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Bone Mineral Density and Age-Related Maculopathy in Older Women

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OBJECTIVES: To determine whether bone mineral density (BMD) is associated with age-related maculopathy (ARM) risk in older women.

DESIGN: Cross-sectional analysis at Year 10 (1997/98) of the Study of Osteoporotic Fractures (SOF).

SETTING: Four clinical centers in the United States.

PARTICIPANTS: One thousand forty-two randomly sampled SOF participants who attended the Year 10 clinic visit.

MEASUREMENTS: ARM status was determined from fundus photographs using a modification of the Wisconsin Age-Related Maculopathy Grading System 6-level severity scale used in the National Health and Nutrition Examination Survey III. Total hip BMD was measured at Year 10 using dual-energy x-ray absorptiometry. Information on potential confounders, including age, reproductive hormone exposures, body mass index, smoking, alcohol consumption, nutrition, education, diabetes mellitus, hypertension, and physical activity, was ascertained with questionnaires.

RESULTS: The prevalence of ARM was 50% (46% had early ARM and 4% had late ARM). After potential confounder adjustment, greater BMD was associated with lower odds of ARM (odds ratio (OR) per 1 standard deviation increase in BMD = 0.82, 95% confidence interval (CI) = 0.70–0.96). Women in the highest quartile of BMD

had lower odds of ARM than those in the lowest quartile (OR = 0.63, 95% CI = 0.41–0.97) and those in the lowest three quartiles combined (OR = 0.66, 95% CI = 0.48–0.91).

CONCLUSION: Higher levels of BMD may be associated with lower risk for ARM. The underlying mechanism is unknown, although BMD may be a marker for lifetime endogenous estrogen exposure. Future studies are needed to replicate these findings and further investigate the nature of the relationship between BMD and ARM. *J Am Geriatr Soc* 55:740–746, 2007.

Key words: age-related macular degeneration; age-related maculopathy; bone density

Age-related maculopathy (ARM), a disease characterized by progressive loss of central vision, is a leading cause of severe vision impairment in persons aged 65 and older in developed countries.¹ It is estimated that approximately 9 million people aged 40 and older in the United States have some form of ARM, with 1.75 million having late ARM, which is associated with the most-severe vision loss, and 7.3 million having characteristics associated with early ARM and thus at high risk of progressing to advanced disease.² Large drusen and abnormalities of the retinal pigment epithelium, including hyperpigmentation and hypopigmentation, characterize early ARM.³ Drusen are extracellular deposits of proteins, lipids, and cellular debris that accumulate between the retinal pigment epithelium and Bruch's membrane and are considered to be the hallmark lesions of ARM.^{4,5} Geographic atrophy or choroidal neovascularization characterize late ARM. Geographic atrophy refers to well-delineated areas of retinal pigment epithelium loss, often with exposure of choroidal vessels.⁵ Choroidal neovascularization ("wet" or "exudative" ARM) occurs when new blood vessels sprout from the choriocapillaris through Bruch's membrane into

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the subretinal spaces, often resulting in leakage of blood, scarring, and severe vision loss.⁵

The pathogenesis of ARM is poorly understood, and treatment options are limited, especially in “dry” ARM (early ARM and geographic atrophy), which comprises approximately 90% of cases.⁶ The Age-Related Eye Disease Study showed that antioxidant and zinc supplementation decreased risk of disease progression, with little effect on prevention of disease onset.⁷ Thus, identifying preventive measures remains an important goal.

Although evidence supporting a higher prevalence of ARM in women than in men has been inconclusive,^{8–12} there has been great interest, but little consensus, as to whether reproductive hormone exposures may be associated with disease risk. For example, the 1992 Eye Disease Case Control Study group observed an inverse association between exogenous postmenopausal hormone therapy (estrogen alone (ET) or estrogen plus progestin (HT)) and exudative ARM, although the same study observed greater odds of ARM associated with parity greater than zero.¹³ The Beaver Dam Eye Study found a modest, borderline protective association of years of ET or HT use with any ARM cross-sectionally (odds ratio (OR) = 0.98, 95% confidence interval (CI) = 0.96–1.00; N = 2,761),¹⁴ although a later study of 5-year incident ARM did not support this finding.¹⁵ Although several studies examined the association between ET or HT and ARM, observational studies of ET and HT have inherent biases and should be interpreted with caution, as highlighted by the Women’s Health Initiative findings regarding HT and coronary heart disease that directly contradicted prior observational data.

