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Clinical Research Article

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FSH Level and Changes in Bone Mass and Body Composition in Older Women and Men

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Abbreviations: aBMD, areal bone mineral density; AGES, Age, Gene/Environment Susceptibility; BMA, bone marrow adiposity; BMD, bone mineral density; BMI, body mass index; CHAMP, Concord Health and Aging in Men Project; CV, coefficient of variation; DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; LLOQ, lower limits of quantitation; OR, odds ratio; QCT, quantitative computed tomography; SWAN, Study of Women's Health Across the Nation; vBMD, volumetric bone mineral density

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Abstract

Context: FSH may have independent actions on bone remodeling and body fat regulation. Cross-sectionally, we have shown that serum FSH is associated with bone mineral density (BMD) and body fat in older postmenopausal women, but it remains unknown whether FSH predicts bone and fat changes.

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Objective: We examined whether baseline FSH level is associated with subsequent bone loss or body composition changes in older adults.
Setting, Design, Participants: We studied 162 women and 158 men (mean age 82 ± 4 years) from the Age, Gene/Environment Susceptibility (AGES)-Bone Marrow Adiposity cohort, a substudy of the AGES-Reykjavik Study of community-dwelling older adults. Skeletal health and body composition were characterized at baseline and 3 years later.
Main Outcomes: Annualized change in BMD and body composition by dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT). Models were adjusted for serum estradiol and testosterone levels.
Results: There was no evidence for an association between baseline FSH level and change in BMD or body composition by DXA or QCT. For femoral neck areal BMD, adjusted mean difference (95% CI) per SD increase in FSH was 1.3 (-0.7 to 3.3) mg/cm^2/y in women, and -0.2 (-2.6 to 2.2) mg/cm^2/y in men. For visceral fat, adjusted mean difference (95% CI) per SD increase in FSH was 1.80 (-0.03 to 3.62) cm^2/y in women, and -0.33 (-3.73 to 3.06) cm^2/y in men.
Conclusions: Although cross-sectional studies and studies in perimenopausal women have demonstrated associations between FSH and BMD and body composition, in older adults, FSH level is not associated with bone mass or body composition changes.

Key Words: follicle-stimulating hormone (FSH), bone loss, adiposity, body composition, aging

FSH, a gonadotropin secreted by the anterior pituitary, has traditionally been viewed as a reproductive hormone exerting its effects solely on gonadal tissues. However, increasingly studies have suggested possible extragonadal functions of FSH, including regulation of bone mass (1, 2) and body fat (3, 4). In humans, serum FSH levels strongly correlate with the rate of bone loss during the menopausal transition (5-8). The onset of rapid bone loss coincides with a gradual increase in FSH in the 5 years leading up to menopause, which together precede the drop in estrogen by 2 to 3 years. In aging men, slow and progressive bone loss occurs in conjunction with a steady annual increase in FSH of 3.5% (9), although elevated FSH has not been shown to be independently associated with lower bone mass or changes in bone turnover in young to middle-aged men (10, 11). Meanwhile, coincident age-related increases in adiposity are also observed in both men and women. A rapid increase in central abdominal fat and abdominal obesity is observed during the menopause transition (12-14), and a greater increase in FSH is associated with greater increase in fat mass (15).

In vitro, FSH has been shown to increase osteoclast differentiation and stimulate bone resorption via an isoform of the FSH receptor on bone (1, 16-18). There is evidence that FSH receptor is expressed in murine and human adipocytes, and its activation results in upregulation of core fat genes (3, 4). In mice, in vivo treatment with anti-FSH antibodies resulted in a higher bone mass that was independent of estrogen levels (19-21). FSH blockade also led to a significant reduction in visceral and subcutaneous fat (3). Although not all rodent models have identified independent actions of FSH on bone homeostasis (22, 23), these preclinical data, combined with the clinical observations, suggest a potential role for FSH in the accelerated bone loss and fat accumulation early in the menopausal transition and possibly with aging.

Given the bone and fat changes during the menopausal transition and the osteoprotective and antiobesity effects of FSH blockade established in rodent models, an FSH-blocking agent may have a potential role in treating postmenopausal osteoporosis and obesity. However, there are considerable knowledge gaps in the relationship among FSH, bone, and adiposity in older humans. It is older postmenopausal women and older men who are at greatest risk for adverse bone outcomes, but clinical studies to date have not explored the independent contribution of FSH to bone loss, shift in body composition, and fracture risk in older adulthood. Cross-sectionally, in the older postmenopausal women in the Age Gene/Environment Susceptibility (AGES)-Reykjavik cohort study, we found that higher FSH was associated with lower bone density, decreased bone strength, and lower fat mass independent of estradiol and testosterone levels (24). Now, to determine the temporal relationships among FSH, bone loss, and change in body composition, we performed a longitudinal analysis of the same cohort and assessed the effects of FSH on incident vertebral fractures as an exploratory analysis. We hypothesized that higher FSH level predicts greater bone loss, fat gain, and increased vertebral fracture incidence in older men and women.

Materials and Methods

Participants

The AGES-Reykjavik study is a longitudinal, observational study of community-dwelling older adults living in and around Reykjavik, Iceland. The study was designed to examine genetic susceptibility and gene/environment interactions as contributors to phenotypes of old age, as previously described (25). A total of 5764 adults between the ages of 67 and 93 years completed the baseline AGES-Reykjavik visit between 2002 and 2006. A second study visit, completed by 3411 participants, occurred between 2007 and 2011 (Fig. 1).

Two subgroups of participants attending this second AGES-Reykjavik visit were recruited for the bone marrow adiposity (BMA) Ancillary Study. Eligibility for AGES-BMA included completion of quantitative computed tomography (QCT) scans at the AGES-Reykjavik second visit and no contraindications to magnetic resonance imaging. AGES-BMA substudy participants were brought in as 2 cohorts, with 303 participants in 2010 to 2011 (subgroup A) and 241 participants in 2014 to 2015 (subgroup B). A second AGES-BMA visit occurred after a mean follow-up of 4.7 ± 0.1 years in subgroup A (n = 172) and 1.7 ± 0.1 years in subgroup B (n = 197). Of the 175 participants who did not return for the AGES-BMA follow-up visit, 79 (45%) declined or were unable to participate, 56 (32%) died, and 40 (23%) were lost to follow-up. Of the 369 participants who attended the AGES-BMA follow-up visit, 3 were excluded from the analysis because of missing FSH measurements at the AGES-BMA baseline visit, 5 were excluded for not having QCT measurements at both AGES-BMA baseline and follow-up, and 39 were excluded for use of medications known to affect FSH and/or bone mineral density (BMD) at AGES-BMA baseline and/or follow-up, namely hormone replacement therapy (estradiol or testosterone), selective estrogen receptor modulators, glucocorticoids, antiestrogens, aromatase inhibitors, GnRH analogs, or antiandrogens. In addition, 2 female participants were excluded, 1 for suspected estradiol exposure given high estradiol and low FSH levels, and the other for an FSH level 4.9 SD above the mean, leaving 320 participants in the analytic sample (162 women and 158 men) (Fig. 1). In power calculations during study planning, we determined that the samples of 158 women and 152 men provided 80% power in 2-sided tests with a type I error rate of 5% to detect adjusted correlations of <0.10 between FSH and changes in continuous outcomes. The ancillary study was approved by the National Bioethics Committee in Iceland (VSN: 14-001-V3 and VSN: 07-062-V9), the National Institute on Aging, and the University of California, San Francisco, institutional review board. All participants provided written informed consent.

