

Socioeconomic status, race, and bone turnover in the Midlife in the US Study

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Abstract

Summary Among a group of 940 US adults, economic adversity and minority race status were associated with higher serum levels of markers of bone turnover. These results suggest that higher levels of social stress may increase bone turnover.

Introduction To determine socioeconomic status (SES) and race differences in levels of bone turnover.

Methods Using data from the Biomarker Substudy of the Midlife in the US (MIDUS) study (491 men, 449 women), we examined cross-sectional associations of SES and race with serum levels of bone turnover markers (bone-specific alkaline phosphatase [BSAP], procollagen type I N-terminal propeptide [PINP], and *N*-telopeptide [Ntx]) separately in men and women. Linear multivariable regression was used to control for body weight, menopausal transition stage, and age.

Results Among men, low family poverty-to-income ratio (FPIR) was associated with higher turnover, but neither education nor race was associated with turnover. Men with

FPIR <3 had 1.808 nM BCE higher Ntx ($P=0.05$), 3.366 U/L higher BSAP ($P=0.02$), and 7.066 higher PINP ($P=0.02$). Among women, neither education nor FPIR was associated with bone turnover, but Black women had 3.688 nM BCE higher Ntx ($P=0.001$), 5.267 U/L higher BSAP ($P=0.005$), and 11.906 $\mu\text{g/L}$ higher PINP ($P=0.008$) compared with non-Black women.

Conclusions Economic adversity was associated with higher bone turnover in men, and minority race status was associated with higher bone turnover in women, consistent with the hypothesis that higher levels of social stresses cause increased bone turnover. The magnitude of these associations was comparable to the effects of some osteoporosis medications on levels of turnover.

Keywords Bone resorption · Bone turnover · Bone-specific alkaline phosphatase · BSAP · Income · *N*-telopeptide · Ntx · PINP · Poverty · Procollagen type I N-terminal propeptide · SES · Socioeconomic status

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Introduction

Low socioeconomic status (SES) is linked to poor health across multiple chronic diseases and across a variety of markers of sub-clinical disease [1]. Indeed, a large body of research has documented SES gradients in biomarkers from nearly every major physiological system, including the hypothalamic–pituitary–adrenal axis (e.g., urinary and salivary cortisol), the sympathetic nervous system (e.g., urinary catecholamines), the parasympathetic system (e.g., heart rate variability), the cardiovascular system (e.g., resting blood pressure), glucose metabolism (e.g., glycosylated hemoglobin), lipid metabolism (e.g., lipoprotein levels and body mass index), and inflammation (e.g., serum C-reactive protein) [1]. Although SES is often treated as a potential confounder in osteoporosis epidemiology research, SES is rarely the central focus of osteoporosis research. In particular, studies have not yet elucidated associations of SES with bone turnover.

In postmenopausal women and elderly men, bone turnover rate is an important determinant of bone fragility [2]. In large epidemiological studies of women, high bone turnover marker levels are associated with increased risk of fracture independently of age, bone mineral density, and prior fracture [3–7]. To our knowledge, no prior studies have focused on associations of SES with serum levels of *N*-telopeptide, bone-specific alkaline phosphatase, or procollagen type I N-terminal propeptide.

In the USA, SES is strongly linked to race/ethnicity, in that minority race/ethnicity groups are disproportionately more represented in low socioeconomic strata and traditional SES indicators such as education and income do not fully capture the complexities of the socioeconomic circumstances faced by minority groups [8–12]. Hence, any examination of SES effects on health in the US needs to also examine race differences.

Accordingly, we used data from the Midlife in the US (MIDUS) II Biomarker Project to determine associations of race, family-adjusted poverty-to-income ratio and education with serum levels bone turnover markers, accounting for body weight, age, and menopausal transition stage.

