Multisystem Dysregulation and Bone Strength: Findings From the Study of Midlife in the United States

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Context: Accumulated dysregulation across multiple physiological systems, or allostatic load (AL), has been proposed as the biological pathway from psychosocial adversity to poor health.

Objective: The objective of the study was to examine whether AL, constructed using biomarkers and medication data from seven systems (sympathetic, parasympathetic, hypothalamic-pituitary-adrenal axis, cardiovascular regulation, inflammation, and lipid and glucose metabolism), is associated with lower bone strength in a national sample.

Design: This was a cross-sectional study.

Setting and Participants: Seven hundred three community-dwelling men and women from the Study of Midlife in the United States participated in the study.

Outcome Measures: Bone mineral density (BMD) was measured in the femoral neck and lumbar spine. Femoral neck BMD was combined with bone size and body size to create composite indices of femoral neck strength relative to load in three failure modes: compression, bending, and impact.

Results: In mixed-effects linear regression controlling for clustering within families and adjusted for age, gender, race/ethnicity, body mass index, menopausal transition stage, childhood socioeconomic status, adult finances, education level, and study center, each SD increment in AL score was associated with between 0.10 and 0.11 SD decrements in lumbar spine BMD and each of the three composite strength indices (all values of $P < .05$). Gender modified the association of AL only with femoral neck BMD; each SD increment in AL score was associated with 0.21 SD decrement in femoral neck BMD in men ($P < .01$) but not in women.

Conclusions: Accumulation of dysregulation across systems was modestly associated with lower bone strength. This study adds to the accumulating evidence that multisystem dysregulation, or AL, predicts a variety of adverse health outcomes. **(*J Clin Endocrinol Metab* 99: 1843–1851, 2014)**

Accumulated dysregulation across multiple physiological systems has been proposed as the biological pathway from psychosocial adversity to poor health (1). The conceptual model is that frequent activation of the stress response leads to dysfunction of the regulatory physiological systems of the stress response apparatus, mani-

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Abbreviations: AL, allostatic load; BP, blood pressure; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; FNAL, femoral neck axis length; FNW, femoral neck width; FPIR, family-adjusted poverty-to-income ratio; HPA, hypothalamic-pituitary-adrenal axis; HT, hormone therapy; LDL, low-density lipoprotein cholesterol; MIDUS, Midlife in the United States; MIDUS II, second MIDUS study; UCLA, University of California, Los Angeles.

fested as changes in resting levels, blunting of the acute response, and delayed turn-off (1, 2). Such dysregulation has been documented in levels of catecholamines, corticosteroids, blood pressure (BP), resting heart rate, heart rate variability, and inflammatory cytokines, in individuals exposed to frequent or chronic stressors (3–5).

Allostatic load (AL), an index of such dysregulation across systems, has been shown to predict a number of adverse health outcomes, including mortality (6–8), decline in functional status (6, 9, 10), decline in cognitive function (9–11), incident cardiovascular disease (10), depressive disorder (12), and frailty (13). We postulated that AL would also be associated with lower bone strength, the pathophysiology that underlies osteoporotic fractures.

Low areal (2-dimensional projected) bone mineral density (BMD) as measured by dual-energy x-ray absorptiometry (DXA) is a marker of low bone strength and a strong predictor of fracture risk (14). Its clinical usefulness is, however, somewhat hampered by its inability to correctly stratify fracture risk across race/ethnicity groups (15) and between persons with diabetes and nondiabetics (16). In contrast, composite indices of femoral neck strength, which integrate femoral neck size and body size with femoral neck BMD to gauge femoral neck strength relative to load (impact forces) during a fall (17), are indeed inversely associated with incident fractures (17, 18) and, unlike BMD, are also consistent with fracture risk differences between diabetes and nondiabetes (19) and across race/ethnicity groups (20). In addition, unlike BMD, the composite strength indices can predict fracture risk in middle-aged women without requiring race/ethnicity information (18).

We hypothesized that higher levels of AL would be associated with both lower BMD and lower composite indices of femoral neck strength relative to load.

Materials and Methods

Study sample

Data came from the Midlife in the United States (MIDUS) National Study of Health and Well-Being (21, 22). The first wave of MIDUS collected demographic and psychosocial data in 1995–1996 on a national sample of English-speaking, noninstitutionalized adults between 25 and 75 years of age residing in the coterminous United States (recruited by random digit dialing) and oversampled twin pairs and siblings. In the second wave of data collection 9–10 years later (MIDUS II), the sample was refreshed with African American residents recruited from Milwaukee, Wisconsin, specifically to increase the representation of urban African Americans. Details of the study design, recruitment, and retention are available (http://www.icpsr.umich.edu/icpsrweb/nacda/).