Biochemical assays

Samples were collected after an overnight fast within 2 weeks of the baseline bone and body composition measurements. Serum was stored at -80°C. FSH levels were measured on archived serum in June 2017 as a single batch

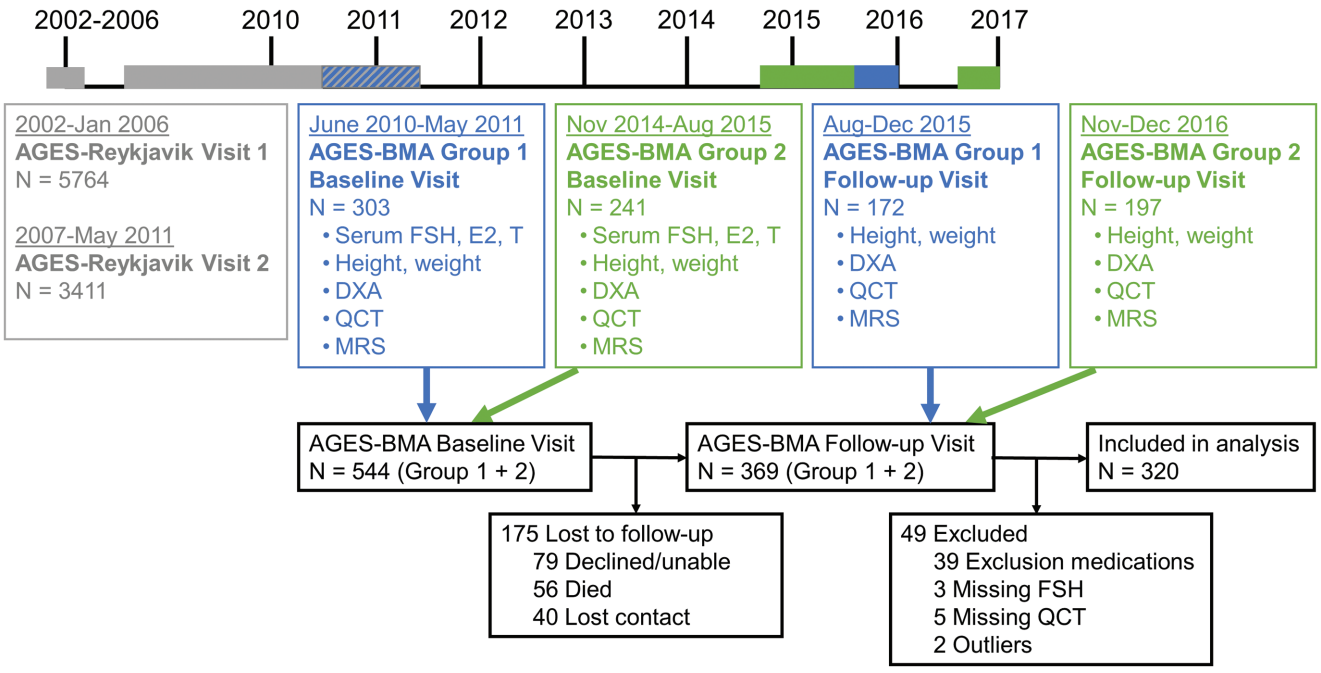

Figure 1. Study timeline, study measurements, and participants included in analysis.

using an ELISA (ALPCO, Salem, NH, USA). The assay had a sensitivity of 1 IU/L, an intra-assay coefficient of variation (CV) of 3.0%, and an inter-assay CV of 4.5%. This ELISA kit had no cross-reactivity with high levels of human chorionic gonadotropin (1000-50 000 IU/L), LH (5-250 IU/L), and TSH (5-250 mIU/L). All samples were measured in duplicate.

Sex hormones were also measured on the archived serum in January 2016 as a single batch (Endoceutics Clinique, Quebec, Canada). Total estradiol and testosterone were analyzed using gas chromatography/mass spectrometry (Shimadzu Nexera/Qtrap 6500, Shimatdzu, Kyoto, Japan). Lower limits of quantitation (LLOQ) were 1 pg/mL for estradiol and 50 pg/mL for testosterone. The inter-assay CVs at the LLOQ were 4.7% for estradiol and 3.7% for testosterone. Values were extrapolated below the LLOQ, using Analyst software (AB Sciex, Concord, Canada), for 1 estradiol level and 2 testosterone levels below the LLOQ.

QCT measures of volumetric BMD

At the baseline and follow-up visits, QCT scans were obtained for the lumbar spine and hip using a 4-detector system (Sensation; Siemens Medical Systems, Erlangen, Germany), as previously described (26). A reference standard (3-sample calibration phantom; Image Analysis Inc, Columbia, KY) was placed under the participant's spine and hips and scanned simultaneously. The lumbar spine scanning included a helical study of the L1 and L2 vertebrae (120 kVp, 150 mAs, 1-mm slice thickness, pitch = 1). A helical study of the hip (120 kVP, 140 mAs, 1-mm slice thickness, pitch = 1) included the proximal femur from a point 1 cm superior to the acetabulum to a point 3 to 5 mm inferior to the lesser trochanter. Scanner stability was monitored using stringent and reproducible daily quality assurance tests based on a phantom test, including measurements of slice geometry, spatial uniformity, density linearity, spatial resolution, and noise. The imaging center also performed weekly measurements to monitor density linearity of the calibration phantom described above and calibrated the scanner monthly against water.

QCT images were transferred to a network of computer workstations and processed to extract measures of volumetric BMD (vBMD) using analysis techniques previously described (27). For each trabecular, integral, and cortical region of interest, vBMD (mg/cm^3), bone mineral content (mg), and bone volume (cm^3) were computed. Integral BMD of the spine used the entire mid-vertebra excluding transverse elements. Spine trabecular BMD was calculated from an elliptical region in the anterior mid-vertebra. Spine compressive strength index (mg^2/cm^4) was computed from the cross-sectional area (mvCSA) and integral BMD of the mid-vertebral region (mvBMD): spine compressive strength index = mvBMD^2 × mvCSA. All scans were analyzed using the same algorithm.