Methods

The Midlife in the US (MIDUS) recruitment and data collection methods

The Midlife in the US (MIDUS) National Study of Health and Well-Being study design, described in detail previously [13–15], was initiated in 1995–1996 by the MacArthur Midlife Research Network to investigate the role of behavioral, psychological, and social factors in age-related

variation in physical and mental health of Americans aged 25 to 74 years. Random digit dialing survey of over 7,000 individuals in the coterminous United States (with oversampling in five cities) resulted in recruitment of 4,244 participants. MIDUS also recruited 950 siblings (same biological mother and father) of 529 randomly selected participants of the random digit dialing sample. Finally, a twin sample was recruited from a national omnibus survey in which a representative national sample of 50,000 households was screened for the presence of a twin. From this survey, MIDUS recruited a twin sample of 957 cooperating twin pairs ($n=1914$) aged between 25 and 74 years. Therefore, the original MIDUS sample consisted of $4,244+950+1,914=7,108$ participants [13, 15]. Two self-administered questionnaires were mailed to participants who completed the initial 30-min phone interview.

Of the original 7,108 MIDUS participants who completed the phone survey, 4,963 (70%) were successfully recontacted and completed the MIDUS II 30-min phone interview and two self-assessment questionnaires 9–10 years later using the original protocol [15]. To augment the original MIDUS I minority sample, a new city-specific sample of African Americans ($N=592$) was recruited from Milwaukee, WI. Sociodemographic characteristics of participants are described at <http://www.icpsr.umich.edu/icpsrweb/NACDA/>.

Each participant provided written informed consent. Each participating MIDUS center obtained institutional review board approval [13].

The MIDUS II biomarker project

The MIDUS II Biomarker project was designed to elaborate on the links among psychosocial experience, biological indicators of physiological function, and health. Among 3,191 eligible MIDUS II participants (including the Milwaukee sample but not including the siblings oversample, primarily for cost containment) who were deemed medically able to travel without excessive risk to participant or project staff, 1,255 agreed to participate in the MIDUS II Biomarker project, and were assigned to one of the three data collection sites, based on their place of residence. Between July 2004 and May 2009, data were collected at three research centers: University of California at Los Angeles, Georgetown University, and University of Wisconsin. The study provided transportation for each participant to attend the nearest of the three data collection centers. The Biomarker sample was comparable to the larger MIDUS cohort from which the sample was recruited on demographic (age, racial/ethnic status, marital status, income levels) and health characteristics (e.g., self-rated health, number of chronic health conditions, impairments in

activities of daily living), with one exception—the Bio-marker sample having higher levels of educational attainment (e.g., 42.1% college degree or greater vs. 34.5% in the larger sample) [13]. Using standardized protocols, each participant was asked to provide a medical history and a fasting early morning blood sample. Using standardized protocols, blood pressure, body weight, waist circumference, and hip circumference measurements were obtained for each participant. Blood samples were frozen for shipping to the laboratory which performed the assays.

Assay methods

Bone turnover marker concentrations were measured from fasting blood samples collected before breakfast at the clinical research centers. Serum bone-specific alkaline phosphatase (SBAP), procollagen type I N-terminal propeptide (PINP), and *N*-telopeptide levels (Ntx) were measured in the laboratory of Dr. Neil Binkley at the University of Wisconsin using commercially available kits: Metra BAP (Quidel Corporation, San Diego, CA) enzyme-linked immunoassay for bone-specific alkaline phosphatase, Osteomark competitive-inhibition enzyme-linked immunosorbent assay (Wampole Laboratories, Princeton, NJ) for serum *N*-telopeptide, and Orion Diagnostica (Orion Diagnostics, Espoo, Finland) radioimmunoassay for serum procollagen type I N-terminal propeptide.

Inter-assay coefficients of variation for the assays were 2.5% for PINP, 4.5–6.3% for BSAP, and 7.8–9.1% for Ntx. Intra-assay coefficients of variation for the assays were as follows 6.5% for PINP, 5.8% for BSAP, and 4.6% for Ntx. Minimum detectable concentrations were 2 µg/L for PINP, 0.7 U/L for BSAP, and <3.2 BCE (bone collagen equivalents) for Ntx.