Of the 3191 MIDUS II participants deemed medically safe to travel, 1255 agreed to participate in the MIDUS II Biomarker Project, which required a 2-day commitment including travel to one of the three study centers: University of California, Los Angeles (UCLA); Georgetown University, and University of Wisconsin-Madison. The reasons for nonparticipation included travel burden, family obligations, and being too busy. Participants provided medical history information and got DXA scans using standardized protocols. Data collection occurred between July 2004 and May 2009. Each participant provided informed consent. Each MIDUS center obtained institutional review board approval (21). The characteristics of the MIDUS II participants were similar to those of the MIDUS I participants (22), and the characteristics of the MIDUS Biomarker Project participants were similar to those of the MIDUS II participants as a whole (21).

Of the 1255 participants in the MIDUS II Biomarker Project, we excluded data from 356 participants who lacked BMD measurements (which was added to the Biomarker Project partway into data collection at two of the three study centers), 93 participants who used medications known to influence bone strength (oral corticosteroids, alendronate, anastrozole, calcitonin, ibandronate, leuprolide, letrozole, raloxifene, risedronate, tamoxifen, zoledronic acid, T, finasteride, dutasteride), 87 women whose menopausal transition stage could not be determined, 13 participants without socioeconomic status data, and three participants missing AL scores, leaving an analytic sample size of 703.

Bone strength measurements

At the MIDUS II Biomarker Project visit to one of the three study centers, DXA scans of the lumbar spine (L1–L4) and left hip were performed using GE Healthcare Lunar Prodigy (University of Wisconsin-Madison) or Hologic 4500 (UCLA and Georgetown University) scanners by certified technologists. Funding for DXA scans at UCLA and Georgetown University was obtained after the Biomarker Project had commenced; thus, BMD data were not available for every participant at these two centers. Adjudication of all DXA scans occurred centrally by physicians at University of Wisconsin-Madison. Three times per week and on all days on which scans were obtained, instruments were calibrated and phantom scan data were acquired. Ten scans of a Bone Fide Phantom on the densitometers at the three study centers were used to cross-calibrate BMD measurements across the centers. The linear regression equation developed from these calibration scans were used to correct BMD values from two of the three centers to make the data comparable across study centers.

DXA scans provided the 2-dimensional projected areal BMD in the lumbar spine and the femoral neck, the femoral neck axis length (FNAL), and the femoral neck width (FNW) (Figure 1). Weight and height were measured using standard protocols. Composite indices of femoral neck strength relative to load in three different failure modes during a fall were created as follows (17):

$$\text{Compression Strength Index (CSI)} = \frac{BMD * FNW}{Weight}$$

$$\text{Bending Strength Index (BSI)} = \frac{BMD * FNW^2}{FNAL * Weight}$$

$$\text{Impact Strength Index (ISI)} = \frac{BMD * FNW * FNAL}{Height * Weight}$$

The compression strength index reflects the ability of the femoral neck to withstand axial compressive loading, the bending strength index does its ability to withstand bending, and the

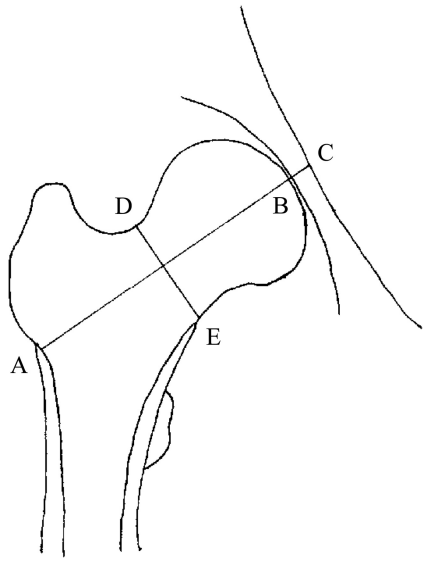

Figure 1. Femoral neck size measurements. AB is the femoral neck axis length (FNAL): the distance from the base of the greater trochanter to the apex of the femoral head. DE is the femoral neck width (FNW): the smallest thickness of the femoral neck along any line perpendicular to the femoral neck axis.

impact strength index does its ability to absorb the energy of impact in a fall from standing height.