Regarding endogenous estrogen exposure, the Blue Mountains Eye Study found modestly, but significantly so, lower risk for early ARM with longer reproductive life, measured according to greater length of time between menarche and menopause (OR = 0.97, 95% CI = 0.95–0.99; N = 1,899).¹⁶ In addition, the Rotterdam Study found that women who reached early menopause surgically after unilateral or bilateral oophorectomy before age 45 had a higher prevalence of ARM than women who reached menopause at age 45 and older (relative risk = 3.8, 95% CI = 1.1–12.6; N = 354),¹⁷ although there was no association between those reaching early menopause naturally and ARM.

Although exogenous postmenopausal hormone therapy and markers of lifetime endogenous estrogen exposure such as number of reproductive years, ages at menarche and menopause, and surgical menopause have been examined in relation to ARM risk, the association between bone mineral density (BMD) and ARM has not been investigated. BMD has been considered a surrogate marker for lifetime endogenous estrogen exposure. Bone contains estrogen receptors and is sensitive to circulating estrogen levels.^{18,19} Furthermore, it is believed that estrogen deficiency is the predominant cause of postmenopausal bone loss.²⁰ Parity, days of menstruation, ages at menarche and menopause, and number of reproductive years are associated with BMD.^{21,22} Endogenous estrogen levels were shown to be positively associated with BMD in older women,²³ and greater BMD is associated with higher risk for breast cancer.²⁴

Because of the lack of data regarding the association between BMD and ARM, the present study sought to

explore the association between BMD and ARM in Caucasian women aged 75 and older.

METHODS

Subjects

Subjects consisted of a random sample of participants attending the Year 10 clinic visit of the Study of Osteoporotic Fractures (SOF), a multicenter prospective cohort study originally designed to identify risk factors for osteoporotic fractures. A cohort of 9,704 Caucasian women aged 65 and older were recruited from community-based listings (health plan membership lists, voter registration lists, and Department of Motor Vehicles tapes) and enrolled in SOF between 1986 and 1988 at the following clinical centers: The Kaiser Foundation Research Institute and Center for Health Research, Portland, Oregon; the Epidemiology Clinical Research Center at the University of Minnesota, Minneapolis, Minnesota; Monongahela Valley Clinic of the University of Pittsburgh, Monessen, Pennsylvania; and the University of Maryland Osteoporosis Clinic, Baltimore, Maryland. Of the 9,704 women enrolled at baseline, approximately 7,672 were eligible for the Year 10 clinic visit in 1997/98. Of those eligible, 4,820 (63%) attended the clinic visit. Fundus photographs were taken at Year 10 and were graded for a subset of subjects that included 1,123 randomly sampled Caucasians that had not had an incident first fracture in the previous 5-year interval. In this random sample, fundus photographs were gradable in one or both eyes for 1,065 (95%) subjects. Of those with gradable photos, total hip BMD measurement was available for 1,042. Thus, 1,042 subjects were included in the present study. The subjects in the random sample who were not included in the present analysis (n = 81) were slightly older (median age 80 vs 79; *P* = .05) and more likely to have rated themselves as in fair or poor health (30% vs 18%; *P* = .007) than subjects included in the study. They did not differ in terms of other measures of estrogen exposure, such as surgical menopause, age at menopause, or ET or HT use. The institutional review boards at each institution approved SOF, all participants gave written informed consent, and the University of California at Los Angeles medical institutional review board approved the study.

Measurement of ARM

Two independent reviewers graded 45° stereoscopic fundus photographs for ARM in a masked fashion using a modification of the Wisconsin Age-Related Maculopathy Grading System²⁵ used in the National Health and Nutrition Examination Survey III.^{26,27} ARM characteristics were summarized using a six-level severity scale used in the Beaver Dam Eye Study²⁸ and modified for use with 45° stereoscopic photographs (Figure 1). Late ARM was defined as the presence of subfoveal geographic atrophy or exudative ARM (level 50 or 60) in at least one eye. Early ARM was defined as soft drusen ($\geq 95 \mu\text{m}$) with drusen area less than $960 \mu\text{m}$ and retinal pigment epithelium depigmentation or drusen area of $960 \mu\text{m}$ or more with or without pigmentary abnormalities (level 30 or 40) in at least one eye with no evidence of late ARM in either eye.