Dual energy X-ray absorptiometry measures of areal BMD and prevalent and incident radiographic vertebral fractures

At the baseline and follow-up visits, participants underwent dual energy X-ray absorptiometry (DXA) scanning of the hip and anteroposterior spine for assessment of areal BMD (aBMD; mg/cm^2) and scans of the lateral spine for assessment of vertebral fracture. All scans were obtained on 1 GE Healthcare Lunar iDXA scanner (GE Healthcare, Madison, WI, USA; software version 11.4). A spine phantom demonstrating high level of reproducibility (<1% CV) was scanned regularly throughout the course of the study to monitor scanner performance. Vertebral fractures were assessed from DXA scans using the quantitative morphometry method. Semiquantitative gradings were not obtained (28). Vertebral height was measured at each evaluable level using 6 points in each vertebral body from T7 to L4. The automatic vertebral morphometry was reviewed by 2 radiographers with 5 to 10 years of vertebral fracture assessment experience, who corrected the marker placement manually if needed. Using these 6 points, the software calculated the anterior, middle, and posterior heights and their ratios as well as the average height of each vertebra. The software automatically estimated the extent of anterior or middle vertebral height reduction with respect to posterior height, classifying the vertebrae as normal (<20% reduction) or fractured (wedge, biconcave, or crush), and grading as mild (20%-25% reduction), moderate (25%-40% reduction), or severe (>40% reduction) fractures according to the criteria of Genant et al (29). A grade of moderate or severe was considered evidence of a prevalent vertebral fracture for these analyses (30). An incident radiographic vertebral fracture was defined as a new or worsening fracture at the follow-up visit, based on a change in grade of at least 1 (not including a change from grade 0 to 1) between the baseline and follow-up visits.

Body composition

Body composition measures were obtained at the baseline and follow-up visits. Height and weight were measured by study personnel and body mass index (BMI) was derived from these measurements. Abdominal visceral adipose tissue area (cm^2) and subcutaneous adipose tissue area (cm^2) were obtained by QCT imaging (Sensation; Siemens Medical Systems) using a 10-mm cross-section through the L4/L5 intervertebral space at 140 kVp, 330 mAs. The

visceral adipose tissue compartment was distinguished from subcutaneous adipose tissue manually by tracing along the fascial plane defining the internal abdominal wall, and the adipose areas were calculated using specialized software (University of California, San Francisco, CA, USA) (31, 32). Total body fat mass (kg), total body lean mass (kg), and appendicular lean mass (kg) were measured with total body DXA (GE Healthcare Lunar iDXA scanner, software version 11.4). Appendicular lean mass index was calculated as appendicular lean mass/height^2 (kg/m^2).

Other measurements

At the baseline visit, an interviewer administered a questionnaire including demographics, smoking habits, and history of medical conditions. At the baseline and follow-up visits, participants were asked to bring in all medications and supplements used in the previous 2 weeks, which were recorded and coded according to the Anatomical Therapeutic Chemical Classification System. Fasting glucose and creatinine were measured in serum obtained at the baseline visit. Diabetes was defined by self-report, diabetes medication use, and/or fasting glucose ≥ 7 mmol/L (126 mg/dL) at the baseline visit. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (33).

Statistical analyses

Baseline characteristics of participants were summarized using means and SD for continuous measures and counts and percentages for categorical measures. Annualized absolute change in the outcome measures, including BMD and body composition, was determined by subtracting the baseline value from the follow-up value, divided by the number of years between the baseline and follow-up visits. For the changes in QCT outcomes, outliers above or below the mean change ± 3 SD were trimmed at the mean change ± 3 SD; no more than 7 outliers had to be trimmed for any outcome, and trimming achieved normal distributions. Change in DXA outcomes were normally distributed and did not require trimming. Linear regression models were used to determine the associations between baseline serum FSH and annualized absolute change in bone and body composition outcomes for men and women separately, with results presented as the mean difference and the 95% CIs in outcomes per sex-specific SD increase in baseline FSH. Logistic regression models were used to evaluate the likelihood of incident vertebral fracture for every SD increase in serum FSH separately for men and women. All analyses were stratified by sex, and all models included age, subgroup (A or B), estradiol, testosterone, diabetes status, eGFR, and current smoking status. All covariates were assessed at baseline and were selected a priori based on known or biologically plausible associations with FSH and change in BMD and change in body composition (9, 34-36). Two sensitivity analyses were performed for change in bone outcomes: (1) with baseline bisphosphonate users excluded from the models and (2) with further adjustment for BMI in the models. All analyses were performed with SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics and follow-up time

A total of 162 women and 158 men were included in this analysis (Table 1). Mean ± SD age at the AGES-BMA baseline visit was 80.9 ± 4.2 years in women and 82.7 ± 4.2 years in men. The mean baseline eGFR for both sexes was in the range of stage 2 chronic kidney disease. Average time between visits was 3.3 ± 1.5 years for women and 2.7 ± 1.5 years for men. Comparing the baseline characteristics of those included in this analysis to those enrolled in AGES-BMA but not included in this analysis, the only difference was that women in this analysis had a higher mean total testosterone level than women not included (24.9 ± 15.2 ng/dL vs 21.0 ± 16.9 ng/dL, $P = 0.003$). All other characteristics were similar.

Baseline FSH and changes in bone density

Mean ± SD FSH level was 71.6 ± 21.9 IU/L in women and 18.9 ± 17.4 IU/L in men.

Women lost trabecular bone mass by vBMD at all 3 sites: lumbar spine (-1.6 mg/cm^3/y, $P < 0.01$), total hip (-1.8 mg/cm^3/y, $P < 0.01$), and femoral neck (-3.9 mg/cm^3/y, $P < 0.01$) (Table 2). There was also a decline in aBMD at the total hip (-8.6 mg/cm^2/y, $P < 0.01$) and femoral neck (-6.8 mg/cm^2/y, $P < 0.01$). Similarly, in men, loss of trabecular vBMD occurred at all 3 sites (-2.1 mg/cm^3/y at the spine, -1.2 mg/cm^3/y at the total hip, and -3.7 mg/cm^3/y at the femoral neck; $P < 0.01$), and loss of areal BMD was seen at the total hip (-7.8 mg/cm^2/y, $P < 0.01$) and femoral neck (-9.0 mg/cm^2/y, $P < 0.01$). Cortical bone measurements were either unchanged or increased in both sexes, and there was no change in spine compressive strength nor aBMD at the lumbar spine.

