)	
Appendicular fracture after the MT (Y/N), *n* (%)	64 (11.8)	

Shieh et al, JBMR 2022

Midlife/menopause related changes in body composition are associated with bone loss and increased fracture risk

Table 2. Associations of total percent lean mass loss and total percent fat mass gain during the MT with BMD level at the end of the MT[a]

	Associations per SD lean mass loss or SD fat mass gain during the MT with BMD at the end of the MT[b,c,d]			
	Femoral neck (FN) BMD (g/cm^2)		Lumbar spine (LS) BMD (g/cm^2)	
	Beta (95% CI)	*p*	*Beta* (95% CI)	*p*
Cumulative lean mass loss (per SD)	−0.010 (−0.013, −0.006)	<0.0001	−0.004 (0.009, 0.000)	0.09
Cumulative fat mass gain (per SD)	0.026 (0.007, 0.045)	0.009	0.026 (0.002, 0.050)	0.03

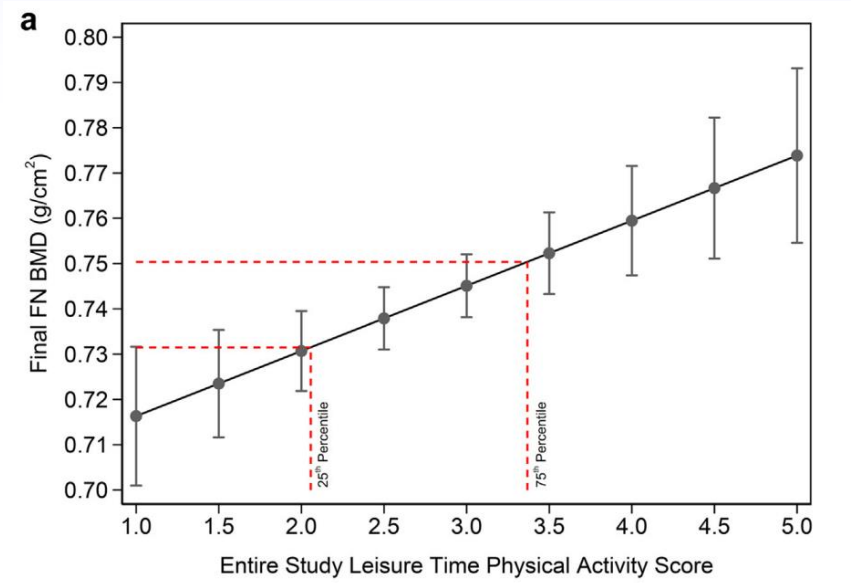
Table 3. Associations of total percent lean mass loss and total percent fat mass gain during the MT with incident fractures after the MT[a]

	Associations per SD lean mass loss or SD fat mass gain during the MT with incident fracture after the MT[b,c,d]					
	Base model[e]		Base model + femoral neck BMD[f]		Base model + lumbar spine BMD[g]	
	HR (95% CI)[d]	*p*	HR (95% CI)[d]	*p*	HR (95% CI)[d]	*p*
Lean mass loss (per SD)	1.63 (1.22, 2.17)	0.001	1.58 (1.18, 2.10)	0.002	1.65 (1.24, 2.21)	0.001
Fat mass gain (per SD)	1.29 (0.99, 1.67)	0.05	1.31 (1.02, 1.69)	0.03	1.39 (1.07, 1.79)	0.01

Shieh et al, JBMR 2022

Leisure time physical activity (walking) associated with stable spine & femoral neck BMD over 17 years

Characteristic[a]	Analysis sample[b] (N = 875)
Age (years), *Mean (SD)*	45.5 (2.5)
Body Mass Index (kg/m^2), *Mean (SD)*	27.4 (6.7)
Menopausal status, %	
Premenopausal	67%
Early perimenopausal	33%
Late perimenopausal	
Early postmenopausal	
Race/ethnicity, %	
Black	45%
White	27%
Chinese	13%
Japanese	14%
Education, %	
≤High school	21%
Some college	31%
Baccalaureate degree	24%
> Baccalaureate education	24%
Family poverty-to-income ratio, *Mean (SD)*	3.66 (2.65)
LTPA ordinal score, *Mean (SD)*	2.67 (1.03)
METhr wk^{-1}, *Median [p25th, p75th]*	3.6 [0.1, 11.5]
Lumbar spine BMD, *Mean (SD)*	1.08 (0.14)
Femoral neck BMD, *Mean (SD)*	0.846 (0.134)



