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TITLE

Menopause-related changes in body composition are associated with subsequent bone mineral density and fractures: Study of Women's Health Across the Nation

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RUNNING TITLE

Body composition, bone density, fractures

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jbmr.4759

DISCLOSURE STATEMENT

AS, ASK, CK, and GAG have nothing to disclose.

DATA AVAILABILITY

Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in References. The analyzed data are publicly available and can be accessed at https://www.swanstudy.org/.

ABSTRACT

During the menopause transition (MT), lean mass decreases and fat mass increases. We examined the associations of these body composition changes during the MT (2 years before to 2 years after the final menstrual period) with bone mineral density (BMD) at the end of the MT and fracture after the MT. We included 539 participants from the Study of Women's Health Across the Nation who were not taking bone-beneficial or -detrimental medications before or during the MT. Using multivariable linear regression, we assessed the independent associations of % lean mass loss and % fat mass gain during the MT (mutually adjusted) with femoral neck (FN) and lumbar spine (LS) BMD at the end of the MT, adjusted for pre-MT BMD, pre-MT lean and fat mass, race/ethnicity, SWAN study site, age, and cigarette use. We used Cox proportional hazards regression to quantify the relations of % lean loss and % fat gain during the MT with fracture after the MT. The Cox model was adjusted for the covariates above plus post-MT use of bone-detrimental medications, and censored at the first use of bone-beneficial medications; we further controlled for FN or LS BMD at the end of the MT. Adjusted for covariates, each SD (6.9%) increment in lean mass loss was associated with 0.010 g/cm^2 lower FN BMD ($p<0.0001$); each SD (19.9%) increment in fat mass gain was related to 0.026 g/cm^2 greater FN ($p=0.009$) and LS ($p=0.03$) BMD. Each SD increment in lean mass loss and fat mass gain was associated with 63% ($p=0.001$) and 28% ($p=0.05$) greater fracture hazard after the MT; associations were essentially unchanged by BMD adjustment. MT-related lean mass loss and fat mass gain were associated differentially with BMD; both were independently related to more fractures. Mitigating MT-related body composition changes may reduce fracture risk.

KEY WORDS

Menopause, body composition, lean mass, fat mass, bone mineral density, fracture

INTRODUCTION

Body composition changes substantively and rapidly during the menopause transition (MT). Using a time relative to the final menstrual period (FMP) construct, the Study of Women's Health Across the Nation (SWAN) demonstrated that lean mass and fat mass increase slowly until 2 years before the FMP. At that time, changes in body composition accelerate: lean mass begins to decrease, and the rate of increase in fat mass doubles. These losses and gains persist until 2 years after the FMP, when lean mass stabilizes below and fat mass plateaus above their respective premenopausal levels (1). In relation to body composition, we define the MT as the 4-year period spanning from 2 years before through the 2 years after the FMP (when the greatest body composition changes occur). Premenopause precedes the MT, and postmenopause follows it.

MT-related changes in body composition are accompanied contemporaneously by an acceleration in osteoporosis and fracture risk (2-4). Specifically, during the MT, higher bone turnover and negative remodeling balance lead to rapid bone loss and large cumulative declines in bone mineral density (BMD) over a short period of time (in some cases, >1 SD [1 BMD T-score unit] over the 4-year MT period) (2, 5). Although women are still near their peak bone mass at the start of the MT, faster bone turnover and BMD decline during the MT are risk factors for non-hip appendicular fractures during the first postmenopausal decade, regardless of starting BMD (2-4). Sustaining a non-hip appendicular fracture confers up to a two-fold increase in risk of subsequent spine or hip fracture (6-9). These findings suggest that preventing MT-related bone loss and non-hip appendicular fractures in early postmenopause could be an *early*, powerful approach to reducing osteoporosis, spine fractures, and hip fractures in later life.

Skeletal muscle exerts trophic effects on bone by loading the skeleton and producing paracrine and endocrine factors; it also protects against falls (10-12). Accordingly, declining lean mass may cause more fractures by contributing to both lower BMD and more falls. Plausible relationships of fat mass gain with BMD and fracture are complex, as both protective and detrimental pathways have been described (13-16). Adipose tissue mass could benefit BMD through increased mechanical loading and peripheral aromatization of androgens to estrogen; it may also deter fractures by providing cushioning around vulnerable bone sites to absorb some of the impact forces from a fall (14-16). Conversely, fat is a source of osteoclastogenic pro-inflammatory cytokines, which are negatively related to BMD (17, 18). Higher body weight also results in greater ground impact during falls (13).

The objective of this study was to examine whether lean mass loss and fat mass gain *during* the MT are associated with BMD at the *end* of the MT and incident fracture hazard *after* the MT. Specifically, we formulated 2 questions: 1) are total percent loss in lean mass and total percent gain in fat mass during the MT associated with femoral neck (FN) and lumbar spine (LS) BMD at the end of the MT; 2) do percent loss in lean mass and percent gain in fat mass during the MT predict incident fracture after the MT; and if so, are the associations independent of BMD at the end of the MT? We conducted this study in SWAN, a longitudinal study of the MT with up to 17 repeated assessments of body composition, BMD, and fractures.

METHODS

SWAN is a multi-center, longitudinal study of 3,302 diverse, community-dwelling women. At study inception, participants were between 42-52 years, and in premenopause (no change from usual menstrual bleeding pattern) or early perimenopause (less predictable menstrual bleeding but bleeding at least once every three months). Potential participants were excluded if they did not have an intact uterus and at least one ovary, or were using hormone therapy (HT). Seven clinical sites recruited participants: Boston; Chicago; Detroit; Pittsburgh; Los Angeles; Newark; and Oakland. The SWAN Bone Cohort included 2,365 women from five sites (excludes Chicago and Newark, where BMD and body composition by dual energy x-ray absorptiometry (DXA) were not measured). Since study inception in 1996, a total of one baseline visit and 16 follow-up visits have occurred at a median [p25, p75] interval of 1.1 [1.0, 1.4] years between successive visits. Each SWAN clinical site obtained Institutional Review Board approval and all participants provided written informed consent.