Neither women nor men demonstrated statistically significant associations between baseline FSH and changes in any of the BMD or strength measures, in fully adjusted models (Table 3, Fig. 2). Among women, the mean difference in annualized femoral neck aBMD change (95% CI) per SD increase in FSH was 1.3 (-0.7 to 3.3) mg/cm^2/y. This

Table 1. Baseline characteristics, stratified by sex

	Women (n = 162)	Men (n = 158)
Age, y, mean ± SD	80.9 ± 4.2	82.7 ± 4.2
FSH, IU/L, mean ± SD	71.6 ± 21.9	18.9 ± 17.4
Total testosterone, ng/dL, mean ± SD	24.9 ± 15.2	393.9 ± 164.8
Total estradiol, pg/mL, mean ± SD	5.3 ± 4.5	20.0 ± 6.9
Diabetes, n (%)	8 (4.9)	25 (15.8)
Current smoker, n (%)	16 (9.9)	2 (1.3)
eGFR, mL/min/1.73 m^2, mean ± SD	65.8 ± 15.1	62.5 ± 15.2
Time between visits, y, mean ± SD	3.3 ± 1.5	2.7 ± 1.5
Bone parameters, mean ± SD		
Lumbar spine BMD		
Areal BMD, mg/cm^2	1067.1 ± 175.6	1253.7 ± 217.3
Trabecular vBMD, mg/cm^3	65.5 ± 29.1	75.9 ± 31.2
Integral vBMD, mg/cm^3	180.3 ± 34.2	194.3 ± 37.6
Compressive strength index, mg^2/cm^4	123.7 ± 89.1	204.4 ± 150.6
Total hip BMD		
Areal BMD, mg/cm^2	832.4 ± 119.3	975.0 ± 145.0
Trabecular vBMD, mg/cm^3	50.2 ± 30.1	67.7 ± 34.2
Integral vBMD, mg/cm^3	210.0 ± 36.8	226.6 ± 40.7
Cortical vBMD, mg/cm^3	507.0 ± 35.8	528.0 ± 35.7
Femoral neck BMD		
Areal BMD, mg/cm^2	786.4 ± 105.7	903.0 ± 135.7
Trabecular vBMD, mg/cm^3	27.3 ± 35.2	41.9 ± 40.1
Integral vBMD, mg/cm^3	219.8 ± 38.5	230.5 ± 41.7
Cortical vBMD, mg/cm^3	522.8 ± 41.8	538.4 ± 41.7
Prevalent vertebral fracture, n, %	29 (18.0)	34 (21.5)
Body composition parameters, mean ± SD		
Weight, kg	71.1 ± 12.3	82.4 ± 11.6
BMI, kg/m^2	27.5 ± 4.4	26.7 ± 3.3
Visceral fat area, cm^2	168.6 ± 68.1	221.9 ± 83.9
Subcutaneous fat area, cm^2	295.3 ± 103.7	204.4 ± 68.8
Total body fat mass, kg	29.9 ± 8.7	27.2 ± 7.7
Percent total body fat mass, %	41.4 ± 6.2	32.5 ± 5.4
Total body lean mass, kg	39.0 ± 4.6	52.4 ± 5.7
Percent total body lean mass, %	55.8 ± 6.0	63.9 ± 5.1
Appendicular lean mass index, kg/m^2	6.4 ± 0.8	7.4 ± 0.8

Abbreviations: BMD, bone mineral density; BMI, body mass index; eGFR, estimated glomerular filtration rate; vBMD, volumetric bone mineral density.

indicates that the annual change in femoral neck aBMD associated with a difference of 1 SD in FSH was within the range of -0.09% to +0.42% of the average baseline femoral neck aBMD in women. Results were similar when adjusting the model for only age, subgroup, and sex hormones. In a sensitivity analysis excluding the 2 men (1.3%) and 12 women (7.4%) on bisphosphonate therapy, findings were similar. Likewise, further adjustment for BMI in the models did not change the point estimates meaningfully.

Baseline FSH and incident vertebral fractures

Incident radiographic vertebral fractures were observed in 26 women (16.1%) and 27 men (17.1%). No statistically significant association was identified between baseline FSH and adjusted odds for incident vertebral fracture per SD increase in baseline FSH (odds ratio [OR] in women: 1.40, 95% CI, 0.87-2.28; OR in men: 0.72, 95% CI, 0.39-1.31).

Baseline FSH and changes in body composition

Women and men had slight declines in weight (-0.3 kg/y in women, -0.5 kg/y in men; $P < 0.01$) and total body lean mass (-0.1 kg/y in women, -0.2 kg/y in men; $P < 0.01$) during the follow-up period (Table 2). In addition, women had a very modest mean decrease in total body fat mass (-0.2 kg/y, $P = 0.02$) and men had a decrease in subcutaneous fat area (-3.7 cm^2/y, $P < 0.01$).

In neither women nor men were statistically significant associations detected between baseline FSH and change in

Table 2. Annualized absolute BMD and body composition change

	Women (n = 162)		Men (n = 158)	
	Mean (95% CI)	*P*	Mean (95% CI)	*P*
Bone changes				
Lumbar spine BMD				
Areal BMD, mg/cm^2/y	-3.8 (-8.7 to 1.1)	0.12	+0.3 (-5.6 to 6.2)	0.92
Trabecular vBMD, mg/cm^3/y	-1.6 (-2.3 to -0.8)	<0.01	-2.1 (-3.0 to -1.3)	<0.01
Integral vBMD, mg/cm^3/y	-0.4 (-1.1 to 0.3)	0.22	-0.6 (-1.4 to 0.1)	0.09
Compressive strength index, mg^2/cm^4/y	-0.8 (-3.3 to 1.7)	0.54	-0.9 (-4.1 to 2.4)	0.60
Total hip BMD				
Areal BMD, mg/cm^2/y	-8.6 (-10.3 to -6.9)	<0.01	-7.8 (-9.6 to -6.1)	<0.01
Trabecular vBMD, mg/cm^3/y	-1.8 (-2.2 to -1.5)	<0.01	-1.2 (-1.5 to -0.8)	<0.01
Integral vBMD, mg/cm^3/y	-1.9 (-2.4 to -1.3)	<0.01	-1.0 (-1.6 to -0.4)	<0.01
Cortical vBMD, mg/cm^3/y	-0.2 (-0.8 to 0.5)	0.65	+1.0 (0.2 to 1.8)	0.01
Femoral neck BMD				
Areal BMD, mg/cm^2/y	-6.8 (-8.6 to -4.9)	<0.01	-9.0 (-11.3 to -6.7)	<0.01
Trabecular vBMD, mg/cm^3/y	-3.9 (-4.8 to -2.9)	<0.01	-3.7 (-4.6 to -2.8)	<0.01
Integral vBMD, mg/cm^3/y	-0.4 (-1.1 to 0.3)	0.26	+0.1 (-0.7 to 0.8)	0.84
Cortical vBMD, mg/cm^3/y	+2.4 (0.9 to 3.9)	<0.01	+1.8 (0.2 to 3.4)	0.03
Incident vertebral fracture, n, %	26 (16.1)	--	27 (17.1)	--
Body composition changes				
Weight, kg/y	-0.3 (-0.5 to -0.1)	<0.01	-0.5 (-0.8 to -0.2)	<0.01
BMI, kg/m^2/y	-0.03 (-0.1 to 0.04)	0.40	-0.1 (-0.2 to 0.02)	0.10
Visceral fat area, cm^2/y	-0.9 (-2.6 to 0.9)	0.33	-0.8 (-4.0 to 2.3)	0.61
Subcutaneous fat area, cm^2/y	-2.4 (-5.0 to 0.2)	0.07	-3.7 (-6.0 to -1.4)	<0.01
Total body fat mass, kg/y	-0.2 (-0.4 to -0.03)	0.02	-0.2 (-0.4 to 0.03)	0.09
Percent total body fat mass, %/y	-0.1 (-0.3 to 0.04)	0.13	-0.1 (-0.3 to 0.1)	0.47
Total body lean mass, kg/y	-0.1 (-0.2 to -0.1)	<0.01	-0.2 (-0.4 to -0.1)	<0.01
Percent total body lean mass, %/y	+0.1 (-0.03 to 0.3)	0.11	+0.1 (-0.1 to 0.3)	0.42
Appendicular lean mass index, kg/m^2/y	+0.003 (-0.02 to 0.02)	0.78	-0.01 (-0.04 to 0.02)	0.53