Greendale et al Lancet 2023

CLINICAL TRIAL

JBMR®

2018

High-Intensity Resistance and Impact Training Improves Bone Mineral Density and Physical Function in Postmenopausal Women With Osteopenia and Osteoporosis: The LIFTMOR Randomized Controlled Trial

Steven L Watson,[1,2] Benjamin K Weeks,[1,2] Lisa J Weis,[3] Amy T Harding,[1,2] Sean A Horan,[1,2] and Belinda R Beck[1,2,3]

58+ yo women with T score < -1 (spine or hip), postmenopause, no bone harmful/beneficial medications, and no recent fracture, randomized to:

- Supervised training for 8 months (30 mins twice weekly, and including deadlifts, overhead press, squats, jumping chin ups with drop landings), n=49
- Low intensity control for 8 months (twice weekly, 10 minutes, no more than 3 kg hand weights) (n=52)

44% with osteoporosis, 56% osteopenia at one site; 28% with osteoporotic fx in past 10 years

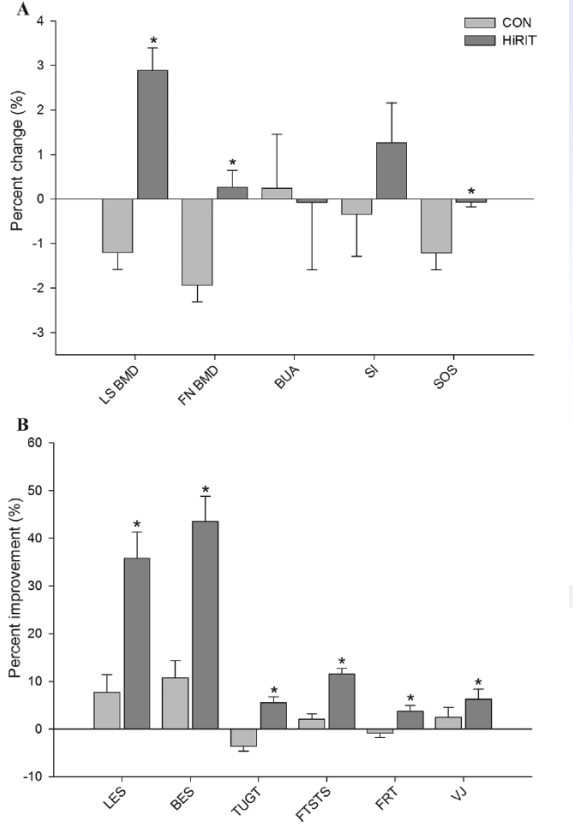


Fig. 2. Eight-month change (± SE) in (*A*) bone and (*B*) physical performance for HiRIT and CON after an 8-month exercise intervention in postmenopausal women with low bone mass ($n = 101$). LS = lumbar spine; BMD = bone mineral density; FN = femoral neck; BUA = broad-band ultrasound attenuation; SI = stiffness index; SOS = speed of sound; LES = leg extensor strength; BES = back extensor strength; TUGT = timed up-and-go test; FTSTS = five times sit-to-stand; FRT = functional reach test; VJ = vertical jump. *Indicates between-group difference ($p < 0.05$).