Allostatic load scoring

During the Biomarker Project visit, a wide range of biomarkers representing seven physiological systems were collected. Measures of sympathetic nervous system activity included overnight urinary epinephrine and norepinephrine. Measures of parasympathetic nervous system activity included the following heart rate variability parameters at rest: low- and high-frequency spectral power, the SD of R-R (heartbeat to heartbeat) intervals, and the root mean square of successive differences. Indicators of hypothalamic-pituitary-adrenal axis (HPA) axis activity included an overnight urinary cortisol measurement and measurement of serum dehydroepiandrosterone sulfate. Measures of cardiovascular regulation included resting systolic BP, resting pulse pressure (systolic minus diastolic pressure), and resting heart rate. Measures of inflammation included serum levels of C-reactive protein, IL-6, e-selectin, intracelleular adhesion molecule-1, and fibrinogen. Levels of glycosylated hemoglobin, fasting blood glucose, and the homeostasis model assessment of insulin resistance served as measures of glucose metabolism. Indicators of lipid metabolism included high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, body mass index (BMI), and waist to hip ratio (23).

We computed AL score (range 0–7) as the sum of seven system-level dysregulation scores. Dysregulation scores (range 0–1) for each of the seven systems were calculated as the proportion of that system's biomarkers in the highest-risk quartile of its distribution (upper or lower quartile, depending on whether high or low values of the biomarker typically confer greater risk for adverse health outcomes). The quartile cut points used for the scoring were based on biomarker distributions in the MIDUS II Biomarker sample (without the Milwaukee oversample to achieve a national distribution). Resulting cut points turned out to be very close to disease/treatment thresholds for clinical risk factors such as BP, glucose, lipids, and BMI (Table 1). Regardless of the measured biomarker value, a participant who reported the use of medications to lower a clinical risk factor was automatically assigned the highest-risk quartile of that biomarker. These medications included antihypertensive medications, heart rate reducing medications (eg, beta blockers and atrioventricular nodal blockers), diabetes medications, cholesterol-lowering medications (counted as high LDL), and fibrates (counted as high triglycerides). For sensitivity analysis, we created an alternate version of AL that was based solely on measured values of biomarkers.

System dysregulation scores were computed only for participants with data on half or more of the system's biomarkers. Fewer than 20 participants got system scores based on incomplete biomarker data. AL score was computed only for participants who had scores for at least six of the seven systems. For 49 patients who were missing only the parasympathetic system score, we imputed AL score from the participants' scores on the other six systems, age, gender, and race/ethnicity, using a regression equation derived from those with complete biomarker data. For four participants who were each missing exactly one of the other six system scores, the missing system score was imputed as zero (because the sample median for four of the seven system scores was zero).

Table 1. Cut Points for System-Level and AL Scoring

Biomarkers by System	Cut Points
Sympathetic nervous system	
Urine epinephrine, mg/g of creatinine	≥2.54
Urine norepinephrine, mg/g of creatinine	≥33.3
Parasympathetic nerve system (heart rate variability)	
Low-frequency power, msec^2	≤114
High-frequency power, msec^2	≤54.2
R-R interval SD, msec	≤23.5
Root mean square successive differences, msec	≤11.8
HPA axis	
Urine cortisol, mg/g of creatinine	≥21.0
Serum dehydroepiandrosterone sulfate, μg/dL	≤51.0
Cardiovascular regulation	
Systolic BP, mm Hg[a]	≥143
Resting pulse pressure, mm Hg	≥65
Resting heart rate, beats per min[a]	≥77
Inflammation	
Serum C-reactive protein, mg/L	≥3.18
Serum IL-6, ng/L	≥3.18
E-selectin, ng/mL	≥50.6
Intracellular adhesion molecule-1, mg/L	≥330
Fibrinogen, mg/dL	≥390
Glucose metabolism	
Blood glycated hemoglobin, %[a]	≥6.1
Fasting blood glucose, mg/dL[a]	≥105
Homeostasis model assessed insulin resistance	≥4.04
Lipid metabolism	
BMI, kg/m^2	≥32.3
Waist to hip circumference ratio	≥0.97
LDL, mg/dL[a]	≥128
HDL, mg/dL	≤41.4
Serum triglycerides, mg/dL[a]	≥160

[a] Scored as high risk if taking medications that are generally prescribed to lower these risk factors, even if the measured biomarker is below the cut point.