Level	Description
10	No drusen, or hard drusen or small drusen <95 μ m in diameter only, regardless of area of involvement, and no pigmentary abnormality present
20	Hard drusen or small drusen <95 μ m in diameter, regardless of area of involvement, with increased retinal pigment present but no RPE depigmentation; or soft drusen (≥ 95 μ m) with drusen area <960 μ m and no pigment abnormalities present
30	Soft drusen (≥ 95 μ m) with drusen area <960 μ m and RPE depigmentation present; or soft drusen with drusen area ≥ 960 μ m with or without increased retinal pigment but no RPE depigmentation
40	Soft drusen (≥ 95 μ m) with drusen area ≥ 960 μ m and RPE depigmentation present with or without increased retinal pigment
50	Geographic atrophy under the fovea
60	Exudative macular degeneration with or without geographic atrophy present

RPE = retinal pigment epithelium.

Figure 1. Age-related maculopathy (ARM) 6-level severity scale. No ARM = level 10 or 20 in both eyes. Early ARM = level 30 or 40 in at least one eye, but not levels 50 or 60 in either eye. Late ARM = level 50 or 60 in at least one eye.

BMD Measurement

Total hip BMD was measured at the SOF Year 10 clinic visit in g/cm², using dual-energy x-ray absorptiometry using the Hologic QDR 2000 (Bedford, MA). The BMD quality assurance and quality control protocols have been previously described.²⁹

Covariates Measured

Covariates measured were age at Year 10, surgical menopause, age at menopause, exogenous postmenopausal hormone exposure, smoking history (pack-years), body mass index (BMI), diabetes mellitus, hypertension, alcohol consumption, years of education, self-reported health status, physical activity, study recruitment site, daily fruit intake, and daily vegetable intake. Surgical menopause, age at menopause, and years of education were ascertained using the baseline questionnaire. ET and HT use was determined from data collected at the clinic and self-administered questionnaires from baseline, Year 6, and Year 10. In the analysis, this variable was defined as women reporting a history of having ever used ET or HT. Pack-years of smoking (current and past) was determined at baseline and calculated as the number of cigarettes smoked per day divided by 20 multiplied by the number of years smoked. BMI, diabetes mellitus, hypertension, alcohol consumption, and self-reported health status were ascertained using the Year 10 questionnaire. BMI was determined as weight divided by height (kg/m²), using each woman's self-reported height at age 25 because of the loss of height experienced by women with low bone mass. Diabetes mellitus and hypertension status were determined by asking whether a doctor had ever told the subject that she had diabetes mellitus or hypertension. Use of thiazide diuretics, a common treatment for hypertension, has been reported to be associated with BMD, although inclusion of thiazide diuretic use in the models instead of hypertension status did not change the results. Therefore, only hypertension status was included. Alcohol consumption was defined as the number of alcoholic beverages consumed per week, and self-rated health status was determined by asking subjects to rate their health, compared with that of other people their own age, as

excellent, good, fair, poor, or very poor. Physical activity at Year 10 was defined as the number of kcal burned per week from walking and was calculated by multiplying the number of blocks walked per day by 7 and assigning 8 kcal per block walked. Daily fruit intake was defined as the number of servings of fruit and fruit juices consumed daily, and vegetable intake was defined as the number of servings of vegetables consumed daily, as calculated using the Block food frequency questionnaire from Block Dietary Data Systems (Berkeley, CA), which subjects received and completed before their clinic visit.^{30,31}

Statistical Analysis

All statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC). Chi-square tests and Kruskal-Wallis tests were used to determine whether baseline variables differed between subjects according to BMD quartile. Because of the small number of subjects with late ARM in this sample (n = 40), the outcome was "any ARM." Comparisons of baseline variables between subjects with and without any ARM were made using chi-square tests and Wilcoxon rank-sum tests.

BMD was analyzed continuously to estimate the odds of ARM associated with each standard deviation increase in BMD. In addition, BMD was analyzed categorically according to quartile, with the first (lowest) quartile serving as the referent group for the second, third, and fourth (highest) quartiles. Quartiles were based on the distribution of the 1,042 subjects with gradable fundus photographs and BMD status available. Age-adjusted and multivariable-adjusted ORs for the association between BMD and the prevalence of ARM were estimated with logistic regression analysis. Variables were entered into the model based on prior associations with BMD or ARM in the literature or their association with BMD or ARM in bivariate analyses at a significance level of $P \leq .25$. Although age at menopause was associated with BMD in bivariate analyses, it was not included in the model as a result of the large number of subjects that would be excluded from analyses because of missing values for this variable (n = 189). The final multivariable model included age, BMI, surgical menopause, ET or HT use, smoking, alcohol consumption, education, diabetes mellitus, hypertension, physical activity, study recruitment site, and self-rated health status.