Blood glycosylated hemoglobin levels were quantified with a Cobas Integra analyzer (Roche Diagnostics, Indianapolis, IN) at Meriter Labs (Madison, WI). Fasting glucose assays were performed at ARUP laboratories (Salt Lake City, UT).

Bone mineral density measurement

Hip and lumbar spine bone mineral density (BMD) was measured by dual energy X-ray absorptiometry (GE Lunar Prodigy at the Madison site, Hologic 4500 scanner at the University of California, Los Angeles and Georgetown sites). Calibration was performed at all sites by Bona Fide Phantom (Bio-Imaging Technologies, Newtown, PA). Scans from all research center three sites were analyzed centrally in Madison by trained technologists and physicians.

Menopausal transition stage classification

From self-reported menstrual patterns, we classified menopausal stage according to the following definitions: premenopausal (no change in regularity of menses), early perimenopausal (had menses in last 3 months with change in regularity of menses), late perimenopausal (last menses 3–12 months previously with change in regularity of menses), and postmenopausal (no menses in prior 12 months).

Using questionnaires asking about menopausal hormone therapy and oral contraceptive use, as well as direct staff review of all medication bottles at the research center, we ascertained the use of exogenous sex steroid hormone therapy (FDA-approved preparations of estrogen and/or progestogen). We defined current/recent use of menopausal hormone therapy as current use, or use within the past year, of menopausal hormone therapy. We subdivided postmenopausal women into two menopausal stage categories: postmenopausal, not using hormones and postmenopausal, using hormones.

Women who underwent hysterectomy without bilateral oophorectomy were considered to have unclassifiable menopause stage unless hysterectomy was subsequent to the final menstrual period, in which case they were considered to be postmenopausal. Female participants aged 58 years or older who did not supply menstrual pattern information were assumed to be postmenopausal. Women reporting use of exogenous sex steroid hormone therapy within the past 12 months were considered to have unclassifiable menopausal status with two exceptions. If participants had undergone bilateral oophorectomy, or if their final menstrual period was at least 12 months prior to initiation of hormone therapy, they were considered to be “postmenopausal, using hormone therapy”. Due to the small number of late perimenopausal women ($N=6$), we combined late peri- and post-menopausal women not using hormone therapy into a single menopausal transition stage category called late peri-/postmenopausal not using hormones.

Socioeconomic status and race assessment

Phone interviewers asked participants to classify their highest educational level achieved according to 12 possible categories ranging from no school to doctoral or other professional degree. If highest education level was disparate by two or more steps on the 12-category classification on the MIDUS I and MIDUS II assessments for a participant, educational level was considered to be missing.

Total household income at MIDUS II assessment was calculated as the sum of earnings, pension, social security

of respondent, spouse, and other household members, and government assistance and adjusted to 2006 dollars.

We calculated family-adjusted poverty-to-income ratio (FPIR) for each participant as the ratio of the participant's total household income to the US Census Bureau poverty threshold specific to the participant's age, whether the participant currently lived with a spouse or partner, the number of children in the family under age 18 years living in the participant household, and the year of data collection. Thus, an FPIR of 3, for example, means that the participant's total household income is the times the census-bureau-defined poverty level for his/her family.

Race/ethnicity was self-identified as white, Black/African-American, other, or multiracial. If a participant reported a different primary race at the MIDUS I and II assessments, then the participant was classified as multiracial.

Other questionnaire-based covariates

Birth date was self-reported. At the visit in which bone turnover markers were collected, participants were asked to rate physical activity intensity (self-rated light, moderate, or heavy), frequency (number of sessions/week), and duration (minutes/session) [16, 17].