Covariate measurements

Race/ethnicity was self-identified as white, black/African American, other, or multiracial. Menopausal transition stage in women was determined from self-reported menstrual patterns and use of sex steroid hormones (from self-report and examination of medication bottles brought to the study center) as follows: premenopausal (no change in regularity of menses), early perimenopausal (one or more menses in last 3 months with change in regularity of menses), late perimenopausal (last menses more than three but less than 12 months previous), postmenopausal (ie, no menses in prior 12 months) and not taking menopausal hormone therapy (HT), and postmenopausal taking menopausal menopausal HT. Because there were very few women who were late perimenopausal, they were combined with postmenopausal women not on menopausal HT. We classified men by age into one of three categories: younger than 50 years, 50–59 years, and 60 years or older. The choice of age categories in men was guided by previous observations that bone loss in men does not start until age 50 years (24) and to age-match the oldest group to the postmenopausal women (25).

Childhood socioeconomic advantage score was calculated by summing three components (possible range 0–6): being on welfare during childhood (0, yes; 2, no), childhood financial level relative to others (0, worse off; 1, same; 2, better), and highest parental education (0, < high school; 1, high school/general educational development certificate; 2, at least some college). Adult financial advantage score was calculated by summing four components (possible range 0–8): family-adjusted poverty-to-income ratio (FPIR) (0 for FPIR < 3; 1 for FPIR ≥ 3 but < 6; 2 for FPIR ≥ 6, reflecting approximate tertiles of its distribution), self-rated current financial situation (0, worst; 1, average; 2, best), sufficient money to meet needs (0, not enough; 1, just enough; 2, more than enough), and degree of difficulty paying bills (0, very; 1, not very; 2, not at all). The participant's educational level was also ascertained and collapsed to a three-category variable: 1 (no college) vs 2 (some college or associate's degree) vs 3 (bachelor's degree or more) (26).

Questionnaires assessed smoking status (current, former, or never), total pack-years of cigarette smoking; heavy alcohol consumption in the past month (more than seven drinks per week or more than three drinks per occasion regularly for women, more than 14 drinks per week, or more than four drinks per occasion regularly for men); and current physical activity level: summary scores were determined by adding the reported times for light (weight of 1), moderate (weight of 2), and vigorous (weight of 3) activity.

Statistical analysis

Gender-stratified locally weighted scatterplot smoothing plots of each of the five bone strength measures (femoral neck BMD, lumbar spine BMD, and the three composite strength indices) as a function of AL showed no strong threshold effect; instead bone strength either trended downward or stayed flat as AL increased (Figure 2, A and B). We therefore examined AL as a continuous predictor and used mixed-effects regressions to control for clustering within families (twins and siblings) and adjust for race/ethnicity (white vs nonwhite), gender, age categories in men (<50 y, 50–59 y, ≥60 y), menopausal transition stage in women (premenopausal, early perimenopausal, late peri-/postmenopausal not taking HT, and postmenopausal taking HT), two continuous variables to capture age-related declines (one tracked age in men after age 60 y, and one tracked age in late peri-/postmenopausal women), BMI (as a linear plus squared terms and interaction with gender), childhood socioeconomic advantage score (ordinal), adult financial advantage score (ordinal), education level (categories), a binary indicator for imputed AL score, a binary indicator of medication used to lower risk factors (BP, resting heart rate, blood glucose, LDL cholesterol, and/or triglycerides), and study center (categories).

