Published in final edited form as:

Biol Res Nurs. 2009 January ; 10(3): 248–256. doi:10.1177/1099800408323452.

Allostatic Load and Frailty in the Women's Health and Aging Studies

S. L. Szanton, CRNP, PhD, J. K. Allen, RN, ScD, C. L. Seplaki, PhD, K. Bandeen-Roche, PhD, and L. P. Fried, MD, MPH

From the Johns Hopkins University School of Nursing (SSL, AJK, FLP), Johns Hopkins University School of Public Health (SCL, BRK, FLP), and Johns Hopkins University School of Medicine (AJK, FLP), Johns Hopkins University, Baltimore, Maryland

Abstract

Background—Frailty involves decrements in many physiologic systems, is prevalent in older ages, and is characterized by increased vulnerability to disability and mortality. It is yet unclear how this geriatric syndrome relates to a preclinical cumulative marker of multisystem dysregulation. The purpose of this study was to evaluate whether allostatic load (AL) was associated with the geriatric syndrome of frailty in older community-dwelling women.

Methods—We examined the cross-sectional relationship between AL and a validated measure of frailty in the baseline examination of two complementary population-based cohort studies, the Women's Health and Aging studies (WHAS) I and II. This sample of 728 women had an age range of 70–79. We used ordinal logistic regression to estimate the relationship between AL and frailty controlling for covariates.

Results—About 10% of women were frail and 46% were prefrail. AL ranged from 0 to 8 with 91% of participants scoring between 0 and 4. Regression models showed that a unit increase in the AL score was associated with increasing levels of frailty (OR = 1.16, 95% CI = 1.04–1.28) controlling for race, age, education, smoking status, and comorbidities.

Conclusion—This study suggests that frailty is associated with AL. The observed relationship provides some support for the hypothesis that accumulation of physiological dysregulation may be related to the loss of reserve characterized by frailty.

Keywords

frailty; allostatic load; older adults; physiologic dysregulation

clinicians and researchers have become increasingly interested in the geriatric syndrome of frailty (Bergman et al., 2007; Walston et al., 2006). Frailty, though measured in different ways, involves decrements in many systems, is prevalent in older ages, and is characterized by increased vulnerability to disability and mortality (Bandeen-Roche et al., 2006; Fried et al., 2001; Fried, Ferrucci, Darer, Williamson, & Anderson, 2004; Rockwood, Mitnitski, Song, Steen, & Skoog, 2006; Woods et al., 2005). Discovering why some older adults become frail while others do not is becoming increasingly urgent as the older adult population escalates.

Many factors have been associated with frailty (Bartali et al., 2006; Barzilay et al., 2007; Cappola et al., 2003; Leng, Xue, Tian, Walston, & Fried, 2007; Michelon et al., 2006; Semba et al., 2006). Broadly categorized, these factors include intrinsic physiologic aging changes (Cappola et al., 2003; Morley & Baumgartner, 2004), diseases and conditions such as heart failure and cancer (Cohen & Mather, 2007), and factors extrinsic to the individual, such as low nutrient intake (Bartali et al., 2006). In this study, we explore the relationship between allostatic load (AL) and frailty as an examination of an extrinsic factor possibly related to frailty.

AL is the term proposed for cumulative physiologic dysregulation as a response to a lifetime of regulating the internal milieu of the body to the external demands of daily life (McEwen & Stellar, 1993; McEwen, 1998). AL is a preclinical marker of patho-physiologic processes hypothesized to precede the onset of disease or disability (Seeman, Singer, Ryff, Dienberg, & Levy-Storms, 2002). AL has been found to vary by sociodemographic factors such as race and socioeconomic status (Geronimus, Hicken, Keene, & Bound, 2006) as well to predict cardiovascular disease, cognitive decline, and mortality (Seeman et al., 2004; Seeman, McEwen, Rowe, & Singer, 2001).