Analytic sample

For this study, we included data from MIDUS II Biomarker participants with complete information on all three bone turnover markers: serum bone-specific alkaline phosphatase (BSAP), procollagen type I N-terminal propeptide (PINP), and *N*-telopeptide level (Ntx). Of the 1,255 participants of the MIDUS II Biomarker study, 126 participants reported the use of medications known to influence osteoporosis (oral corticosteroids, alendronate, anastrozole, calcitonin, ibandronate, leuprolide, letrozole, raloxifene, risedronate, tamoxifen, zoledronic acid, testosterone, finasteride, dutasteride), and ten were missing information regarding one or more bone turnover marker levels. A further 135 participants could not undergo menopause transition stage classification ($N=50$ data missing or participant pregnant/breastfeeding, $N=30$ unclassifiable due to exogenous sex steroid use, $N=55$ hysterectomy without bilateral oophorectomy prior to last menstrual period). Of the 984 remaining participants, we excluded 44 participants for whom we lacked complete information regarding SES measures. Thus, the analytic sample for this study was comprised of 940 participants (491 men, 449 women).

Statistical analysis

We performed cross-sectional sex-specific analyses using multivariable linear regression. Each of the three bone turnover markers (SBAP, PINP, and Ntx) served as the outcome of a separate regression model. The main predictor variables in individual regression models were race/ethnicity (Black vs. non-Black) and one SES indicator—either FPIR (<3 , $3-5.99$, ≥ 6 , corresponding to FPIR tertiles) or maximum educational level attained (high school or less vs. some college or more). We adjusted for body weight (kilograms), research center site (University of California at Los Angeles, Georgetown University, or University of Wisconsin), hip BMD, lumbar spine BMD, and either menopausal transition stage (for women) or age (for men only, classified as <50 years old, $50-64$ years old, or ≥ 65 years old [2]). Because immobilization is associated with increases in bone resorption and physical activity episodes increase bone turnover marker levels, we added physical activity level as a covariate to the statistical models described above [18, 19]. We similarly added a covariate representing diabetes mellitus (self-report of diabetes mellitus or use of diabetes medications, glycosylated hemoglobin level ≥ 6.5 , and/or fasting glucose level ≥ 126 mg/dL) as a covariate, based on the reported influence of diabetes mellitus on turnover [20–22].

All statistical tests were two-sided. P values ≤ 0.05 were considered statistically significant. All statistical analyses were using with STATA SE version 10.1 (StataCorp LP, Texas, USA) and used STATA's cluster option to account for within-family correlations among twins and siblings.

Results

Compared with the excluded MIDUS II Biomarker Study participants, the participants included in this study were more likely to be Black (20% vs. 10%) and younger (males less than 50 years old 31% vs. 4%, premenopausal 15% vs. 4%, early perimenopausal 12% vs. 4%; data not shown). Included participants also had slightly higher Ntx (14.663 vs. 12.992 nM BCE) and PINP (87.093 vs. 77.688 $\mu\text{g/L}$) levels (data not shown). The main reasons for exclusion from the analytic sample were inability to reliably determine menopause stage category or lack of bone turnover marker measurement.

Twenty percent of participants in the analytic sample were Black, and mean body weight was 87.1 kg (Table 1). Median FPIR was 4.11; mean FPIR was 5.13 (SD 4.29). Approximately one third of participants had maximum achieved education of high school or less than high school.

Table 1 Selected characteristics of participants

	Mean±SD or number (%)
<i>N</i> -telopeptide level, nM BCE (mean (SD))	14.663 (6.990)
Bone-specific alkaline phosphatase level, U/L (mean (SD))	28.621 (11.310)
Procollagen type I propeptide, µg/L (mean (SD))	60.564 (29.314)
Body weight (kg), mean (SD)	87.09(20.54)
Women (<i>N</i> =449)	
Premenopausal, number (%)	67 (14.9%)
Early perimenopausal, number (%)	55 (12.3%)
Late peri- or post-menopausal not taking hormones, number (%)	277 (61.7%)
Postmenopausal taking exogenous female sex steroids, number (%)	50 (11.1%)
Males (<i>N</i> =491)	
<50 years old, number (%)	154 (31.4%)
50–64 years old, number (%)	139 (28.3%)
≥65 years old, number (%)	198 (40.3%)
Race/ethnicity	
Non-black, number (%)	750 (79.8%)
Black, number (%)	190 (20.2%)
Education	
High school or less, number (%)	275 (29.2%)
Some college, number (%)	271 (28.8%)
College graduate or more, number (%)	395 (42.0%)
Family-adjusted poverty-to-income ratio ^a	5.13 (4.29)
Research site	
University of California, Los Angeles, number (%)	34.59%
University of Wisconsin, number (%)	43.92%
Georgetown University, number (%)	21.49%