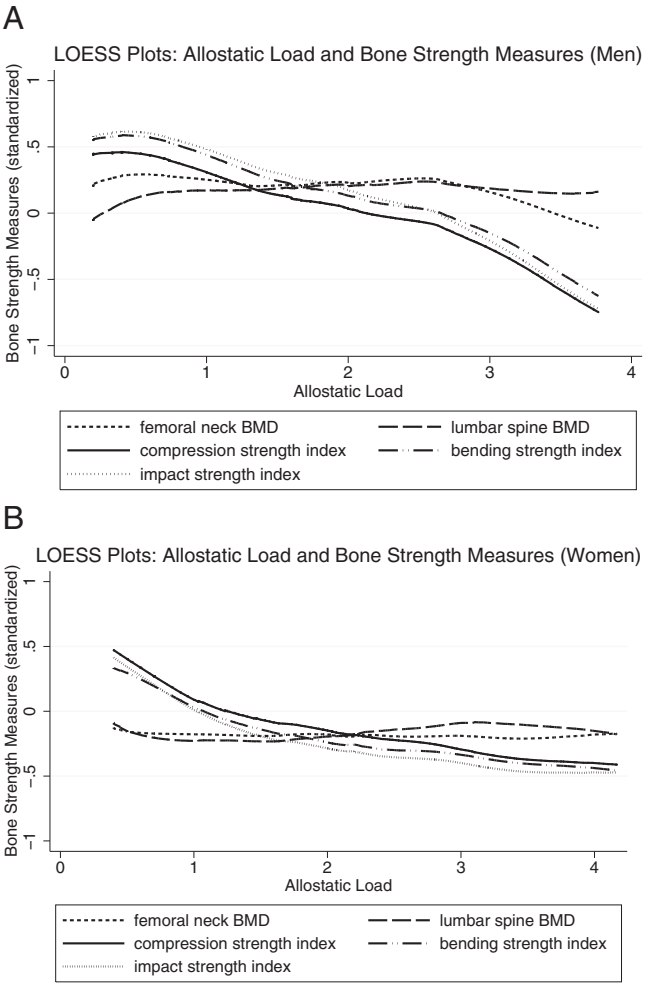

Figure 2. A and B, Locally weighted scatterplot smoothing (LOESS) plots of five bone strength measures as a function of allostatic load, stratified by gender. The extreme five percentiles of the gender-specific allostatic load distribution were excluded from the plots. Each bone strength measure was standardized to have a mean of 0 and a SD of 1.

Because BMI was a part of both AL and three of the five bone strength measures, we included controls for BMI in the models to ensure that AL associations with bone strength were not just artifacts of BMI's influence on both AL and bone strength. We examined the variance inflation factor for AL with the full set of covariates in the model: it was 1.80, suggesting that multicollinearity was not a concern.

Parallel mixed-effects regressions examined each of the seven system dysregulation scores separately as predictors of the five bone strength measures, adjusted for the same set of covariates but with system-specific imputation and medication indicators.

In sensitivity analyses, we examined the alternate AL that ignored medication use and was based only on measured values of all biomarkers. We also added controls for health behaviors:

Table 2. Descriptive Statistics for Study Sample and the Full MIDUS II Biomarker Project Sample:[a] Number (%) or Median (Interquartile Range)

	Study Sample (n = 703)[b]	Biomarker Sample (n = 1255)
Age, y	56 (48, 64)	57 (48, 65)
Gender		
Men	339 (48.2%)	542 (43.2%)
Race		
White	501 (71.3%)	967 (77.2%)
Black/African American	170 (24.2%)	222 (17.7%)
BMI, kg/m^2	29.0 (25.3, 33.6)	28.6 (25.2, 33.0)
Age in men, y		
<50	111 (32.7%)	156 (28.8%)
50–59	103 (30.4%)	153 (28.2%)
≥60 y	125 (36.9%)	233 (43.0%)
Menopausal transition stage in women		
Premenopausal	61 (16.8%)	—
Early perimenopausal	53 (14.6%)	—
Late peri- or postmenopausal not on HT	216 (59.3%)	—
Postmenopausal on HT	34 (9.3%)	—
Childhood socioeconomic advantage score[c]	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)
Adult financial advantage score[d]	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)
Education level		
No college	210 (29.9%)	344 (27.7%)
Some college or associate's degree	201 (28.6%)	371 (29.9%)
Bachelor's degree or more	292 (41.5%)	527 (42.4%)
Study center		
UCLA	212 (30.2%)	433 (34.5%)
Georgetown	94 (13.4%)	289 (23.0%)
University of Wisconsin-Madison	397 (56.5%)	533 (42.5%)
Smoking status		
Never	362 (51.5%)	658 (52.4%)
Former	225 (32.0%)	410 (32.7%)
Current	116 (16.5%)	187 (14.9%)
Smoking, pack-years	0 (0, 11.0)	0 (0, 11.3)
Heavy alcohol consumption[e]	121 (17.3%)	173 (13.9%)
Current physical activity score[f]	310 (70, 825)	320 (70, 720)
BMD, g/cm^2		
Femoral neck BMD	0.83 (0.74, 0.94)	—
Lumbar spine BMD	1.06 (0.93, 1.17)	—
Composite indices of femoral neck strength, g/kg · m		
Compression strength index	3.50 (3.07, 4.06)	—
Bending strength index	1.19 (1.03, 1.37)	—
Impact strength index	0.20 (0.17, 0.23)	—
AL score (range 0–7)[g]	1.90 (1.03, 2.77)	1.90 (1.03, 2.77)
System dysregulation scores (range 0–1)		
Sympathetic system	0 (0, 0.50)	0 (0, 0.50)
Parasympathetic system	0 (0, 0.50)	0 (0, 0.50)
HPA axis	0 (0, 0.50)	0 (0, 0.50)
Cardiovascular regulation	0.33 (0, 0.67)	0.33 (0, 0.67)
Inflammation	0.20 (0, 0.40)	0.20 (0, 0.40)
Glucose metabolism	0.33 (0, 0.67)	0 (0, 0.67)
Lipid metabolism	0.20 (0, 0.40)	0.20 (0, 0.40)