25OHD > 20 ng/mL associated with 45% reduction in risk of fragility fracture over 9.5 y but not a/w BMD change (similar results in Black & White women)

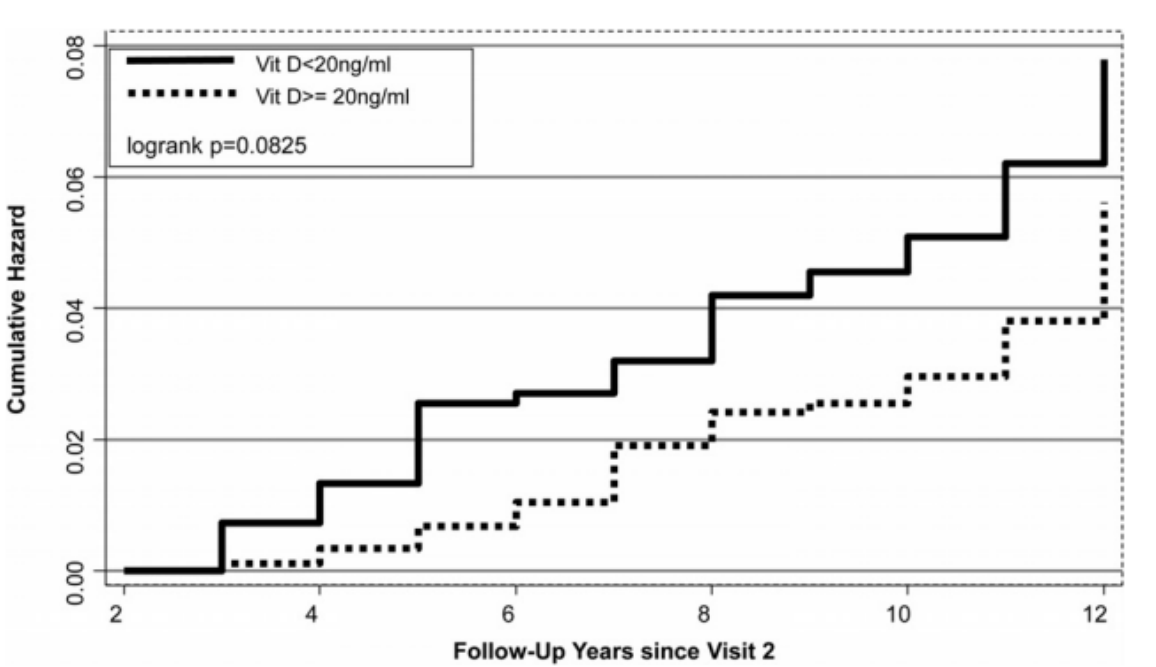


Figure 1. Cumulative hazard of nontraumatic fractures by 25(OH)D: < 20 ng/mL vs ≥ 20 ng/mL.