^a Family-adjusted poverty-to-income ratio=total household income/poverty threshold, where poverty threshold is adjusted for family size

Adjusted SES and race associations with bone turnover in men

Among men, adjusting for age and body weight, a low FPIR was associated with increased turnover, but there were no education or race associations with levels of turnover markers. Men with FPIR <3 had higher levels of each of the three turnover markers than men with FPIR ≥6 (Table 2). However, there were no statistically significant differences in any of the bone turnover markers between men with FPIR 3–5.99 and men with FPIR ≥6 (Table 2). Age and body weight were also not associated with any of the turnover marker levels in men (Table 2).

Unlike FPIR, education was not statistically significantly associated with mean levels of Ntx, BSAP, or PINP (data not shown).

Further adjustment for physical activity level (no. minutes/week of light, moderate, and vigorous physical activity) or for BMD of the lumbar spine and femoral neck did not notably alter the magnitudes of any associations

between race or SES indicators and bone turnover marker levels (data not shown).

Adjusted SES and race associations with bone turnover in women

Among women, adjusted for menopause status and body weight, there were no SES associations with bone turnover, but Black race was associated with higher turnover. All three turnover markers were significantly higher in Black women than in non-Black women (Table 3). In contrast to men, neither FPIR (Table 3) nor education (data not shown) was statistically significantly associated with bone turnover marker levels. In addition to race, body weight and menopausal transition stage were also statistically significantly associated with bone turnover: All three turnover marker levels were higher among late perimenopausal or postmenopausal women not taking hormones, and heavier women had lower levels of PINP and Ntx, but not BSAP (Table 3).

Table 2 Adjusted associations between family poverty-to-income ratio and bone turnover markers among men ($N=491$)

Ntx ^a	Nanomolar BCE difference	SE	<i>P</i> value
Family PIR <3 vs. $\geq 6^b$	1.808	0.900	0.05
Family PIR 3–5.99 vs. ≥ 6	0.294	0.586	0.62
Men 50–59 vs. <50 years	-0.419	0.728	0.52
Men 60+ vs. <50 years	0.104	0.691	0.88
Black vs. non-Black	0.011	1.066	0.99
Body weight	-0.022	0.019	0.24
BSAP	U/L Difference		
Family PIR <3 vs. ≥ 6	3.366	1.422	0.02
Family PIR 3–5.99 vs. ≥ 6	-0.874	0.905	0.34
Men 50–59 vs. <50 years	-1.216	1.147	0.29
Men 60+ vs. <50 years	0.640	1.217	0.60
Black vs. non-Black	1.727	1.818	0.34
Body weight	0.029	0.031	0.35
PINP	$\mu\text{g/L}$ difference		
Family PIR <3 vs. ≥ 6	7.066	3.246	0.03
Family PIR 3–5.99 vs. ≥ 6	-3.888	2.371	0.10
Men 50–59 vs. <50 years	-6.846	2.866	0.02
Men 60+ vs. <50 years	-4.995	2.776	0.07
Black vs. non-Black	2.942	4.095	0.47
Body weight	-0.074	0.069	0.29

^a Multivariable linear regression includes age category, race (Black vs. non-Black), body weight in kilograms, and clinical study site

BSAP serum bone-specific alkaline phosphatase, PINP serum procollagen type I N-terminal propeptide, Ntx serum N-telopeptide

^b Family poverty-to-income ratio, where reference is ≥ 6

Further adjustment for physical activity level (no. minutes/week of light, moderate, and vigorous physical

activity) or for BMD of the lumbar spine and femoral neck did not notably alter the magnitudes of any associations

Table 3 Adjusted associations between family poverty-to-income ratio and bone turnover markers among women ($N=449$)