[a] Common reasons for exclusion of MIDUS II Biomarker Project participants from the study sample were missing BMD (n = 356), use of medications known to influence bone (n = 93), and unclassifiable menopausal transition stage (n = 87).

[b] Sample sizes were smaller than 703 for smoking pack-years (n = 638), heavy alcohol consumption (n = 698), current physical activity score (n = 701), and the parasympathetic system score (n = 668).

[c] Childhood socioeconomic advantage score (range 0–6) on welfare (0, yes; 2, no) + financial status relative to others (0, worse off; 1, same; 2, better) + parental education (0, less than high school; 1, high school/general educational development certificate; 2, some college or more).

[d] Current adult financial advantage score (range 0–8) for family income (0 if FPIR < 3; 1 if FPIR ≥ 3 but < 6; 2 if FPIR ≥ 6) + self-rated financial situation (0, worst; 1, average; 2, best) + enough money to meet needs (0, not enough; 1, just enough; 2, more than enough) + degree of difficulty paying bills (0, very; 1, not very; 2, not at all).

[e] More than seven drinks per week or more than three drinks per occasion regularly for women, more than 14 drinks per week or more than four drinks per occasion regularly for men in the past month.

[f] Current physical activity level score was calculated by adding the reported times for light (weight of 1), moderate (weight of 2), and vigorous (weight of 3) activity.

[g] Total score of AL was computed only for participants who had scores for at least six of the seven systems, with the missing system score imputed (for 53 participants).

smoking status (current, former, or never), pack-years of smoking, heavy alcohol consumption (yes vs no), and physical activity score (ordinal). Finally, we tested for potential interactions between AL and gender.

All statistical tests were two sided. Values of $P < .05$ were considered statistically significant for main effects and $P < .15$ for interactions. Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc) and STATA version 12.1 (StataCorp LP).

Results

The study sample (n = 703) was similar to the complete MIDUS Biomarker Project samples (n = 1255) with respect to most characteristics (Table 2), except that University of Wisconsin-Madison (in which the African American refresher sample was examined) was more heav-

ily represented in the study sample because it was able to get funding to collect DXA scans before the other two centers.

The median age in the study sample was 56 years, 48% were men, and 71% were white. The mean AL score was 1.95 and SD was 1.15. The median and interquartile range for AL score were 1.77 and 0.93–2.55 in men and 2.03 and 1.03–2.89 in women, respectively. The seven system dysregulation scores that contributed to AL had means between 0.21 and 0.37 and SDs between 0.26 and 0.36. The pairwise Spearman correlation coefficients between the system dysregulation scores ranged from −0.11 to 0.37. The Pearson (and Spearman) correlation coefficient between BMI and AL was 0.34 (and 0.37).

In mixed-effects linear regression controlling for clustering within families and adjusted for covariates, each SD increment in AL score was associated with between 0.10 and 0.11 SD decrements in lumbar spine BMD and each of the three composite strength indices (one value of $P < .01$ and three values of $P < .05$). In parallel models with individual system dysregulation scores, higher levels of the parasympathetic and glucose dysregulation scores were each strongly associated with lower bone strength (Table 3).