Previous research has shown that aspects of AL are related to aspects of frailty; major physiologic regulatory systems represented in AL are related to components of frailty. For example, declines in strength are associated with low levels of insulin-like growth factor (IGF-1) in the setting of high levels of interleukin 6 (IL-6; Barbieri et al., 2003; Visser et al., 2002) and exhaustion is associated with inflammation (Kop et al., 2002). However, while there has been significant work on pairwise associations between individual factors and frailty components, the relationship between multicomponent AL and the multisystem clinical syndrome of frailty is not established. Because multiple components of the systems may interact simultaneously, additional information could be observed from the relationships between these two summary indicators beyond the pairwise relationships already established. We hypothesized that AL, as a physiologic expression of cumulative life experience to external inputs, would be related to an indicator of decreased reserve such as frailty.

Methods

Study Population and Measures

Data are from the Women's Health and Aging Studies (WHAS) I and II, two prospective population-based cohort studies that recruited community-dwelling older women complementary with respect to physical function status. Participants in WHAS I were eligible if they were women aged 65 or older, had difficulty in two or more areas of physical function (thus representing the one third most disabled older women in the community), and had a Mini-Mental State Examination of at least 18. Participants in WHAS II were eligible if they were women between 70 and 79 years of age, had difficulty in no or only 1 area of physical function (thus drawn from among the two thirds least disabled), and had at least a 24 on the Mini-Mental State Examination. Sampling for both studies have been described elsewhere (Fried, Bandeen-Roche, Chaves, & Johnson, 2000; Guralnik, Fried, Simonsick, Kasper, & Lafferty, 1995). Briefly, WHAS participants were randomly selected from a Medicare sampling frame from 12 zip codes of Eastern Baltimore City and Baltimore County. Baseline assessments were performed in 1992–1995 in WHAS I and 1994–1996 in WHAS II. About 71% of the 1,409 women screened and eligible for WHAS I and 49.5% of the 880 women who were screened and eligible for WHAS II agreed to participate.

In WHAS I, among those eligible, participants were slightly younger, more often African-American, and had more formal education than nonparticipants, but differences were not significant (Guralnik et al., 1995). In WHAS II, nonparticipants had poorer self-rated health status, were less educated, and had lower income than those who participated (Chaves, Garrett,

& Fried, 2000). Baseline data from the 70- to 79-year-old participants of WHAS I and WHAS II were pooled for this analysis. This limited the total number of possible participants to 768. The Johns Hopkins Medical Institutional Review Board approved the research protocols. Each participant provided written informed consent.

Sampling Weights

Data were weighted in all analyses to account for the sampling design and to correct for nonresponse. Original weights, described in Guralnik et al. (1995), were calculated for each participant based on the probability of selection into the study (Guralnik et al., 1995). These probabilities varied based on disability status, age, and race. In the current analysis, a supplementary weight was necessary to account for different proportions of participants contributing blood data between WHAS I and WHAS II. This weight was calculated by multiplying the original probability weight by the inverse of the probability of contributing blood data. The correction factor was calculated by study and age group. The sampling weights were used to reference back to the entire population of community-dwelling women.

Measures

AL was constructed based on the methods of Seeman and colleagues (McEwen & Seeman, 1999; Seeman et al., 2001) to summarize biomarkers for multiple physiologic systems. The score represents the sum of the number of biomarkers for which the participant's values fall in the quartile of highest clinical risk. Biomarkers included in our calculation of AL were creatinine clearance, glycosylated hemoglobin (HbA1c, a measure of glucose metabolism over 90 days), serum dihydroepiandrosterone sulphate (DHEA-S, an antagonist to the HPA axis; Kimonides, Khatibi, Svendsen, Sofroniew, & Herbert, 1998), interleukin 6 (IL-6, a measure of inflammation), insulin-like growth factor 1 (IGF-1, which may play a role in oxidative stress; Holzenberger et al., 2003), ratio of total cholesterol to high density lipoprotein, triglycerides, systolic blood pressure, and diastolic blood pressure and body mass index (BMI; Table 1 of quartile cutpoints for illustration). Our calculation of AL differs from that of recent formulations by Seeman and colleagues (Seeman et al., 2004) in that we do not have data on cortisol, epinephrine, norepinephrine, or waist/hip ratio. We use DHEA-S to reflect the HPA axis, and BMI as a substitute for waist/hip ratio. Other studies of AL have used this formulation of AL because of variable availability (Szanton, Gill, & Allen, 2005).