Samples

Based on prior studies of MT-associated trajectories of BMD and body composition, we define the MT (the exposure period in this analysis) as the 4-year interval spanning 2 years before to 2 years after the FMP (1). To be in the analysis sample, women needed to be Bone Cohort participants, have a known FMP date, and have body composition assessments at two time points: once close to the start of the MT (~2 years prior to the FMP), and once close to the end of the MT (~2 years after the FMP) (see Outcomes and Exposures for the operationalization of these timing requirements).

Starting with 1,043 SWAN Bone Cohort participants with a known FMP date, we excluded those who: 1) did not have body composition assessments both close to the start of the MT and close to the end of the MT (N=211); 2) sustained a fracture before the end of the MT (N=46); 3) used a bone-beneficial (HT, calcitonin, calcitriol, bisphosphonates, denosumab, and parathyroid hormone) or -detrimental medication (oral or injectable glucocorticoids, aromatase inhibitors, gonadotropin releasing hormone agonists, or anti-epileptic medications) before the end of the MT (N=239); or 4) did not have at least one study visit after the MT, to permit observation of post-MT incident fracture (N=8). This resulted in a sample of 539 participants.

Outcomes

The outcome for our first analysis was BMD at the end of the MT. As described above, the end of the MT is defined as 2 years after the FMP, but participants may not have study visits exactly at that time point. Thus, BMD outcomes were from a visit close to the end of the MT (operationally, from the first available visit at least 2 years after FMP but not more than 4 years after FMP). At each study visit, areal BMD (g/cm^2) at the lumbar spine (LS) and femoral neck (FN) were measured using Hologic instruments (Hologic, Inc., Waltham, Massachusetts). An anthropomorphic spine phantom was circulated to create a cross-site calibration. Boston, Detroit, and Los Angeles sites began SWAN with Hologic 4500A models and subsequently upgraded to Hologic Discovery A instruments. Davis and Pittsburgh started SWAN with Hologic 2000 models and later upgraded to Hologic 4500A machines. When a site upgraded hardware, it scanned ~40 women on its old and new machines to develop cross-calibration regression equations. A standard quality control program included daily phantom measurements, local site

review of all scans, central review of scans that met problem-flagging criteria and central review of a 5% sample of scans.

The second analysis outcome was incident fracture after the MT, with the clock for fracture observation starting at the visit at the end of the MT, operationalized as the first visit that occurred at least 2 years after FMP but not more than 4 years after FMP. Fractures were ascertained by self-report using standardized questionnaires. Questionnaires were administered at the SWAN baseline visit (to identify occurrence and location of fractures prior to SWAN inception, and age at time of fracture) and at each follow-up visit (to determine occurrence and location of fractures since the previous visit). For on-study fractures, SWAN ascertained fracture dates starting at follow-up visit 7; for the first 6 follow-up visits, fracture date was imputed as the midpoint between the participant's previous and index visit. Fracture adjudication was formally initiated starting at visit 7; since inauguration of adjudication, 95% of self-reported fractures were confirmed. Fractures were categorized as low-trauma if they occurred after a fall from a height of less than 6 inches, and did not occur in the setting of a motor vehicle accident, rapid movement (e.g., skating), playing sports, or from impact with heavy or fast-moving projectiles. We excluded craniofacial and digital fractures, but included low- and high-trauma fractures, as both fracture types are associated with low BMD (19, 20).

Primary Exposures

Subtotal body composition (head omitted) was assessed using DXA. Lean mass measurements excluded bone mass to avoid contamination by un-removable metal artifacts. When a participant could not place both arms on the DXA scan bed while maintaining sufficient separation from the

torso to define soft tissue regions, she was repositioned with the left arm off the scan bed. Using data from women who had both arms measured, we used right arm values to impute left arm values, accounting for hand dominance (if unknown, right-handedness was assumed). For right-handed participants, the imputation equations were left arm fat = 0.985 × right arm fat and left arm lean = ([0.932 + 0.00122] × [BMI – 30]). For left-handed participants, raw right arm and left arm values were similar; thus, we substituted their right arm values for left.

Exposures in analyses were total percent loss in lean mass and total percent gain in fat mass during the MT, defined as 2 years before to 2 years after the FMP, corresponding to when body composition changes most rapidly (1). Because study visits did not occur at precisely FMP -2 years and FMP +2 years, we estimated rate of lean mass loss and rate of fat mass gain during the MT using body composition assessments from 2 study visits: one close to the start of the MT, and the second close to the end of the MT. Operationally, the start of the MT was the first visit that occurred no more than 2 years prior to the FMP, and no later than the FMP date. The end of the MT was the first visit that occurred at least 2 years after, but no more than 4 years after, the FMP date. Using these 2 measurements, we estimated the annualized percent loss of lean mass or gain in fat mass during the MT by dividing the percent lean mass lost or percent of fat mass gained from the first to second time points by the number of years from the first measurement to FMP +2 years (when body composition changes plateau), and multiplied by 100. To calculate the cumulative percent loss of lean mass or percent gain in fat mass over the 4-year MT, we multiplied the annualized percent loss of lean mass or gain in fat mass by 4. For the remainder of this manuscript, references to body composition changes during the MT are those cumulative changes estimated over this 4-year period.