Cauley et al, JCEM 2015

The NEW ENGLAND JOURNAL of MEDICINE

Suppl

Meryl S. LeBof
Eunjung
J. Chris Gallag

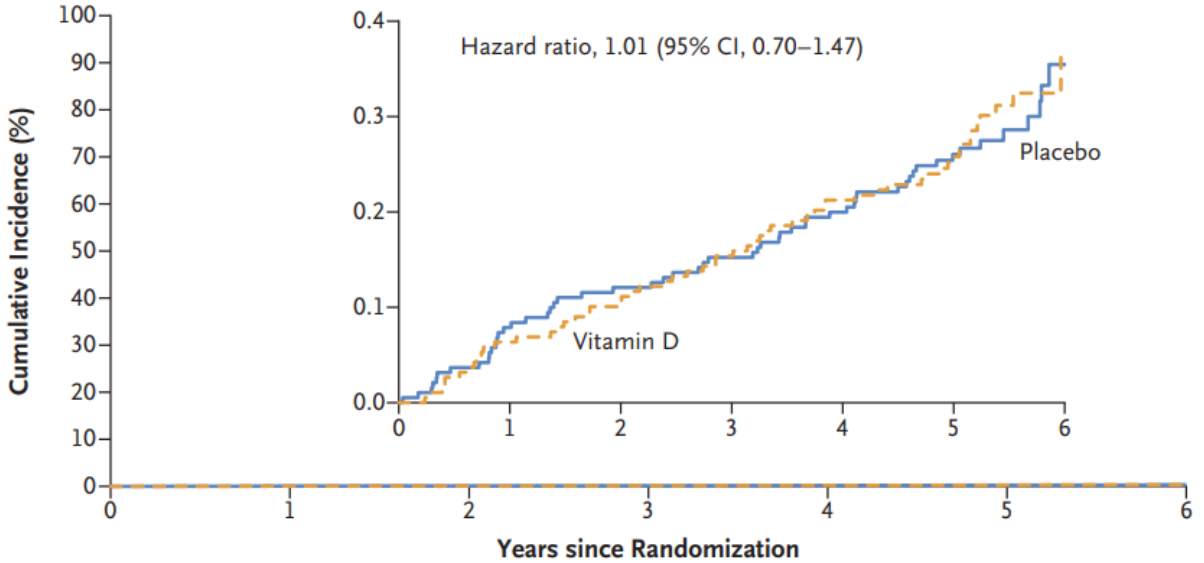
A Total Fractures

100
90

7

Hazard ratio, 0.98 (95% CI, 0.89–1.08)

C Hip Fractures



No. at Risk							
Placebo	12,927	12,915	12,907	12,898	12,776	10,383	847
Vitamin D	12,944	12,929	12,921	12,915	12,773	10,378	843

LeBoff et al, NEJM 2022

Medications and bone loss or fracture across the midlife

- 6 years of SSRI or TCA use not associated with increased BMD loss vs. non-users (Diem et al JCEM 2013)
- No evidence that incident PPI use causes BMD loss over 10 years (Solomon et al JBMR 2015)
- 5 years of opioid use may be associated with increased BMD loss vs. pts on non-opioid analgesics (Yoshida et al Pharmaco Drug Saf 2018)
- Increased risk of fractures w starting BP lowering med vs anti-depressant over 19 y, presumably related to increased falls (Solomon et al Arch of Osteop 2019)
- Metformin initiation not associated with more BMD loss vs. non-initiation (Solomon et al OI 2024)

Factors that impact midlife/MT bone loss or fracture risk

	DECREASED RISK OF MIDLIFE BMD LOSS	INCREASED RISK OF MIDLIFE BMD LOSS
Later age of final menstrual period (age at FMP more important than chronological age)	✓	
Increased leisure time physical activity	✓	
DM/insulin resistance with the MT		✓
Higher BMI	✓	
Increase in fat mass with the MT		✓
Higher AMH levels	✓	
Higher dietary inflammatory index		✓
Higher CRP		✓

What is unknown related to midlife/MT bone loss

- How does midlife/MT bone loss inform bone loss in later years?
- Can we predict who will fracture or have accelerated bone loss in 60s, 70s, and 80s based on:
  - Changes in BMD at midlife
  - Changes in other midlife/MT factors, e.g. AMH, estradiol by LC/MS/MS, HOMA-IR, CRP
- In a woman, who has not fractured but has osteopenia and/or increased fracture risk, WHEN should prescription anti-osteoporosis medication be initiated? In her 50s, 60s, 70s?
- What can be done at the midlife to reduce racial & ethnic disparities in mortality, disability, and destitution with fracture?

Osteoporosis

From the FDA Office of Women's Health

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Women's Health Topics

- Aging
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- Caregiving
- Cholesterol medicines
- Clinical trials

Content current as of:
04/01/2024

Osteoporosis | FDA

How is osteoporosis treated?

There is no way to cure osteoporosis. There are things you can do, listed below, to prevent more bone loss or build new bone mass and strengthen bones. Talk with your health care provider and make a plan to keep your bones healthy.

Lifestyle changes

There are lifestyle changes you can make to lower your risk fo

- Stay physically active. Do weight bearing exercise like wa
- Do not smoke.
- Limit alcohol use.
- Get enough calcium and vitamin D in your diet. Your hea suggest taking calcium and vitamin D pills.

Prescription medicines

There are prescription medicines that you can take. These medicines may come as a pill, a nasal spray, or a shot (injection).