BMD may be a marker for lifetime endogenous estrogen exposure, but it may also be associated with other factors, such as current ET or HT use³² and nutrition.^{33–35} Therefore, to address the possibility that BMD may be acting as a surrogate for these factors, the main analysis was repeated after excluding current ET and HT users, as well as after including variables for daily fruit and vegetable intake in the model to control for their effects.

RESULTS

Baseline characteristics of the sample according to BMD quartile are shown in Table 1. Women with higher BMD tended to be younger, had greater BMI, and were more likely to have diabetes mellitus than women with lower BMD. Furthermore, they were more likely to have taken ET or HT and were older at menopause than women with lower BMD. Of the 1,042 subjects with gradable photos

Table 1. Baseline Characteristics According to Bone Mineral Density Quartile

Characteristic	Quartile 1 (0.236–0.629) n = 260	Quartile 2 (0.630–0.717) n = 261	Quartile 3 (0.718–0.811) n = 261	Quartile 4 (0.812–1.390) n = 260	P-value*
Age					
Median	81.0	8.0	78.0	78.0	<.001
Mean $\pm$ SD	81.6 $\pm$ 4.8	8.4 $\pm$ 4.1	79.4 $\pm$ 3.5	78.6 $\pm$ 3.5	
Body mass index, kg/m ²					
Median	21.3	23.7	25.4	27.6	<.001
Mean $\pm$ SD	21.6 $\pm$ 3.4	23.9 $\pm$ 3.7	25.7 $\pm$ 4.0	27.8 $\pm$ 4.7	
Alcohol					.10
Any in previous 30 days, n (%)					
No	154 (59.2)	138 (52.9)	130 (49.8)	129 (49.6)	
Yes	106 (40.8)	123 (47.1)	131 (50.2)	131 (50.4)	
Drinks/wk, median	1.25	1.25	1.50	0.625	.44
Education, years					
Median	12.0	12.0	12.0	12.0	.41
Mean $\pm$ SD	12.9 $\pm$ 2.7	12.8 $\pm$ 2.9	12.9 $\pm$ 2.6	13.1 $\pm$ 2.6	
Age at menopause					
Median	48.0	5.0	49.0	50.0	.001
Mean $\pm$ SD	47.4 $\pm$ 6.3	48.3 $\pm$ 5.7	48.2 $\pm$ 5.4	49.2 $\pm$ 4.8	
Ever smoker					.93
No, n (%)	160 (61.8)	159 (61.2)	160 (61.3)	152 (59.1)	
Yes, n (%)	99 (38.2)	101 (38.9)	101 (38.7)	105 (40.9)	
Pack-years, median	21.4	17.6	21.8	21.6	.35
Walks for exercise					.59
No, n (%)	157 (60.6)	151 (58.3)	145 (55.6)	158 (60.8)	
Yes, n (%)	102 (39.4)	108 (41.7)	116 (44.4)	102 (39.2)	
Kcal/wk, median	336	560	560	392	.06
Hypertension, n (%)					.53
No	182 (70.0)	178 (68.2)	171 (65.5)	185 (71.2)	
Yes	78 (30.0)	83 (31.8)	90 (34.5)	75 (28.8)	
Diabetes mellitus, n (%)					.01
No	257 (98.8)	249 (95.4)	250 (95.8)	242 (93.1)	
Yes	3 (1.2)	12 (4.6)	11 (4.2)	18 (6.9)	
Hormone use, n (%)					.002
Never	138 (53.1)	122 (46.7)	100 (38.3)	102 (39.2)	
Ever estrogen therapy/hormone therapy [†]	122 (46.9)	139 (53.3)	161 (61.7)	158 (60.8)	
Surgical menopause, n (%)					.37
No	216 (86.4)	226 (91.1)	224 (90.0)	225 (89.3)	
Yes	34 (13.6)	22 (8.9)	25 (10.0)	27 (10.7)	
Self-reported health status, n (%)					.41
Excellent/good	207 (79.6)	221 (84.7)	219 (83.9)	212 (81.5)	
Fair/poor/very poor	53 (20.4)	40 (15.3)	42 (16.1)	48 (18.5)	
Recruitment site, n (%)					.73
Baltimore, Maryland	62 (23.9)	58 (22.2)	61 (23.4)	62 (23.9)	
Minneapolis, Minnesota	95 (36.5)	78 (29.9)	83 (31.8)	91 (35.0)	
Pittsburgh, Pennsylvania	60 (23.1)	76 (29.1)	64 (24.5)	65 (25.0)	
Portland, Oregon	43 (16.5)	49 (18.8)	53 (20.3)	42 (16.2)	

* P-values for continuous variables are based on Kruskal-Wallis tests and those for categorical variables are based on chi-square tests.