P value: test of location (Student *t* test) that mean change in the continuous variable is equal to 0.
Abbreviations: CI, confidence interval; BMD, bone mineral density; BMI, body mass index; vBMD, volumetric bone mineral density.

any of the body composition measures (Table 4, Fig. 3). Among women, 2 associations approached statistical significance. The mean difference in annualized weight change (95% CI) for each SD increase in FSH was 0.20 (-0.01 to 0.42) kg/y ($P = 0.07$), and the mean difference in annualized change in visceral fat area (95% CI) was 1.80 (-0.03 to 3.62) cm^2/y ($P = 0.06$). Considering the 95% CI, results for FSH and weight change in women indicate that the annual change associated with a difference 1 SD in FSH was within the range of -0.01% to +0.59% of the average baseline weight. For visceral fat, the annual change associated with a SD difference in FSH was within the range of -0.02% to +2.15% of the average baseline visceral fat area.

Discussion

We report the first longitudinal analysis of the relationship between baseline serum FSH level and changes in body composition in older women and men. This is also the first longitudinal study to consider the relationship between serum FSH, bone loss, and incident vertebral fracture in older postmenopausal women. Despite preclinical evidence and cross-sectional relationships in this population, we found that FSH level at baseline was not statistically significantly associated with bone loss or body composition changes over 3 years in an older population.

For changes in BMD, we found no statistically significant associations with baseline FSH level. Even at the limits of the 95% CIs, the differences in BMD change per SD increase in baseline FSH level were small. For example, we can exclude an annualized difference in change in total hip aBMD per SD increase in FSH in men that is outside the bounds of our 95% CI of -2.0 to +1.8 mg/cm^2/y. Although the lower limit of the 95% CI (-2.0 mg/cm^2/y) is compatible with our hypothesis that higher FSH is associated with more rapid bone loss, the degree of this increased bone loss is very modest. This additional 2.0 mg/cm^2/y of bone loss corresponds to 0.2% of the baseline total hip aBMD of 975 mg/cm^2. It would take 25 years to reach a difference of 5%, the minimum standard for change that can be

Table 3. Adjusted mean difference in change in BMD per SD increase in baseline FSH

	Women (n = 162)		Men (n = 158)	
	Difference (95% CI)	*P*	Difference (95% CI)	*P*
Lumbar spine BMD				
Areal BMD, mg/cm^2/y	0.8 (-4.4 to 5.9)	0.77	-2.0 (-8.2 to 4.3)	0.54
Trabecular vBMD, mg/cm^3/y	0.1 (-0.8 to 0.9)	0.85	-0.7 (-1.6 to 0.2)	0.14
Integral vBMD, mg/cm^3/y	0.4 (-0.3 to 1.1)	0.22	-0.3 (-1.1 to 0.5)	0.49
Compressive strength index, mg^2/cm^4/y	-0.5 (-3.2 to 2.1)	0.70	-1.3 (-4.9 to 2.3)	0.47
Total hip BMD				
Areal BMD, mg/cm^2/y	0.6 (-1.3 to 2.4)	0.55	-0.1 (-2.0 to 1.8)	0.93
Trabecular vBMD, mg/cm^3/y	-0.2 (-0.5 to 0.2)	0.35	0.1 (-0.3 to 0.5)	0.64
Integral vBMD, mg/cm^3/y	-0.2 (-0.7 to 0.3)	0.45	-0.2 (-0.8 to 0.5)	0.63
Cortical vBMD, mg/cm^3/y	-0.5 (-1.1 to 0.2)	0.18	-0.2 (-1.0 to 0.6)	0.64
Femoral neck BMD				
Areal BMD, mg/cm^2/y	1.3 (-0.7 to 3.3)	0.20	-0.2 (-2.6 to 2.2)	0.84
Trabecular vBMD, mg/cm^3/y	-0.6 (-1.5 to 0.4)	0.24	-0.1 (-1.0 to 0.9)	0.91
Integral vBMD, mg/cm^3/y	0.04 (-0.6 to 0.7)	0.90	0.1 (-0.7 to 0.9)	0.77
Cortical vBMD, mg/cm^3/y	-0.6 (-2.1 to 0.8)	0.40	-0.8 (-2.5 to 0.9)	0.37

P value: linear regression for FSH coefficient equal to 0 (no effect). Model adjusted for age, subgroup (A or B), estradiol, testosterone, diabetes, eGFR, smoking.
Abbreviations: BMD, bone mineral density; eGFR, estimated glomerular filtration rate; vBMD, volumetric bone mineral density.

detected by DXA (37). Therefore, we feel confident there was not a clinically meaningful relationship between FSH and changes in bone outcomes.

For change in weight and visceral fat, our results for women approached statistical significance, and the CIs for these results cannot exclude possible modest associations. For example, our best estimate for change in visceral fat in women corresponded with an average increase of 1.80 cm^2/y for each SD increase in baseline FSH level, whereas the upper limit of our 95% CI corresponded with an increase of 3.62 cm^2/y. This additional 3.62 cm^2 gain in visceral fat area is 2.1% of the baseline visceral fat area at 168.6 cm^2, meaning that it would take 2 to 3 years to have an extra 5% gain in visceral fat per SD increase in FSH. Although the magnitude of this change may appear small, it might be clinically meaningful especially given an average annual decrease in visceral fat of -0.9 cm^2/y among all women in this analysis.