In interaction testing, gender modified the association of AL with femoral neck BMD ($P = .11$) but not with the other four measures ($P > .25$). In gender-stratified analysis (sample size: men 339, women 364), AL was significantly associated with femoral neck BMD in men ($P < .01$) but not in women ($P = .56$). Controlling for clustering within families and adjusted for the same set of covariates as above (except for gender), each SD increment in AL score was associated with 0.21 SD decrement in femoral neck BMD in men [95% confidence interval (CI) −0.34, −0.09] and with 0.03 SD decrement in femoral neck BMD in women (95% CI −0.14, 0.08). Of the seven systems, only the cardiovascular regulation score was associated with femoral neck BMD in men: each SD increment in the cardiovascular regulation score was associated with 0.17 SD decrement in femoral neck BMD in men (95% CI −0.28, −0.06).

In sensitivity analysis with the alternate AL (without medication data), the associations with bone strength were very similar except for the association with lumbar spine BMD, which became nonsignificant ($P = .12$). Also, additional adjustment for health behaviors (smoking, heavy alcohol intake, and physical activity level) did not attenuate the standardized effect sizes (data not shown).

Discussion

As hypothesized, accumulation of dysregulation across multiple physiological systems was associated with lower bone strength: Higher AL was associated with lower lumbar spine BMD and lower values of all of the three composite indices of femoral neck strength relative to load. Compared with an individual with AL score of 1.03 (the 25th percentile value), an individual with AL score of 2.77 (the 75th percentile value) had 0.15–0.17 SD lower lumbar spine BMD and the composite strength indices. In men, higher AL was also associated with lower femoral neck BMD: femoral neck BMD in a man with an AL score at 2.55 (the 75th percentile in men) was 0.18 SD lower

Table 3. Adjusted[a] Effect Sizes[b] (and 95% Confidence Intervals) for Cross-Sectional Associations of AL Score and System Dysregulation Scores With Bone Strength Measures

	Femoral Neck BMD (Mean 0.84, SD 0.14)	Lumbar Spine BMD (Mean 1.06, SD 0.18)	Femoral Neck Compression Index (Mean 3.59, SD 0.87)	Femoral Neck Bending Index (mean 1.21, SD 0.28)	Femoral Neck Impact Index (Mean 0.20, SD 0.04)
AL	−0.082 (−0.166, 0.002)	−0.103 (−0.198, −0.009)[c]	−0.111 (−0.200, −0.023)[c]	−0.100 (−0.177, −0.023)[c]	−0.101 (−0.171, −0.030)[d]
System dysregulation scores					
Sympathetic nervous system	−0.033 (−0.11, 0.040)	−0.050 (−0.13, 0.028)	−0.010 (−0.084, 0.064)	−0.028 (−0.10, 0.044)	−0.032 (−0.096, 0.032)
Parasympathetic nervous system	−0.067 (−0.13, −0.0056)[c]	−0.0038 (−0.081, 0.073)	−0.075 (−0.13, −0.023)[d]	−0.073 (−0.14, −0.0065)[c]	−0.078 (−0.14, −0.019)[c]
HPA axis	−0.024 (−0.091, 0.044)	0.011 (−0.065, 0.087)	−0.023 (−0.088, 0.042)	0.019 (−0.045, 0.084)	0.037 (−0.022, 0.096)
Cardiovascular regulation	−0.027 (−0.11, 0.052)	−0.059 (−0.16, 0.043)	−0.041 (−0.11, 0.024)	−0.041 (−0.12, 0.039)	−0.031 (−0.10, 0.039)
Inflammation	0.027 (−0.052, 0.11)	0.0027 (−0.080, 0.085)	−0.037 (−0.10, 0.027)	−0.023 (−0.092, 0.046)	−0.016 (−0.077, 0.045)
Glucose metabolism	−0.053 (−0.14, 0.035)	−0.054 (−0.15, 0.042)	−0.089 (−0.16, −0.016)[c]	−0.108 (−0.18, −0.032)[d]	−0.103 (−0.18, −0.030)[d]
Lipid metabolism	−0.002 (−0.092, 0.088)	−0.011 (−0.11, 0.089)	−0.039 (−0.11, 0.032)	−0.051 (−0.14, 0.034)	−0.040 (−0.11, 0.034)

[a] From mixed-effects linear regression controlling for clustering within families and adjusted for age, gender, race/ethnicity, BMI, menopausal transition stage, childhood socioeconomic advantage score, adult financial advantage score, education level, and study center.

[b] Units: SD of bone strength measure per SD increment in predictor.

[c] $P < .05$.

[d] $P < .01$.

than the femoral neck BMD in a man with AL score at 0.93 (the 25th percentile in men).