Covariates

We selected covariates *a priori* based on knowledge of variables known or hypothesized to be associated with the analysis exposures (lean mass loss, fat mass gain) and outcomes (BMD, fracture) (21). We included two sets of covariates: potential confounders (variables associated with both independent and dependent variables), and established, strong predictors of the outcomes (BMD or fracture), even if they were not associated with the independent variables, specifically to reduce unmodeled variance in the dependent variable. Confounders included as covariates were age (years) (22), cigarette use (yes/no) (22, 23), and race/ethnicity (22, 24). Predictors of BMD or fracture included as covariates were lean mass (grams [kg]) at the start of the MT (11), fat mass (kg) at the start of the MT (11), and LS or FN BMD (g/cm^2) at the start of the MT (25). For all SWAN analyses, we include study site as a covariate, to account for within-site correlations (clustering). Values for age, BMI, and cigarette use were obtained from the visit at the end of the MT. For the analysis with fracture after the MT as outcome, we adjusted for use of bone-detrimental medications during the observation period for fracture. Exposure was modeled as the proportion of visits starting from the end of the MT until time of censoring that use of a bone-detrimental medication was reported. We did not adjust for exposure to bone-beneficial medications during the observation period for fracture; rather, participants were censored at first reported use.

Data Analysis

We generated descriptive statistics for all variables to assess their distribution. We compared the proportion of women who sustained fractures by racial/ethnic group using the Chi-squared test.

Our first analysis examined the associations of total percent loss of lean mass and total percent gain in fat mass during the MT with BMD at the end of the MT. We used multivariable linear regression with percent loss of lean mass and percent gain in fat mass during a 4-year MT as predictors (tested in the same model), and LS or FN BMD at the end of the body composition exposure period as outcome. Models adjusted for start-of-MT LS or FN BMD, lean mass and fat mass at the start of the MT, age at the end of the MT, BMI at the end of the MT, cigarette use at the end of the MT, race/ethnicity, and study site.

Our second analysis examined whether total percent loss of lean mass and total percent gain in fat mass during the MT were associated with incident fracture after the MT, and if they were, whether the associations were independent of BMD at the end of the MT. We used Cox proportional hazards regression with percent loss of lean mass and percent gain in fat mass during the MT as predictors (tested in the same model), and time to first fracture after the MT as dependent variable (fracture clock starting at the end of the MT). Participants who started bone-beneficial medications during the fracture observation period were censored at first reported use. We censored women at initiation of bone-beneficial medications (rather than adjusting for their use) because, as osteoporosis treatments, they are generally prescribed for prolonged time periods, and substantially impact fracture risk (26). Women who did not fracture, and did not use bone-beneficial medications were censored at their last observation. Of the 539 women in the analysis sample, 43 were lost to follow-up before the 16th follow-up (the last visit used in this

analysis). Base model covariates were lean mass and fat mass at the start of the MT, age at the end of the MT, BMI at the end of the MT, cigarette use at the end of the MT, race/ethnicity, and study site. To examine whether the potential assocations of lean mass loss or fat mass gain with fracture were independent of BMD, final models additionally controlled for LS or FN BMD at the end of the MT. We confirmed that the proportionality of hazards assumption was met for all Cox models.

In all models, we added quadratic terms for percent lean mass loss and percent fat mass gain to assess for the presence of non-linearity in all predictor-outcome relations. Because these quadratic terms did not make statistically significant contributions, they were dropped from all models. Thus, final models had percent lean mass loss and percent fat mass gain as simple linear predictors only.

We also conducted three additional sets of sensitivity analyses. Accounting for lean mass and fat mass at the start of the MT in models may artifactually overestimate the effects of lean mass loss and fat mass gain if there is measurement error (27). Thus, in our first sensitivity analyses, we re-ran the above models without adjusting for starting values of lean mass or fat mass. In the second set of sensitivity analyses, instead of adjusting for starting lean mass and fat mass, we controlled for average lean mass and fat mass over the MT. Adjusting for average lean mass and fat mass can cause underestimation of the effect of body composition change, a conservative bias (28). Third, because initiation of bone-beneficial medications could be considered a competing risk with fracture, we conducted analyses of time to the combined event of either first fracture or first use of bone-beneficial medications after the MT in Cox proportional hazards regression.

Statistical analyses were performed using STATA 16. We used a 2-tailed signficiance level of 0.05.

RESULTS

Participant Characteristics

Table 1 presents the characteristics of the 539 participants that comprise the analysis sample. Approximately one quarter were Black, one third East Asian (Chinese or Japanese), and the remaining White. Average age at the start of the MT was 50 years (range 42 to 58 years). Mean BMI at the start of the MT was 27.7 kg/m^2 (range 16.8 to 55.1 kg/m^2). When broken down by race/ethnicity, BMI averaged 31.1, 23.3, 23.8, and 28.4 kg/m^2 in African American, Chinese, Japanese, and White women, respectively. Overall lean mass averaged 38.5 kg and 38.2 kg at the start and end of the MT, respectively. Mean cumulative percent loss in lean mass during the MT was modest (0.7%), but variability was large: 25% of participants lost 4.7% or more lean mass during the MT. Mean fat mass at the start and end of the MT were 27.2 and 28.1 kg, respectively. This corresponded to an average cumulative fat mass gain of 6.0%, with 25% of women gaining 9.0% or more of fast mass during the MT.

Cumulative Lean Mass Loss and Fat Mass Gain During the MT as Predictors of BMD at the End of the MT

Mean BMD at the end of the MT was 0.780 g/cm^2 at the FN, and 0.983 g/cm^2 at the LS. In multivariable, linear regression, controlled for lean and fat mass at the start of the MT, LS or FN BMD at the start of the MT, age, cigarette use, race/ethnicity, and study site, greater loss of lean mass was associated with lower BMD at the FN, but not the LS, whereas greater gain in fat mass was associated with greater BMD at both sites (Table 2). When adjusted for covariates, each SD greater cumulative loss of lean mass was associated with 0.010 g/cm^2 lower FN BMD

($p<0.0001$), while each SD greater cumulative gain in fat mass related to 0.026 g/cm^2 greater FN ($p=0.009$) and LS ($p=0.03$) BMD.