It has been shown previously that baseline FSH levels were strongly correlated with the rate of bone loss during the menopausal transition, measured by both DXA and bone turnover marker levels (6-8, 38-45). The Study of Women's Health Across the Nation (SWAN), in particular, further found that the magnitude of change in serum FSH best predicted the changes in spine and hip BMD transmenopausally (8). However, in the 2 to 5 years after the final menstrual period, when FSH levels plateau and remain relatively stable thereafter (46), SWAN showed that serum FSH was no longer associated with rates of lumbar spine or hip bone loss (47). In addition, a randomized controlled trial of a GnRH agonist to suppress FSH did not show a reduction in bone turnover markers after 105 days in postmenopausal women in their mid-60s (48). These findings are consistent with our observations in this AGES-BMA cohort of older postmenopausal women about 30 years out from menopause. First, our previous cross-sectional analysis in AGES-BMA did demonstrate that FSH was negatively associated with bone density and strength in older postmenopausal women (24). Now, we find no evidence of longitudinal relationships between higher FSH level and decline in bone mass and strength. We thus postulate that the signal we observed in the cross-sectional analysis reflected what had happened decades ago during the menopausal transition, when FSH changed rapidly. We further hypothesize that the effects of FSH on bone are attenuated in older age because of more stable FSH levels, likely resulting in FSH receptor down-regulation. In men, for whom there is not a prominent physiologic shift in FSH level as there is for women, the stability of FSH level may also explain why we found no association between FSH and bone either cross-sectionally or longitudinally.

FSH has not been found to be associated with BMD in younger men. A recent study of the effect of elevated FSH in infertile men with spermatogenic failure found that there were no differences in BMD compared with age-matched healthy men both at baseline and at follow-up 15 years later (10). A randomized trial showed that suppressing FSH with GnRH agonists and testosterone replacement in young eugonadal men did not change the bone turnover markers compared with placebo (11). Although a case-control study of middle-aged men described a negative association between FSH and BMD at the lumbar

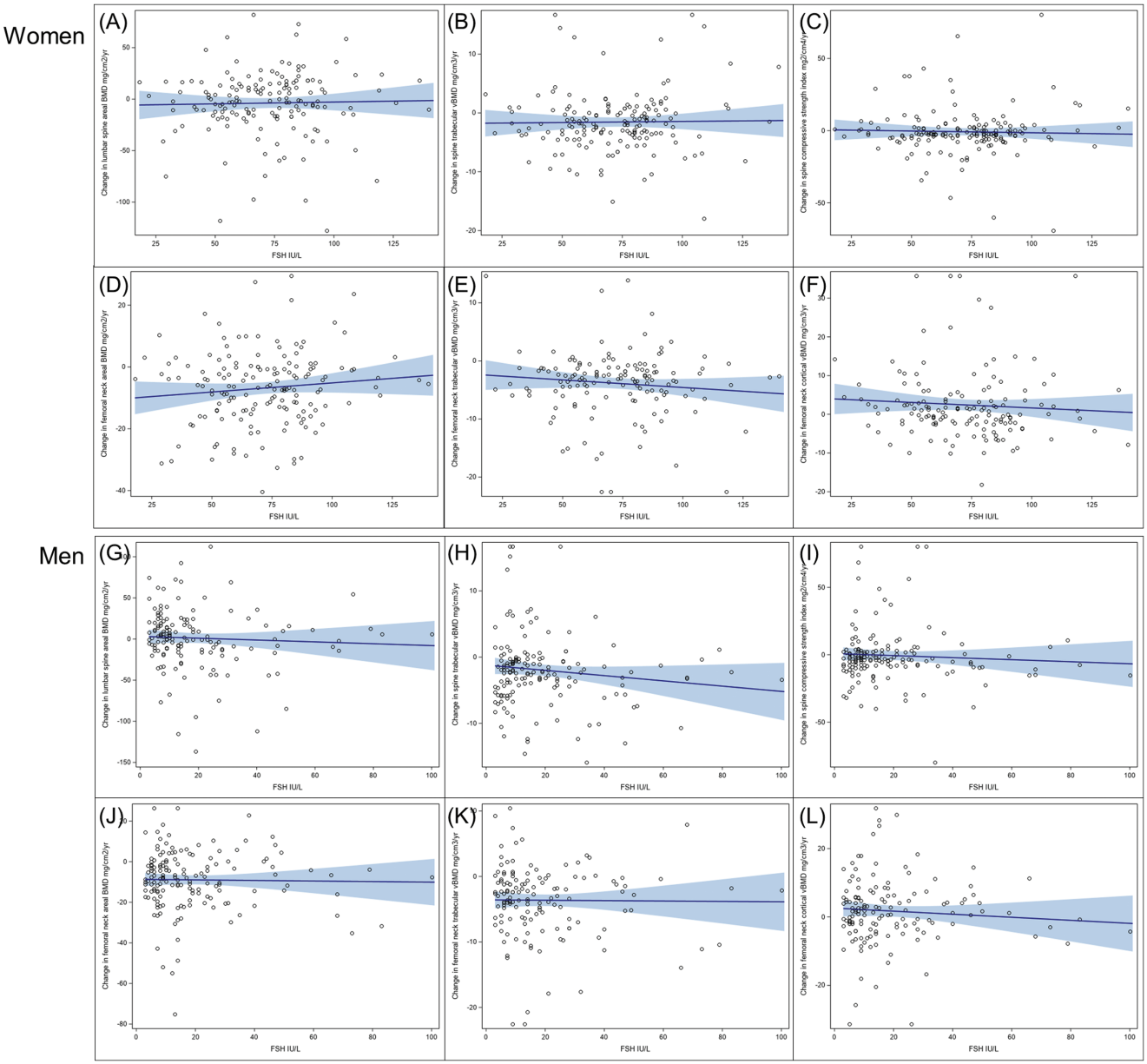

Figure 2. Adjusted annualized absolute change in BMD as a function of baseline FSH. Linear regression graphs adjusted for age, subgroup, estradiol, testosterone, diabetes, eGFR, and smoking, representing the association between baseline FSH and annualized absolute change in (A, G) lumbar spine aBMD, (B, H) spine trabecular vBMD, (C, I) spine compressive strength index, (D, J) femoral neck aBMD, (E, K) femoral neck trabecular vBMD, and (F, L) femoral neck cortical vBMD in women and men, respectively. The 95% CI is shaded in light blue. aBMD, areal bone mineral density; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; vBMD, volumetric bone mineral density.