[†] Estrogen + progestin.

SD = standard deviation.

and BMD measurements, 476 (45.7%) had evidence of early ARM only, although 16 of these subjects were gradable for ARM in only one eye. There were 40 subjects (3.8%) with late ARM.

BMD was associated with ARM in bivariate and multivariable analyses (Tables 2 and 3). The proportions of subjects in the first and second quartiles with any ARM were relatively similar, whereas subjects in the third and

fourth quartiles were increasingly less likely to have ARM. Subjects in the fourth quartile were least likely to have early ARM, whereas those in the third quartile were slightly less likely than those in the other three quartiles to have late ARM (Table 2). Greater BMD was inversely associated with ARM in age-adjusted, age- and smoking-adjusted, and multivariable-adjusted models (Table 3). In the final multivariable-adjusted model, the odds of ARM decreased 18%

Table 2. Prevalence of Age-Related Maculopathy (ARM) According to Bone Mineral Density Quartile (g/cm²)

	Quartile 1 (0.236–0.629) n = 260	Quartile 2 (0.630–0.717) n = 261	Quartile 3 (0.718–0.811) n = 261	Quartile 4 (0.812–1.39) n = 260	
ARM Status	n (%)				P-value
None	119 (45.8)	116 (44.4)	135 (51.7)	156 (60.0)	.006
Early*	129 (49.6)	134 (51.3)	120 (46.0)	93 (35.8)	
Late	12 (4.6)	11 (4.2)	6 (2.3)	11 (4.2)	

*Sixteen subjects had early ARM in one eye and an ungradable photo in the second eye.

for every standard deviation increase in BMD (Table 3, Model 1). When BMD was analyzed according to quartile, subjects in the fourth quartile of BMD had 37% lower odds of ARM than those in the first quartile (OR = 0.63, 95% CI = 0.41–0.97) (Table 3, Model 2). Neither excluding current ET/HT users from the analysis nor controlling for fruit and vegetable intake changed the observed associations (data not shown). Given that the odds of ARM for subjects in the second and third quartiles were not significantly different from odds for those in the first, the first, second, and third quartiles were combined as the referent group in a subsequent analysis to increase power and test for a threshold effect. Subjects in the fourth quartile had a significantly lower odds of ARM than subjects in the first, second, and third quartiles combined (OR = 0.66, 95% CI = 0.48–0.91) (Table 3, Model 3). To investigate the presence of a threshold effect more precisely, BMD was further divided into deciles and entered into the logistic regression model with the first (lowest) decile as the referent group. It appeared that the subjects with BMD in the upper 30% of the distribution had lower odds of ARM than those in the lower 70% (Figure 2). These findings support a threshold effect, with the BMD threshold of 0.79 g/cm² similar to but slightly lower than that identified by the upper BMD quartile (0.81 g/cm²).

DISCUSSION

An inverse association was observed between BMD and ARM. For every standard deviation increase in BMD, the odds of ARM decreased 18%. Furthermore, women in the

fourth quartile of BMD had 37% lower odds of ARM than women in the first quartile (Table 3). In addition, it appears that there may be a threshold effect of BMD on ARM risk. When the fourth quartile was compared with the first, second, and third quartiles collectively, the effect for the fourth quartile remained similar, although the results were more precise (OR = 0.66, 95% CI = 0.48–0.91). Further analysis of BMD according to decile supported a threshold effect, with subjects in the upper 30% of BMD having lower ARM risk than those in the lower 70% (Figure 2).

To the authors' knowledge, this study is the first to examine the association between BMD and ARM. BMD may serve as a marker for lifetime endogenous estrogen exposure, and if so, these results suggest that endogenous estrogen exposure may be protective against ARM. As mentioned previously, several studies have investigated the association between other surrogates for lifetime endogenous estrogen exposure and ARM, such as number of reproductive years, ages of menarche and menopause, and parity, but results have been conflicting.^{13–17,36–39} One possible explanation for the inconsistent findings is that these surrogates do not reflect an end-organ response of endogenous estrogen exposure, as BMD as a biomarker might, and thus may be less specific. In the current study, an association was found with BMD that was independent of ET or HT and reproductive history.