Lean Mass Loss and Fat Mass Gain During the MT as Predictors of Incident Fractures after the MT

Mean duration of follow-up time after the MT was 14.6 years (range 0.8 to 22.8 years). During that time frame, a total of 64 women sustained an incident fracture. The percentages of women with fractures were similar between African American (12.7%) and White (13.8%) participants ($p=0.7$), and between Chinese (8.0%) and Japanese (8.9%) participants ($p=0.8$). Fractures most commonly occurred at non-hip appendicular sites, e.g., wrist (N=12), ankle (N=10), and arm (N=8). In Cox proportional hazards regression model, greater total percent lean mass loss and greater total percent fat mass gain were associated with greater rates of incident fracture (Table 3). In the base model, which controlled for lean and fat mass at the start of the MT, age, cigarette use, exposure to bone-detrimental medications, race/ethnicity, and study site, each SD greater cumulative loss of lean mass and gain in fat mass were associated with 63% ($p=0.001$) and 29% ($p=0.053$) greater fracture hazards, respectively. These effect sizes were unaltered by adjustment for FN or LS BMD at the end of the MT.

Sensitivity Analyses

In the first sensitivity analyses, omitting lean mass and fat mass at the start of the MT as covariates did not substantially influence the relation between body composition changes and study outcomes (data not shown). In the second set of sensitivity analyses, the associations of lean mass loss and fat mass gain with BMD at the end of the MT and with incident fracture after

the MT were essentially unaltered by controlling for average lean mass and average fat mass over the MT (instead of lean mass and fat mass at the start of the MT) (data not shown). Finally, analyses of time to the combined event of either first fracture after the MT (N=64) or first use of bone-beneficial medications (N=51) produced hazard ratios that were nearly identical to those for fracture only (data not shown).

DISCUSSION

We examined the longitudinal associations of lean mass loss and fat mass gain during the MT with BMD at the end of the MT and incident fractures after the MT. Both loss in lean mass and gain in fat mass are common during the MT, but there is substantial between-women variability in the magnitude of these body composition changes. We found that greater lean mass loss during the MT was associated with lower BMD at the end of the MT in the FN, but not in the LS. In contrast, greater fat mass gain was associated with higher BMD at both the FN and LS. Despite their divergent effects on BMD, both greater lean mass loss and greater fat mass gain during the MT were associated with more subsequent fractures. In this mid-life cohort, fractures occurred most commonly at non-hip appendicular sites. Observed body composition-fracture relations were independent of FN and LS BMD at the end of the MT, suggesting that MT-related changes in body composition contribute to these fractures through pathways besides BMD.

Numerous prior investigations have examined the relations between body composition and BMD in pre- or postmenopausal women, but nearly all prior analyses were cross-sectional, and results were inconsistent (11, 29-34). Some studies found that greater lean mass was associated with higher BMD, but others found no association (11, 29, 31, 32). Reported relations between fat mass and BMD also varied: depending on the study, greater fat mass was associated with higher or lower BMD, or not related to BMD at all (29-32, 35). Null findings in prior studies could be due to insufficient sample size: a meta-analysis of 44 studies that examined the association of body composition with BMD found that studies with <200 participants were less likely to detect an effect of either lean mass or fat mass on BMD (11). Adequate power to detect an association

with BMD is especially pertinent to fat mass, because it is a weaker determinant of BMD than lean mass (11).

Our *longitudinal* analysis of the relation between cumulative changes in body composition during the MT with BMD at the end of the MT had several advantages. First, we controlled for BMD before the MT, an approximation of peak BMD and critical determinant of subsequent BMD (2, 36). Second, the MT is an optimal time to examine the association of body composition with BMD because changes in both are larger (i.e., the physiologic signal stronger) than during pre- or postmenopause, making it more feasible to discern exposure-outcome relations (1, 2). This is supported by results from 1 prior longitudinal analysis of older women (average age 69 years) by the Dubbo Osteoporosis Epidemiology Study (34). In this cohort, greater fat mass was associated with slower LS BMD loss, but neither greater fat mass nor greater lean mass protected against bone loss at the FN. These null FN findings could be due to the slower FN BMD loss (>6-fold slower than during the MT in midlife SWAN participants) in the older Dubbo sample.

Several longitudinal analyses have examined the relations of single measures of body composition with subsequent hip and major osteoporotic fractures in cohorts of older (mean age >63 years), postmenopausal women (37-40). The Study of Osteoporotic Fractures, the Os des Femmes de Lyon study, Women's Health Initiative, and the Health and Body Composition Study found that greater lean mass and/or greater fat mass protected against subsequent hip or major osteoporotic fractures (37-40). Our study differs from these prior analyses in that our exposure was *change* in lean or fat mass, rather than single measures of body composition. Another difference is that our results suggest that the effects of fat mass on risk of hip vs. non-hip

appendicular fractures are different: in SWAN, greater fat mass gain was a risk factor for subsequent non-hip appendicular fractures despite being associated with higher BMD. This suggests that the beneficial effects of fat mass gain on BMD may be outweighed by the greater risk of fracture due to falls, especially at peripheral sites where there is less cushioning by fat padding (41, 42). Consistent with our findings, the Global Longitudinal Study of Osteoporosis in Women (GLOW) reported that women with obesity were more likely to sustain ankle or upper leg fractures vs. women without obesity (42).

Greater lean mass loss during the MT was associated with lower BMD at the end of the MT at the FN, but not at the LS. We speculate that there could be more skeletal muscle surrounding the hip than the LS; thus, the LS was less susceptible to the potential effects of lean mass loss. In contrast, greater fat mass gain was associated with higher subsequent BMD at both the FN and LS, suggesting that the beneficial effects of adipose tissue on BMD (e.g., via mechanical and endocrine mechanisms (14)) appeared to outweigh potentially deleterious effects of adipose tissue on bone (e.g., production of osteoclastogenic pro-inflammatory cytokines (13)).