spine and femoral neck (49), the study did not adjust for testosterone level. The only other longitudinal study to examine the relationship between sex hormones and bone loss in older men is the Concord Health and Aging in Men Project (CHAMP) in Australia, which reported that serum FSH levels were negatively associated with total hip BMD changes (50, 51). CHAMP analyses included 901 men followed for 5 years. To explore whether the differences between their findings and our findings were due to the greater power in the CHAMP study, we compared the reported associations. The estimated loss of total hip BMD per year in the CHAMP cohort for each 1 SD (15 IU/L) increase in baseline FSH was -15.4 mg/cm^2/y. Our lower limit for change in total hip aBMD for men per SD (17 IU/L) increase in baseline FSH level was just -2.0 mg/cm^2/y. Thus, the association identified by CHAMP was much stronger than associations within the likely range for our cohort. The reason for these contrasting results is not clear. A potential explanation is that CHAMP did not adjust for estrogen or testosterone in its multivariate model.

Table 4. Adjusted mean difference in change in body composition per SD increase in FSH

	Women (n = 162)		Men (n = 158)	
	Difference (95% CI)	*P*	Difference (95% CI)	*P*
Weight, kg/y	0.20 (-0.01 to 0.42)	0.07	0.04 (-0.29 to 0.36)	0.82
BMI, kg/m^2/y	0.07 (-0.02 to 0.15)	0.13	0.01 (-0.09 to 0.12)	0.78
Visceral fat area, cm^2/y	1.80 (-0.03 to 3.62)	0.06	-0.33 (-3.73 to 3.06)	0.85
Subcutaneous fat area, cm^2/y	0.71 (-2.11 to 3.53)	0.62	-0.59 (-2.97 to 1.80)	0.63
Total body fat mass, kg/y	0.15 (-0.04 to 0.33)	0.12	0.06 (-0.18 to 0.30)	0.64
Percent total body fat mass, %/y	0.08 (-0.10 to 0.26)	0.38	0.05 (-0.14 to 0.25)	0.59
Total body lean mass, kg/y	0.04 (-0.06 to 0.14)	0.45	-0.05 (-0.21 to 0.11)	0.56
Percent total body lean mass, %/y	-0.08 (-0.25 to 0.10)	0.40	-0.06 (-0.25 to 0.13)	0.56
Appendicular lean mass index, kg/m^2/y	0.001 (-0.02 to 0.02)	0.94	-0.004 (-0.03 to 0.03)	0.81

P value: linear regression for FSH coefficient equal to zero (no effect). Model adjusted for age, subgroup (A or B), estradiol, testosterone, diabetes, eGFR, smoking.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate.

However, CHAMP reported only weak correlations between testosterone or estradiol and bone loss (50). Another difference between studies is that we excluded participants who took glucocorticoids or medications known to affect the hypothalamic-pituitary-gonadal axis, whereas the CHAMP study did not. Finally, our study measured changes in bone by QCT as well as DXA, and our results were similar across these 2 methods.

The incidence of radiographic vertebral fracture in our AGES-BMA cohort was not statistically different across baseline FSH levels in either men or women. Our power was more limited for this outcome, and our results are also compatible with a modest increase in vertebral fracture risk, particularly in women. In women, the SWAN study evaluated the relationship between sex hormones and self-reported incident fracture risk over the menopausal transition and reported that higher FSH was not correlated with fractures (relative risk = 1.06; 95% CI, 0.95-1.17) (52). Similarly, in men, the CHAMP study did not show a significant adjusted association between higher FSH and any clinical fractures (hazard ratio = 1.08; 95% CI, 0.93-1.22) (50).

Prospective cohort studies have observed shifts in body composition in women going through the menopause transition, specifically accelerated gains in fat mass and losses of lean mass (53-57). Longitudinal data from the SWAN Michigan subcohort found that over 6 years across the menopause transition, increasing levels of FSH were associated with increasing fat mass and waist circumference, even after adjusting for baseline measures and age (15). The direction of the SWAN Michigan findings was consistent with FSH's effects on body fat regulation that have been described in rodent models (3, 4). We now report the first longitudinal analysis of the relationship between a baseline FSH level and subsequent change in body composition in older postmenopausal women, in whom FSH levels are generally high but stable. In our AGES-BMA population, there was an overall clinically small loss of weight, total body fat mass (driven by the loss of subcutaneous fat area), and total body lean mass. These findings are consistent with the observation that body weight decreases after the age of 60 years primarily because of loss of lean mass, whereas there is a preferential increase in visceral fat and a decrease in subcutaneous fat (58, 59). FSH has been implicated to play a role in not only fat accumulation, but also fat mass redistribution in animal models, in that visceral adipocyte cell size is affected to a greater extent than subcutaneous adipocyte cell size (4). In our human cohort, we showed no evidence of an association between FSH and these body composition changes. Interestingly, though, our previously published cross-sectional analysis of the same cohort showed an inverse relationship between FSH and body fat (24), similar to what was seen perimenopausally in other studies (60-62). Given that direction of causality cannot be determined with a cross-sectional design, a possible explanation is that the greater fat mass caused the lower FSH level, via feedback inhibition from greater estrogen production from aromatization in fat tissue.

We hypothesized that FSH would be associated with changes in body composition in older men. A recent randomized clinical trial investigated the metabolic consequences of GnRH agonists, which suppress FSH secretion, vs orchiectomy, which leads to increased FSH, in men with advanced prostate cancer. The study found that those who underwent orchiectomy had greater increases in body weight, total fat mass, and subcutaneous adiposity, with a trend toward higher visceral fat (63). However, as in our longitudinal results in older women, we found that baseline FSH did not predict changes in body composition in this population. Our finding is consistent with previous cross-sectional observational studies in men regardless of age, showing no correlation between FSH and