Previous studies have shown that each SD increment in the composite strength indices was associated with a 34%–41% relative decrement in the rate (hazard) of fracture at any site in women going through the menopausal transition (18) and a 57%–66% relative decrement in the risk of hip fracture over 10 years in postmenopausal women (17). If the AL-related differences in the composite strength indices seen in this study lead to similar fracture risk differences, each SD increment in AL score would be associated with a 4%–6% relative increase in fracture hazard in women going through the menopausal transition and an 8%–11% relative increase in a 10-year hip fracture risk in postmenopausal women.

The median AL score in the study sample was 1.90 and the interquartile range was 1.03–2.77. Because no single system could contribute more than 1 point to the AL score and the median system dysregulation scores were all less than 0.4, this implies that most of the sample had dysregulation in multiple systems. It is this exposure to dysregulation across multiple systems that appears to be the driving factor in lower bone strength. Examined on their own, dysregulation in individual systems was inconsistently associated with lower bone strength. Only parasympathetic system dysregulation was significantly associated with four of the five bone strength measures, and glucose dysregulation was significantly associated with three of the five strength measures. These system-specific findings are consistent with one previous study that documented an association between diminished parasympathetic activity and osteoporosis in postmenopausal women (27) and with one previous study that noted an association between dysglycemia and lower values of the composite strength indices in women going through the menopausal transition (19). Our study extends these findings to a national sample with both genders and a larger age range.

The precise mechanism of parasympathetic regulation of bone is not fully understood, but one hypothesis is that at physiological concentrations, acetylcholine, a neurotransmitter released by parasympathetic innervation, simulates osteoblast proliferation and up-regulates expression of osteoblast genes for bone formation (28, 29). Like ours, previous studies have not consistently found an association between glucose dysregulation and lower BMD; some have even found BMD to be higher (not lower) in diabetes (16). This study does, however, confirm previously seen links between glucose dysregulation and lower bone strength relative to load (19), which may be more relevant to fracture risk than BMD (17–20, 30–32).

Although previous studies have seen associations between lower bone strength and dysregulation in sympathetic, HPA axis, cardiovascular regulation, inflammation, or lipid metabolism systems (33–37), we did not find significant associations in these systems in this diverse, population-based sample. Despite that, dysregulation across multiple systems was strongly associated with lower bone strength: the more the number of systems affected, the lower the bone strength. These findings support the importance of combining information from multiple systems in assessing biological pathways to adverse health outcomes (4, 6, 7, 9).

We found AL was associated with lower femoral neck BMD in men but not in women, which is consistent with previous studies showing some of the effects on bone strength seen only in men (38, 39). The reason for this gender difference is unclear, but one possibility is that the effects of AL are masked by the large changes in bone strength during the menopausal transition (40).

There are some important limitations to this study. First, this is a cross-sectional study, which does not allow us to infer a causal pathway from higher AL to lower bone strength. Second, not everyone in the MIDUS Biomarker Project underwent BMD measurements because of delays in obtaining funding for the DXA scans in two centers, leading to overrepresentation of African Americans in the study sample. Third, those who were medically unsafe to travel to one of the study centers were excluded from the Biomarker Project, which may have led to some selection bias. Also, the inability to determine menopausal transition stage, a major determinant of bone strength, led to the exclusion of some women. In addition, overnight stays at the study centers (away from home and possibly in a different time zone) might disrupt regular sleep patterns, even in participants without sleep disorders, leading to inaccurate assessments of resting neuroendocrine hormone levels from the overnight urinary samples.

Despite these limitations, this study has several strengths. This is the first large study to show that higher AL is associated with lower bone strength. Second, the study used data from a national sample with a wide age range, rigorous classification of menopausal transition stage, and comprehensive assessment of 24 biomarkers across seven systems. The collection of fasting blood assays allowed measurement of LDL cholesterol, triglycerides, and insulin resistance, and the collection of overnight urines allowed for neuroendocrine measurements from the sympathetic and HPA axis systems, and the measurement of heart rate variability allowed assessment of parasympathetic functioning.

In conclusion, accumulation of dysregulation across multiple physiological systems was modestly associated

with lower bone strength in adults from a national sample. This study adds to the accumulating evidence that multisystem dysregulation, or AL, predicts a variety of adverse health outcomes. Further standardization and validation of AL is needed before it can be used clinically for prognostication. Future research will also determine whether AL indeed mediates associations between psychosocial adversity and lower bone strength.

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