Both greater lean mass loss and greater fat mass gain during the MT predicted more subsequent non-hip appendicular fractures. These relations were independent of BMD at the end of the MT, suggesting that MT-related changes in body composition contribute to these fractures via pathways other than BMD. This contrasts with findings from the Study of Osteoporotic Fractures, which showed that accounting for FN BMD completely attenuated the protective effects of lean and fat mass against hip fracture (37). FN BMD likely accounts for a smaller amount of the association of body composition with non-hip appendicular compared to hip

fractures: although FN BMD is associated with risk of appendicular fractures, the gradient of risk is smaller than that for hip fractures (43, 44).

The clinical implication of our study is that mitigating lean mass loss during the MT could protect against FN BMD loss, and that mitigating both lean mass loss and fat mass gain during the MT could help prevent future non-hip appendicular fractures. Preventing bone loss at the FN during the MT is clinically relevant, because total BMD loss at that site can exceed 0.5 SD (~0.5 T-score unit) during the MT. Moreover, once FN BMD is lost, it is difficult to recover: even currently available osteoanabolic agents may not raise FN BMD by 0.5 SD (45). Identifying risk factors for non-hip appendicular fractures is clinically pertinent because they are early signals for skeletal fragility in older age: women with prior non-hip appendicular fractures are up to 2-fold more likely to sustain a future spine or hip fracture (6-9). Future research can examine which subgroups of women are most likely to lose the greatest amount of lean mass and gain the greatest amount of fat mass during the MT, as well as who is most susceptible to the deleterious effects of MT-related body composition changes on fracture risk. This could help identify possible intervention targets for trials to test whether mitigating lean mass loss and fat mass gain during the MT reduces the risk of fractures in postmenopause.

Several study limitations warrant mention. First, to maximize the number of fracture events, we included both low- and high trauma fractures in one composite outcome. We justify this approach because both fracture types are risk factors for future fractures (19, 20). Indeed, outcomes that include low- and high trauma fracture are now included in trials testing the anti-fracture efficacy of pharmacologic agents (46). Second, BMI and rates of incident fracture differ

by race/ethnicity (2, 47). However, we did not have sufficient power to examine whether the association between body composition change and fracture differed by race/ethnicity. Third, causal inference in any observational study is necessarily limited. However, SWAN's many repeated observations allowed us to investigate *changes* in lean and fat mass as exposures, which is a strong observational design.

To conclude, we examined the longitudinal associations of lean mass loss and fat mass gain during the MT with subsequent BMD and fractures. Our results show that MT-related body composition changes are associated risk factors for non-hip appendicular fracture (harbingers of later life fractures), independent of BMD at the end of the MT. This highlights that mitigating MT-related lean mass loss and fat mass gain could be an early, powerful approach to reduce osteoporosis-related fractures in later life.

ACKNOWLEDGEMENT

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495, and U19AG063720). The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

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We thank the study staff at each site and all the women who participated in SWAN.

REFERENCES

1. Greendale GA, Sternfeld B, Huang M, Han W, Karvonen-Gutierrez C, Ruppert K, Cauley JA, Finkelstein JS, Jiang SF, Karlamangla AS. Changes in body composition and weight during the menopause transition. JCI insight. 2019;4(5). Epub 2019/03/08. doi: 10.1172/jci.insight.124865. PubMed PMID: 30843880; PMCID: PMC6483504.

2. Greendale G, Sowers M, Han W, Huang M, Finkelstein J, Crandall C, Lee J, Karlamangla A. 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). J Bone Miner Res. 2012;27(1):111-8. doi: 10.1002/jbmr.534; PMCID: PMC3378821.

3. Shieh A, Greendale GA, Cauley JA, Karlamangla AS. The Association between Fast Increase in Bone Turnover During the Menopause Transition and Subsequent Fracture. J Clin Endocrinol Metab. 2020;105(4). Epub 2019/12/17. doi: 10.1210/clinem/dgz281. PubMed PMID: 31840764; PMCID: PMC7067542.

4. Shieh A, Karlamangla AS, Huang MH, Han W, Greendale GA. Faster Lumbar Spine Bone Loss in Midlife Predicts Subsequent Fracture Independent of Starting Bone Mineral Density. J Clin Endocrinol Metab. 2021;106(7):e2491-e501. Epub 2021/04/28. doi: 10.1210/clinem/dgab279. PubMed PMID: 33903908; PMCID: PMC8208668.

5. Sowers M, Zheng H, Greendale G, Neer R, Cauley J, Ellis J, Johnson S, Finkelstein J. Changes in bone resorption across the menopause transition: effects of reproductive hormones, body size, and ethnicity. J Clin Endocrinol Metab. 2013;98(7):2854-63. Epub 2013 May 10. doi: 10.1210/jc.2012-4113; PMCID: PMC3701268.

6. Barrett-Connor E, Sajjan SG, Siris ES, Miller PD, Chen YT, Markson LE. Wrist fracture as a predictor of future fractures in younger versus older postmenopausal women: results from

the National Osteoporosis Risk Assessment (NORA). Osteoporos Int. 2008;19(5):607-13. Epub 2007/12/07. doi: 10.1007/s00198-007-0508-8. PubMed PMID: 18058055.

7. Cerocchi I, Ghera S, Gasbarra E, Feola M, Tarantino U. The clinical significance of wrist fracture in osteoporosis. Aging clinical and experimental research. 2013;25 Suppl 1:S81-2. Epub 2013/09/21. doi: 10.1007/s40520-013-0083-0. PubMed PMID: 24046048.

8. Gehlbach S, Saag KG, Adachi JD, Hooven FH, Flahive J, Boonen S, Chapurlat RD, Compston JE, Cooper C, Diez-Perez A, Greenspan SL, LaCroix AZ, Netelenbos JC, Pfeilschifter J, Rossini M, Roux C, Sambrook PN, Silverman S, Siris ES, Watts NB, Lindsay R. Previous fractures at multiple sites increase the risk for subsequent fractures: the Global Longitudinal Study of Osteoporosis in Women. J Bone Miner Res. 2012;27(3):645-53. Epub 2011/11/25. doi: 10.1002/jbmr.1476. PubMed PMID: 22113888; PMCID: PMC4881741.

9. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res. 2000;15(4):721-39. Epub 2000/04/26. doi: 10.1359/jbmr.2000.15.4.721. PubMed PMID: 10780864.

10. Lang T, Streeper T, Cawthon P, Baldwin K, Taaffe DR, Harris TB. Sarcopenia: etiology, clinical consequences, intervention, and assessment. Osteoporosis International. 2010;21(4):543-59. doi: 10.1007/s00198-009-1059-y.

11. Ho-Pham LT, Nguyen UDT, Nguyen TV. Association Between Lean Mass, Fat Mass, and Bone Mineral Density: A Meta-analysis. The Journal of Clinical Endocrinology & Metabolism. 2014;99(1):30-8. doi: 10.1210/jc.2013-3190.

12. Gomarasca M, Banfi G, Lombardi G. Chapter Four - Myokines: The endocrine coupling of skeletal muscle and bone. In: Makowski GS, editor. Advances in clinical chemistry: Elsevier; 2020. p. 155-218.

13. Day CP. From Fat to Inflammation. Gastroenterology. 2006;130(1):207-10. doi: 10.1053/j.gastro.2005.11.017.

14. Compston J. Obesity and Bone. Current Osteoporosis Reports. 2013;11(1):30-5. doi: 10.1007/s11914-012-0127-y.

15. Longcope C, Pratt JH, Stephen HS, Fineberg SE. Aromatization of Androgens by Muscle and Adipose Tissue in Vivo*. The Journal of Clinical Endocrinology & Metabolism. 1978;46(1):146-52. doi: 10.1210/jcem-46-1-146.

16. Hars M, Trombetti A. Body composition assessment in the prediction of osteoporotic fractures. Current opinion in rheumatology. 2017;29(4):394-401. Epub 2017/04/11. doi: 10.1097/bor.0000000000000406. PubMed PMID: 28394825.

17. Scheidt-Nave C, Bismar H, Leidig-Bruckner G, Woitge H, Seibel MJ, Ziegler R, Pfeilschifter J. Serum interleukin 6 is a major predictor of bone loss in women specific to the first decade past menopause. J Clin Endocrinol Metab. 2001;86(5):2032-42. Epub 2001/05/10. doi: 10.1210/jcem.86.5.7445. PubMed PMID: 11344203.

18. Charatcharoenwitthaya N, Khosla S, Atkinson EJ, McCready LK, Riggs BL. Effect of blockade of TNF-alpha and interleukin-1 action on bone resorption in early postmenopausal women. J Bone Miner Res. 2007;22(5):724-9. Epub 2007/02/14. doi: 10.1359/jbmr.070207. PubMed PMID: 17295604.

19. Leslie WD, Schousboe JT, Morin SN, Martineau P, Lix LM, Johansson H, McCloskey EV, Harvey NC, Kanis JA. Fracture risk following high-trauma versus low-trauma fracture: a

registry-based cohort study. Osteoporos Int. 2020;31(6):1059-67. Epub 2020/03/17. doi: 10.1007/s00198-019-05274-2. PubMed PMID: 32173782; PMCID: PMC7115893.

20. Cummings SR, Eastell R. Stop (mis)classifying fractures as high- or low-trauma or as fragility fractures. Osteoporos Int. 2020;31(6):1023-4. Epub 2020/03/17. doi: 10.1007/s00198-020-05325-z. PubMed PMID: 32173783.

21. Heinze G, Wallisch C, Dunkler D. Variable selection - A review and recommendations for the practicing statistician. Biom J. 2018;60(3):431-49. Epub 2018/01/03. doi: 10.1002/bimj.201700067. PubMed PMID: 29292533; PMCID: PMC5969114.

22. Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, Oden A, Zethraeus N, Pfleger B, Khaltaev N. Assessment of fracture risk. Osteoporosis International. 2005;16(6):581-9. doi: 10.1007/s00198-004-1780-5.

23. Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. BMJ (Clinical research ed). 1997;315(7112):841. doi: 10.1136/bmj.315.7112.841.

24. Barrett-Connor E, Siris ES, Wehren LE, Miller PD, Abbott TA, Berger ML, Santora AC, Sherwood LM. Osteoporosis and Fracture Risk in Women of Different Ethnic Groups. Journal of Bone and Mineral Research. 2005;20(2):185-94. doi: https://doi.org/10.1359/JBMR.041007.

25. McClung MR. The relationship between bone mineral density and fracture risk. Current Osteoporosis Reports. 2005;3(2):57-63. doi: 10.1007/s11914-005-0005-y.

26. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society* Clinical Practice Guideline. J Clin Endocrinol Metab. 2019;104(5):1595-622. Epub 2019/03/26. doi: 10.1210/jc.2019-00221. PubMed PMID: 30907953.

27. Glymour MM, Weuve J, Berkman LF, Kawachi I, Robins JM. When Is Baseline Adjustment Useful in Analyses of Change? An Example with Education and Cognitive Change. American Journal of Epidemiology. 2005;162(3):267-78. doi: 10.1093/aje/kwi187.

28. Cain KC, Kronmal RA, Kosinski AS. Analysing the relationship between change in a risk factor and risk of disease. Statistics in medicine. 1992;11(6):783-97. doi: https://doi.org/10.1002/sim.4780110609.

29. Salamone LM, Glynn N, Black D, Epstein RS, Palermo L, Meilahn E, Kuller LH, Cauley JA. Body composition and bone mineral density in premenopausal and early perimenopausal women. Journal of Bone and Mineral Research. 1995;10(11):1762-8. doi: https://doi.org/10.1002/jbmr.5650101120.

30. Hsu Y-H, Venners SA, Terwedow HA, Feng Y, Niu T, Li Z, Laird N, Brain JD, Cummings SR, Bouxsein ML, Rosen CJ, Xu X. Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. The American Journal of Clinical Nutrition. 2006;83(1):146-54. doi: 10.1093/ajcn/83.1.146.