Ntx ^a	Nanomolar BCE difference	SE	<i>P</i> value
Family PIR <3 vs. $\geq 6^b$	-0.666	0.863	0.44
Family PIR 3–5.99 vs. ≥ 6	0.677	0.888	0.45
Early peri- ^c vs. pre-menopausal	-0.627	1.396	0.65
Late peri/post no hormone ^d	2.384	0.976	0.02
Post hormone user ^e	-1.573	1.211	0.20
Black vs. non-Black	3.688	1.100	0.001
Body weight	-0.056	0.016	0.001
BSAP	U/L Difference		
Family PIR <3 vs. ≥ 6	-0.063	1.180	0.96
Family PIR 3–5.99 vs. ≥ 6	2.311	1.335	0.08
Early peri- vs. pre-menopausal	0.134	1.788	0.94
Late peri/post no hormone	4.620	1.324	0.001
Post-hormone user	-1.012	1.819	0.58
Black vs. non-Black	5.267	1.852	0.005
Body weight	-0.042	0.028	0.14
PINP	mg/L difference		
Family PIR <3 vs. ≥ 6	-3.448	3.655	0.35
Family PIR 3–5.99 vs. ≥ 6	-1.098	3.583	0.76
Early peri- vs. pre-menopausal	-1.273	5.175	0.81
Late peri/post no hormone	16.107	3.802	<0.001
Post hormone user	-4.553	5.863	0.44
Black vs. non-Black	11.906	4.450	0.008
Body weight	-0.265	0.068	<0.001

BSAP serum bone-specific alkaline phosphatase, PINP serum procollagen type I N-terminal propeptide, Ntx serum N-telopeptide

^a Multivariable linear regression includes menopausal transition stage, race (Black vs. non-Black), body weight in kilograms, and clinical study site

^b Family poverty-to-income ratio, where reference is ≥ 6

^c Early peri: early perimenopausal

^d Late peri-/post- no hormone: late perimenopausal or postmenopausal not currently taking exogenous hormone therapy

^e Post-hormone user: postmenopausal taking exogenous hormone therapy

between race or SES indicators and turnover marker levels (data not shown). The associations between Black race and bone turnover marker levels were not notably attenuated by further adjustment for age since final menstrual period, or presence of self-reported diabetes or diabetes medications (data not shown).

SES effect modification

Associations between SES and bone turnover marker levels did not vary statistically significantly by race, menopausal transition stage, or age category in interaction tests (data not shown).

Discussion

In this study, low income adjusted to family size (specifically, low family poverty-to-income ratio) was statistically significantly associated with higher bone turnover (both formation and resorption) among men but not among women. Among women, bone turnover (both formation and resorption) was significantly higher in Blacks than in non-Blacks. The differences found here represent fairly large effects, approximately 12% absolute difference or 0.24–0.3 standard deviations (SD) difference between men with low and high family poverty-to-income ratios, and 18%–25% or 0.41–0.53 SD difference between Black and non-Black women. The magnitudes of these differences are comparable to the size of effects of the menopause transition or some osteoporosis therapies in women. In this study, the difference in turnover markers between late perimenopausal or postmenopausal women not taking hormones and pre-menopausal women was of the order of 16–27%, or 0.34–0.55 SD. Past studies have suggested declines of approximately 30% in Ntx level in response to some osteoporosis pharmacotherapies [23, 24]. Maximum level of education attained was not statistically significantly associated with turnover marker levels.

To our knowledge, only one prior study has focused specifically on associations of SES with serum levels of Ntx, BSAP, or PINP. In the Newcastle Thousand Families Birth Cohort, there was no statistically significant correlation between social classes (derived by applying the 1990 UK Registrar General's Standard Occupational Classification to the main wage earner in the household) at age 49–51 years and serum levels of C-telopeptide of type 1 collagen [25]. Taken together with our study, this suggests that different aspects of social standing affect bone turnover differently, with education and occupation level having no association with turnover, and income (adjusted for family size) impacting turnover in men and minority race status affecting turnover in women.