The following types of medicines can help treat osteoporosis. Most, but not all, of these medicines have been shown to reduce the risk of bone fracture. Talk with your health care provider about which medicine is right for you:

- Bisphosphonates
- Parathyroid hormone (PTH) analogs
- RANKL inhibitor
- Sclerostin inhibitors
- Calcitonin analogs
- Selective Estrogen Receptor Modulators (SERMs)

All medicines have potential side effects. Talk with your health care provider about which of these medicines may be right for you.

Osteoporosis | FDA

Acknowledgements

Our SWAN WOMEN!







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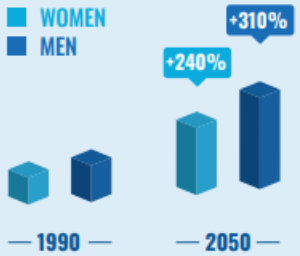
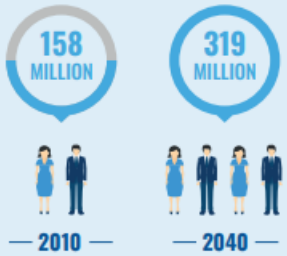
- OSTEOPOROSIS & FRACTURES -
A GLOBAL CRISIS

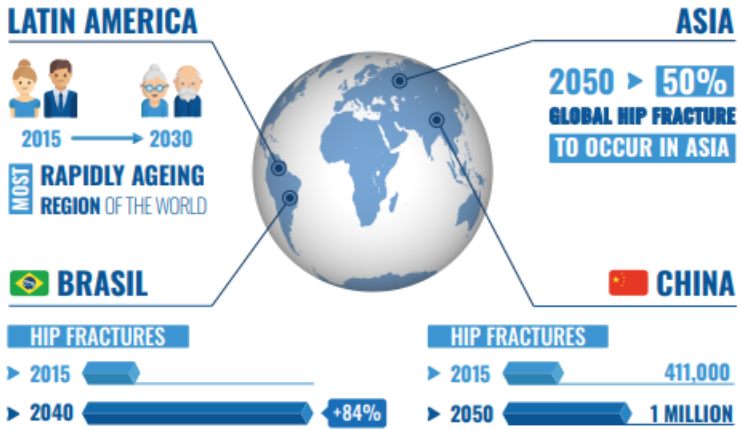
HIP FRACTURE INCREASE



NUMBER OF PEOPLE AT **HIGH RISK OF FRACTURE** TO DOUBLE



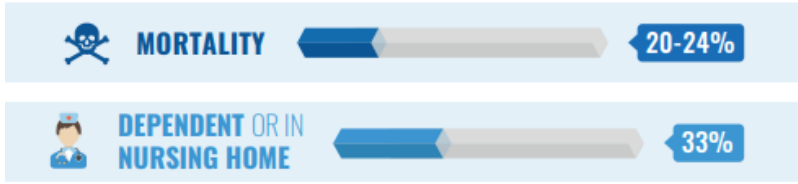
GROWING BURDEN IN ALL REGIONS OF THE WORLD



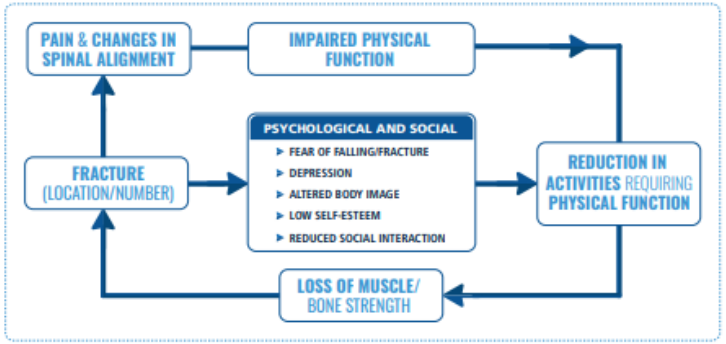
- OSTEOPOROSIS & FRACTURES -
THE SOCIOECONOMIC BURDEN