31. Reid IR, Evans MC, Ames RW. Volumetric bone density of the lumbar spine is related to fat mass but not lean mass in normal postmenopausal women. Osteoporosis International. 1994;4(6):362-7. doi: 10.1007/BF01622199.

32. Park J-H, Song Y-M, Sung J, Lee K, Kim YS, Kim T, Cho S-I. The association between fat and lean mass and bone mineral density: The Healthy Twin Study. Bone. 2012;50(4):1006-11. doi: https://doi.org/10.1016/j.bone.2012.01.015.

33. Zhu K, Hunter M, James A, Lim EM, Cooke BR, Walsh JP. Discordance between fat mass index and body mass index is associated with reduced bone mineral density in women but

not in men: the Busselton Healthy Ageing Study. Osteoporosis International. 2017;28(1):259-68. doi: 10.1007/s00198-016-3710-8.

34. Yang S, Center JR, Eisman JA, Nguyen TV. Association between fat mass, lean mass, and bone loss: the Dubbo osteoporosis epidemiology study. Osteoporosis International. 2015;26(4):1381-6. doi: 10.1007/s00198-014-3009-6.

35. Kim JH, Choi HJ, Kim MJ, Shin CS, Cho NH. Fat mass is negatively associated with bone mineral content in Koreans. Osteoporosis International. 2012;23(7):2009-16. doi: 10.1007/s00198-011-1808-6.

36. Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Looker A, Marcus R, Matkovic V, Weaver C. Peak bone mass. Osteoporosis International. 2000;11(12):985-1009.

37. Ensrud KE, Lipschutz RC, Cauley JA, Seeley D, Nevitt MC, Scott J, Orwoll ES, Genant HK, Cummings SR. Body Size and Hip Fracture Risk in Older Women: A Prospective Study. The American Journal of Medicine. 1997;103(4):274-80. doi: https://doi.org/10.1016/S0002-9343(97)00025-9.

38. Harvey NC, Kanis JA, Liu E, Cooper C, Lorentzon M, Bea JW, Carbone L, Cespedes Feliciano EM, Laddu DR, Schnatz PF, Shadyab AH, Stefanick ML, Wactawski-Wende J, Crandall CJ, Johansson H, McCloskey E. Predictive Value of DXA Appendicular Lean Mass for Incident Fractures, Falls, and Mortality, Independent of Prior Falls, FRAX, and BMD: Findings from the Women's Health Initiative (WHI). Journal of Bone and Mineral Research. 2021;36(4):654-61. doi: https://doi.org/10.1002/jbmr.4239.

39. Sornay-Rendu E, Duboeuf F, Boutroy S, Chapurlat RD. Muscle mass is associated with incident fracture in postmenopausal women: The OFELY study. Bone. 2017;94:108-13. doi: https://doi.org/10.1016/j.bone.2016.10.024.

40. Malkov S, Cawthon PM, Peters KW, Cauley JA, Murphy RA, Visser M, Wilson JP, Harris T, Satterfield S, Cummings S, Shepherd JA, for the Health ABCS. Hip Fractures Risk in Older Men and Women Associated With DXA-Derived Measures of Thigh Subcutaneous Fat Thickness, Cross-Sectional Muscle Area, and Muscle Density. Journal of Bone and Mineral Research. 2015;30(8):1414-21. doi: https://doi.org/10.1002/jbmr.2469.

41. Ishii S, Cauley JA, Greendale GA, Nielsen C, Karvonen-Gutierrez C, Ruppert K, Karlamangla AS. Pleiotropic effects of obesity on fracture risk: the Study of Women's Health Across the Nation. J Bone Miner Res. 2014;29(12):2561-70. Epub 2014/07/06. doi: 10.1002/jbmr.2303. PubMed PMID: 24986773; PMCID: PMC4403760.

42. Compston JE, Watts NB, Chapurlat R, Cooper C, Boonen S, Greenspan S, Pfeilschifter J, Silverman S, Díez-Pérez A, Lindsay R, Saag KG, Netelenbos JC, Gehlbach S, Hooven FH, Flahive J, Adachi JD, Rossini M, Lacroix AZ, Roux C, Sambrook PN, Siris ES. Obesity is not protective against fracture in postmenopausal women: GLOW. Am J Med. 2011;124(11):1043-50. Epub 2011/10/25. doi: 10.1016/j.amjmed.2011.06.013. PubMed PMID: 22017783; PMCID: PMC4897773.

43. Harvey NC, Curtis EM, Dennison EM, Cooper C. The Epidemiology of Osteoporotic Fractures. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism2018. p. 398-404.

44. Stone KL, Seeley DG, Lui L-Y, Cauley JA, Ensrud K, Browner WS, Nevitt MC, Cummings SR. BMD at Multiple Sites and Risk of Fracture of Multiple Types: Long-Term Results From the Study of Osteoporotic Fractures. Journal of Bone and Mineral Research. 2003;18(11):1947-54. doi: https://doi.org/10.1359/jbmr.2003.18.11.1947.

45. Miller P, Hattersley G, Riis B, Williams G, Lau E, Russo L, Alexandersen P, Zerbini C, Hu M, Harris A, Fitzpatrick L, Cosman F, Christiansen C. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial. JAMA. 2016;316(7):722-33. doi: 10.1001/jama.2016.11136.

46. Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, Bagur A, Malouf-Sierra J, Lakatos P, Fahrleitner-Pammer A, Lespessailles E, Minisola S, Body JJ, Geusens P, Möricke R, López-Romero P. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. 2018;391(10117):230-40. Epub 2017/11/14. doi: 10.1016/s0140-6736(17)32137-2. PubMed PMID: 29129436.

47. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19(4):385-97. Epub 2008/02/23. doi: 10.1007/s00198-007-0543-5. PubMed PMID: 18292978; PMCID: PMC2267485.