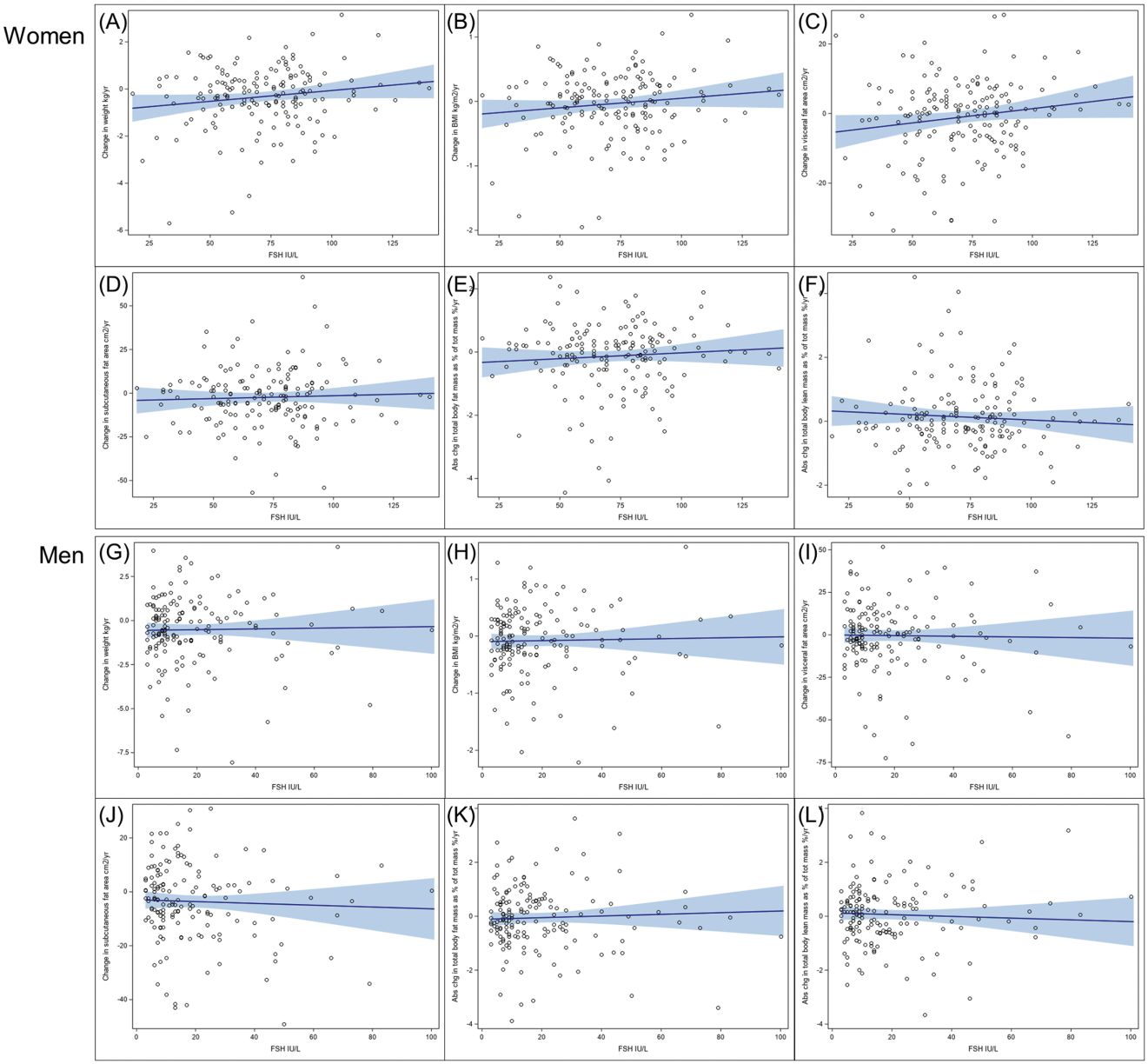

Figure 3. Adjusted annualized absolute change in body composition as a function of baseline FSH. Linear regression graphs adjusted for age, subgroup, estradiol, testosterone, diabetes, eGFR, and smoking, representing the association between baseline FSH and annualized absolute change in (A, G) weight, (B, H) BMI, (C, I) visceral fat area, (D, J) subcutaneous fat area, (E, K) percent total body fat mass, and (F, L) percent total body lean mass in women and men, respectively. The 95% CI is shaded in light blue. BMI, body mass index; eGFR, estimated glomerular filtration rate.

BMI (64-67). This supports our new explanatory model that the effects of FSH are most prominent and clinically apparent during times of marked alterations, such as the menopausal transition.

We excluded 1 female participant from this longitudinal analysis based on her markedly elevated FSH level that was 4.9 SD above the mean (FSH level, 180.0 IU/L). This participant also had substantial decreases in BMD outcomes and increases in body composition measures over 1.8 years of follow-up. She experienced a decrease in total hip aBMD of 4.4%/y and in femoral neck aBMD of 5.1%/y and had an increase in weight of 3.2 kg/y and percent total body fat mass of 3.7%/y. This participant had no reported significant comorbidities, except for mild cognitive impairment, and was not on any medication known to affect these outcomes. She had a prevalent vertebral fracture at the baseline visit. Her notably high FSH level could represent measurement error or it may represent a biologic anomaly. It is, therefore, interesting that this participant with an abnormally high level of FSH happened to experience a large magnitude of change in BMD and body composition outcomes in concordance with our hypotheses. In addition to

requiring a dynamic shift in FSH, there may be a threshold level above which an effect on bone and fat mass may be observed.

A major strength of our study is the longitudinal design with a large cohort of community-dwelling older adults in whom bone health and body composition are well characterized, enabling us to examine the temporal relationships between reproductive hormones and change in bone and fat stratified by sex. Our cohort is sufficiently large based on our power calculation. For bone outcomes, we had measurements using 2 different methods, DXA and QCT. We were able to account for various potential confounders, most importantly sex steroid levels. One limitation is that approximately one-third of participants were lost to follow-up from baseline without repeat imaging. Of those who did not follow up, one-third died whereas the rest lost contact, or declined or were unable to participate. Dropouts in older adult populations are expected because of the high frailty and mortality rate leading to inability to follow-up. Although the baseline characteristics of those who returned for follow-up and those who did not were similar in our study, the high proportion of dropout has a potential biasing effect of preferentially selecting healthier individuals and, therefore, may underestimate bone and fat loss and incident vertebral fractures. The relatively short follow-up duration and the difference in follow-up between the 2 subcohorts were also limitations. However, we addressed the latter by normalizing the outcomes into annualized changes; this assumes that the rate of BMD loss is relatively stable in older adults, an assumption we think is reasonable over the follow-up period in this study. Unmeasured and residual confounding is always a concern in observational studies. In addition, our study was conducted in a population that is predominantly white, and thus the results may not be generalizable to all other groups.

In conclusion, we observed no evidence of longitudinal relationships between baseline FSH and subsequent changes in bone mass and body composition after approximately 3 years in community-dwelling, predominantly white, older postmenopausal women and older men. Likewise, we also did not find evidence that FSH predicts incident vertebral fractures in this population. These findings suggest that the effects of FSH on bone and fat previously reported in preclinical and clinical studies seem to dampen in a more aged population, at a stage of life with relatively high but stable serum FSH levels. More longitudinal clinical studies with longer follow-up and more diverse populations are needed to further characterize the effect of FSH on bone health and fat metabolism and its interaction with other hormones in the older population. Adequately powered studies are needed to assess whether FSH levels influence fracture risk in older adults.

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Additional Information

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Data Availability: Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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