Gender differences in SES and race associations with health have been seen in multiple studies [26, 27] and are thought to be the result of underlying gender differences in biological vulnerability, social coping mechanisms, and access to material, social, and psychological resources [28]. There are also documented gender differences in behavioral and physiological responses to stress, which might underlie the different bone turnover associations with SES and minority race status in women and men [29].

A potential confounder of the race-turnover relationship in women is body weight, because Black women in this study were significantly heavier on average than non-Black women. However, the association of Black race with higher bone turnover marker levels among women was evident with and without adjustment for body weight.

Due to the interference of melanin with vitamin D formation in the skin, African Americans have lower serum levels of 25-hydroxyvitamin D than do Caucasians [30–35]. 1,25(OH) upregulates the expression of several genes in osteoblasts (e.g., osteocalcin and osteopontin) and induces the expression of receptor activator of nuclear factor kappa- β ligand, which promotes osteoclast differentiation and increases osteoclast activity. Vitamin D deficiency is associated with increased levels of both bone resorption and bone formation markers and secondary hyperparathyroidism [36, 37]. Studies have indeed documented higher parathyroid hormone levels in darker-skinned individuals [38–45]. Low vitamin D and high parathyroid hormone levels may therefore be responsible for the higher turnover in Black women. Because vitamin D conversion in the skin is dependent on adequate exposure to sunlight, it is not surprising that bone turnover markers vary substantially according to geographic region [46]. In the Study of Women's Health across the Nation, osteocalcin and urinary Ntx levels were similar among Caucasian compared with African American middle-aged women, but there was substantial regional variation in bone turnover marker levels [47]. Bone turnover was higher in the Northeast and in the Midwest than in California. This regional variation in bone turnover in women may explain why some previous studies have found no differences in bone turnover between Blacks and Caucasians [38, 39, 48–50], while others found lower levels of turnover markers in Blacks compared with Caucasians [38–41, 43–45, 48, 50–57].

Our finding of higher turnover among low SES men and Black women is consistent with the stress-health hypothesis that chronic psychosocial stresses faced by disadvantaged individuals in society lead to deleterious changes in physiology and adverse health outcomes. Also consistent with this hypothesis, many studies have found associations of depression with high bone turnover [58–60]. Individuals with major depression have increased levels of proinflam-

matory cytokines [61–63] and circulating cortisol [64–66], as do socially disadvantaged individuals [67–75]. Inflammatory cytokines such as interleukin-6 promote differentiation and activation of osteoclasts, which promote turnover [76–78]. On the other hand, high levels of circulating cortisol appear to affect turnover by inhibiting the terminal differentiation and activation of osteoblasts [79, 80]. Inflammation and hypercortisolemia thus represent two potential biological pathways by which social disadvantage may impact bone turnover.

Our findings of higher bone turnover among men of lower SES and women of Black race/ethnicity adds to the growing list of negative sub-clinical and clinical outcomes associated with lower SES and/or minority status [81].

However, our study has limitations, especially its cross-sectional design which does not allow inference of causality. We did not examine genetic factors as possible explanations for the noted SES and racial differences in turnover levels, nor did we examine potential sources of stress other than low SES. Serum 25-hydroxyvitamin D and parathyroid hormone levels were also not measured. While this study examined turnover in adults, potentially important differences in turnover in the growing years was not examined. Finally, the moderate sample size may have limited our ability to detect some associations. Strengths of our study include our rigorous classification of menopausal transition stage, a broad range of participant age, the control for body weight and race, the ability to exclude users of medications influencing osteoporosis, and precise laboratory assays. Our specimen collection methods were designed to minimize interference from pre-analytical dietary and circadian variability [2, 19, 46]. Assays were performed in a single central laboratory to avoid between-laboratory analytical variability [19, 82].

Conclusion

In conclusion, we found sex-specific associations of lower family-adjusted poverty-to-income ratio and Black race with higher bone turnover marker levels. Future research should explore whether stress-induced alterations in circulating cortisol, inflammatory marker levels, and sympathetic nervous system activation may be partly responsible for these findings.

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Conflicts of interest None

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