Table 1

Characteristics of the analysis sample (N=539)[1]

Time-varying Characteristics	**Value at the Start of the MT[2,3]**	**Value at the End of the MT[2,4]**
Age (years)	50.7 (2.8)	55.7 (2.8)
Body Mass Index (kg/m^2)	27.3 (6.9)	27.7 (6.7)
Cigarette use (Y/N)	86 (19%)	79 (15%)
Body composition[5]		
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)		
Lumbar spine	1.069 (0.146)	0.983 (0.155)
Femoral neck	0.833 (0.137)	0.780 (0.134)
Fixed variables	**Values**	
Race/ethnicity		
Black	142 (26.3%)	
Chinese	75 (13.9%)	
Japanese	90 (16.7%)	
White	232 (43.0%)	
Body composition changes during the MT		
Lean mass loss (cumulative %)	0.70 (6.93)	
Fat mass gain (cumulative %)	6.0 (19.9)	
Appendicular fracture after the MT (Y/N)	64 (11.8%)	

1. Count (percentage) for categorical variables; mean (SD) for continuous variables
2. MT: menopause transition, defined as starting 2 years before and ending 2 years after the final menstrual period (FMP), spanning the period when body composition changes most rapidly
3. Values close to the start of the MT (first available between 2 years before FMP but not later than at the FMP)
4. Values obtained close to the end of the MT (first available at least 2 years after but not 4 past the FMP)
5. Body composition measured with dual energy x-ray absorptiometry

Table 2

Associations of total percent lean mass loss and total percent fat mass gain during the menopause transition (MT) with bone mineral density (BMD) level at the end of the MT [1]

	Associations per standard deviation (SD) lean mass loss or SD fat mass gain during the MT with BMD at the end of the MT [2,3,4]			
	Femoral neck (FN) BMD (g/cm^2)		Lumbar spine (LS) BMD (g/cm^2)	
	Beta (95% CI)	p-value	*Beta* (95% CI)	p-value
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

1. Associations estimated using multivariable linear regression with FN or LS BMD after the MT as outcome, and cumulative % loss in lean mass and gain in fat mass (tested together) as primary predictors, controlled for lean mass level (kg) and fat mass level (kg) at the start of the MT. Other model covariates were race/ethnicity, study site, age, cigarette use, FN or LS BMD at start of the MT, and use of bone detrimental medications during the MT.
2. Mean and SD of cumulative percent lean mass loss during the MT = 0.7% (6.9%)
3. Mean and SD of cumulative percent fat mass gain during the MT = 6.0% (19.9%)
4. *Beta* coefficients represent the decrement or increment in BMD level per 1 SD increment in exposure.

Table 3

Associations of total percent lean mass loss and total percent fat mass gain during the menopause transition (MT) with incident fractures after the MT [1]

	Associations per standard deviation (SD) lean mass loss or SD fat mass gain during the MT with incident appendicular fracture after the MT [2,3,4]					
	Base model[5]		Base model + Femoral Neck BMD[6]		Base model + Lumbar Spine BMD[7]	
	HR (95% CI)[4]	p-value	HR (95% CI)[4]	p-value	HR (95% CI)[4]	p-value
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

1. Associations estimated using Cox proportional hazards regression with time to first fracture after the MT as outcome, and cumulative % loss of lean mass and cumulative gain in fat mass (tested together) as predictors, controlled for lean mass (kg) and fat mass (kg) levels at start of the MT. Base model covariates were race/ethnicity, study site, age, cigarette use, and exposure to bone-detrimental medication after the MT. Fully adjusted models controlled for FN or LS BMD at the end of the MT.
2. Mean and SD of cumulative percent lean mass loss during the MT = 0.7% (6.9%)
3. Mean and SD of cumulative percent fat mass gain during the MT = 6.0% (19.9%)
4. HR: Hazard ratios represent the decrement or increment in fracture hazard per 1 SD of each exposure.
5. N=539, 64 fractures
6. N=535, 63 fractures
7. N=536, 63 fractures

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Associations of total percent lean mass loss and total percent fat mass gain during the menopause transition (MT) with bone mineral density (BMD) level at the end of the MT [1]

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1. Associations estimated using multivariable linear regression with FN or LS BMD after the MT as outcome, and cumulative % loss in lean mass and gain in fat mass (tested together) as primary predictors, controlled for lean mass level (kg) and fat mass level (kg) at the start of the MT. Other model covariates were race/ethnicity, study site, age, cigarette use, FN or LS BMD at start of the MT, and use of bone detrimental medications during the MT.
2. Mean and SD of cumulative percent lean mass loss during the MT = 0.7% (6.9%)
3. Mean and SD of cumulative percent fat mass gain during the MT = 6.0% (19.9%)
4. *Beta* coefficients represent the decrement or increment in BMD level per 1 SD increment in exposure.

Table 3

Associations of total percent lean mass loss and total percent fat mass gain during the menopause transition (MT) with incident fractures after the MT [1]

	Associations per standard deviation (SD) lean mass loss or SD fat mass gain during the MT with incident appendicular fracture after the MT [2,3,4]					
	Base model		Base model + Femoral Neck Bone Mineral Density (BMD)		Base model + Lumbar Spine BMD	
	HR (95% CI)[4]	p-value	HR (95% CI)[4]	p-value	HR (95% CI)[4]	p-value
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

1. Associations estimated using Cox proportional hazards regression with time to first fracture after the MT as outcome, and cumulative % loss of lean mass and cumulative gain in fat mass (tested together) as predictors, controlled for lean mass (kg) and fat mass (kg) levels at start of the MT. Base model covariates were race/ethnicity, study site, age, cigarette use, and exposure to bone-detrimental medication after the MT. Fully adjusted models controlled for FN or LS BMD at the end of the MT.
2. Mean and SD of cumulative percent lean mass loss during the MT = 0.7% (6.9%)
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4. HR: Hazard ratios represent the decrement or increment in fracture hazard per 1 SD of each exposure.