ENORMOUS HEALTHCARE COSTS

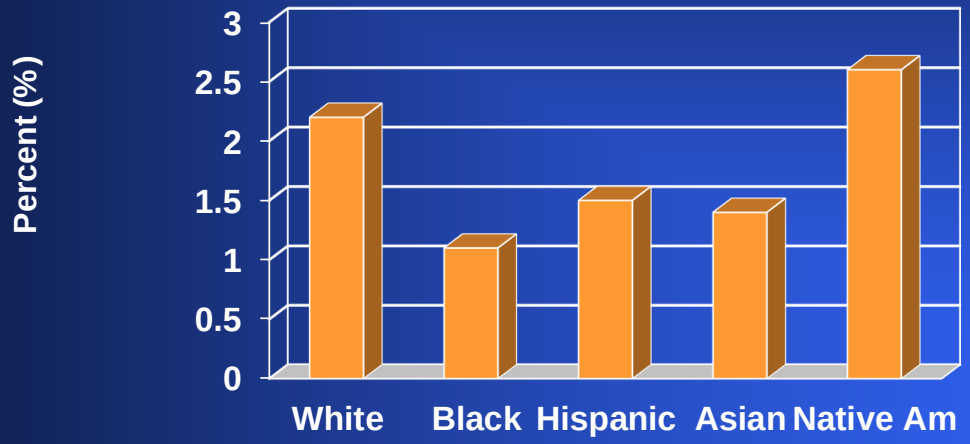
IN THE FIRST YEAR FOLLOWING HIP FRACTURES



CYCLE OF IMPAIRMENT & FRACTURE IN OSTEOPOROSIS



Women's Health Initiative: Annualized Rates (%) of All Clinical Fractures Fracture by Race & Ethnicity



Cauley et al JBMR 2007

WOMEN'S HEALTH INITIATIVE

Number of years since the final menstrual period (FMP) is more closely associated with bone mineral density than chronological age

J Clin Endocrinol Metab. 2021 Sep 19;dgab690. doi: 10.1210/clinem/dgab690.
Online ahead of print.

Associations of age at menopause with postmenopausal bone mineral density and fracture risk in women

Albert Shieh [1], Kristine M Ruppert [2], Gail A Greendale [1], Yinjuan Lian [2], Jane A Cauley [2], Sherri-Ann Burnett-Bowie [3], Carrie Karvonen-Guttierez [4], Arun S Karlamangla [1]

Affiliations + expand

PMID: 34537850 DOI: 10.1210/clinem/dgab690

Abstract

Context: Menopause before age 45 is a risk factor for fractures, but menopause occurs at age 45 or later in ~90% of women.

Objective: To determine, in women with menopause at age 45 or later, whether: 1) years since the

- 1,038 women w known FMP date and a BMD assessment ≥3 years after the FMP at the lumbar spine (LS) or femoral neck (FN).
- MV linear regression to examine the relationship of yrs since FMP to BMD, controlled for chronological age at time of BMD, race/ethnicity, BMI, tobacco, ETOH, site
- Each additional year after the FMP was associated with 0.009 and 0.005 g/cm^2 lower LS and FN BMD, respectively (p=0.0001)
- **In women of the same chronological age, those with an earlier age at FMP have lower lumbar spine and femoral neck BMD**

Fracture hazard was 23%, 31%, and 41% greater in women with FMP at age 45 versus those with final menstrual periods at 50, 52, and 55 years, respectively

J Clin Endocrinol Metab. 2021 Sep 19;dgab690. doi: 10.1210/clinem/dgab690.
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Abstract

Context: Menopause before age 45 is a risk factor for fractures, but menopause occurs at age 45 or later in ~90% of women.

Objective: To determine, in women with menopause at age 45 or later, whether: 1) years since the

- 1,554 women w known FMP date
- Cox proportional hazards regression to examine the association of age at FMP with time from the 40th birthday to first fracture, a/f race/ethnicity, BMI, tobacco, ETOH, prior fracture, DM, site, & meds
- 317 women w incident fxs over 22 years (no meds affecting bone)
- Ankle, wrist, and foot fxs most common
- **Hazard ratio for incident fracture (starting at age 40) was 5% greater for each one-year decrement in age at final menstrual period (p=0.02).**