Although BMD may be considered a marker for lifetime endogenous estrogen exposure, other factors that may potentially explain the observed association also affect BMD.^{40,41} For example, although calcium and vitamin D intake have been shown to have the most consistent effect on BMD, evidence suggests that fruit and vegetable intake may also be associated with BMD.^{33–35} Similarly, several, but not all, studies have suggested that dietary intake, supplementary intake, or plasma levels of antioxidants found in fruits and vegetables, such as vitamins C, E, and A; beta carotene; lutein; and zeaxanthin, may be protective against onset or progression of ARM.^{7,42–46} Furthermore, data suggest that current use of postmenopausal hormone therapy prevents bone loss.³² Neither including variables for daily fruit and vegetable intake nor excluding current ET or HT users from the analysis changed the results, suggesting that the observed association is independent of these factors. Although the effects of smoking, alcohol consumption, physical activity, and daily intake of fruit and vegetables were considered, it is possible that other unmeasured factors associated with healthier lifestyles or shared genetic factors may be responsible for the observed association.

Figure 2. Association between bone mineral density (BMD) and age-related maculopathy according to BMD decile.

Table 3. Association Between Bone Mineral Density (BMD) and Age-Related Maculopathy (ARM)

Model	No ARM (n = 526)	Any ARM (n = 516)	Age Adjusted		Age and Smoking Adjusted		Multivariable Adjusted*	
	n (%)		OR	(95% CI)	OR (95% CI)		OR (95% CI)	
1								
Total hip BMD (SD = 0.14) [†]			0.87	(0.76–0.99)	0.84	(0.73–0.98)	0.82	(0.70–0.96)
2								
Quartile 1 (lowest: referent)	119 (22.6)	141 (27.3)	1.00	Referent	1.00	Referent	1.00	Referent
Quartile 2	116 (22.1)	145 (28.1)	1.16	(0.81–1.65)	1.18	(0.83–1.67)	1.12	(0.77–1.63)
Quartile 3	135 (25.7)	126 (24.4)	0.94	(0.66–1.34)	0.94	(0.66–1.35)	0.85	(0.58–1.26)
Quartile 4	156 (29.7)	104 (20.2)	0.71	(0.50–1.02)	0.72	(0.50–1.04)	0.63	(0.41–0.97)
3								
Quartiles 1–3 (referent)	370 (70.4)	412 (79.8)	1.00	Referent	1.00	Referent	1.00	Referent
Quartile 4	156 (29.7)	104 (20.2)	0.69	(0.52–0.93)	0.69	(0.50–0.94)	0.66	(0.48–0.91)

* Adjusted for age, body mass index, surgical menopause, estrogen therapy/hormone therapy use, smoking history, alcohol consumption, education, diabetes mellitus, hypertension, self-rated health status, physical activity, and study recruitment site.

[†] Odds ratios (ORs) estimated in terms of 1 standard deviation (SD) increase in BMD (g/cm²).

CI = confidence interval.

In addition to those factors mentioned, osteoporosis treatments, such as bisphosphonates, affect BMD. Future studies should consider the effect on ARM risk of therapies that aim to preserve or increase BMD.

This study has several limitations. Because of the small number of late ARM cases in this sample, this study was underpowered to examine the association between BMD and late ARM as a separate outcome. Furthermore, given that BMD and ARM status were determined at Year 10, it cannot be proven that the BMD level measured was reflective of BMD before disease onset, although previous data have shown strong BMD correlations over time. In addition, the women participating in SOF may not be a representative sample of older women in the United States. They are healthier, largely community dwelling, and, in the present analysis, Caucasian; therefore, the results of this study may not be generalizable to less-healthy, non-community-dwelling, nonwhite, or male populations. The mean age of participants in this analysis was 80. Therefore, the results may not be generalizable to younger postmenopausal women.

As with any study, disease or exposure classification is a potential concern. Although measures such as masked grading by two independent reviewers were taken to reduce the likelihood of ARM misclassification, grading is somewhat subjective, although BMD was objectively measured using state-of-the-art techniques with excellent quality assurance and quality control. ARM graders were masked to all subjects' personal data, including BMD measurements. Hence, misclassification would likely be nondifferential and most likely to bias the relationship toward the null. Lastly, residual confounding by unknown confounders or those not able to be controlled for in the analysis could also result in biased estimates of effect.

In summary, women with higher levels of BMD may be at lower risk for ARM. The underlying mechanism is unknown, although BMD may be a marker for lifetime endogenous estrogen exposure. Future studies are needed to

replicate these findings and further investigate the nature and underlying mechanisms of the relationship between BMD and ARM.

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