Nonfasting baseline blood samples were obtained by venipuncture, processed, placed on ice, and sent the same day to Quest Diagnostics, Inc. (Teterboro, NJ). Creatinine clearance was calculated using the Cockcroft-Gault formula that models renal function based on creatinine, body mass, and age (Cockcroft & Gault, 1976). Glycosylated hemoglobin was measured using low-pressure cation exchange chromatography (Glycomat, Palo Alto, CA). DHEA-S was measured by enzyme-linked immunosorbent assay (ELISA, American Laboratory Products Company, Salem, NH). Plasma IL-6 was measured using an enzyme-linked immunosorbent assay (Quantikine human interleukin-6; R&D Systems, Inc., Minneapolis, MN). IGF-1 was measured by Radioimmuno Assay with ethanol extraction (Nichols Institute Diagnostics, San Juan Capistrano, CA) at the time of blood collection. Total cholesterol, triglycerides, and high density lipoprotein were measured using an automated enzymatic method. Systolic and diastolic blood pressures were measured 3 times according to JNC 6 guidelines (Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, 1997) and the average of the 3 measures is used here. BMI, measured during baseline physical evaluation, was calculated as weight in kilograms divided by the square of height in meters.

Participants missing values from more than 3 components of the variables measuring AL were excluded (N = 34). We imputed biomarker values for participants with 1–3 missing observations (total imputed values = 149) using a weighted multiple linear regression model

of each participant's 8 to 10 available AL components. The mean and distribution of the resulting imputed values were checked for consistency with the nonimputed distributions. The sample size after exclusions was 728 women. Participants who did not provide blood samples had significantly more disability in activities of daily living ($p < .05$), but did not differ in number of chronic diseases, frailty status, or education.

Measurement of Frailty

Participants were defined as frail, prefrail, or nonfrail using standardized criteria, developed by Fried and colleagues (Bandein-Roche et al., 2006; Fried et al., 2001; see Table 2 for categorization details), relating to weight loss/underweight, slow walking speed, weakness, self-reported exhaustion, and low physical activity. Participants were considered frail by standardized criteria if they were positive for three or more of these characteristics. Participants were considered prefrail if they had 1–2 of the characteristics and nonfrail if they had none. Weight loss/underweight was determined by $\geq 10\%$ weight loss since the age of 60 or a BMI less than 18.5. Slow walking speed was determined as those in the lowest quintile of usual walking pace across 4 m. Low grip strength was measured as the lowest quintile using a Jamar Dynamometer. Exhaustion was measured by whether a participant had a positive answer to any of the following three items: description of low energy level (defined as less than 3 on a 0–10 Likert scale with 0 = *no energy* and 10 = *the most energy you have ever had*), description of being unusually tired in the last month, or unusually weak in the last month. Energy expenditure was measured with the Minnesota Leisure Time Activity Questionnaire; participants who reported 90 kcals expended per week based on 6 activities were considered to exhibit low energy expenditure (Folsom, Jacobs, Caspersen, Gomez-Marín, & Knudsen, 1986). These activities were walking, performing strenuous household or outdoor chores, dancing, bowling, and exercise.

Covariates

Multivariable regression models included controls for race, age, education, and numbers of chronic diseases as these have been related to both frailty and AL. Education was grouped as <8 years, 8–11 years, 12 years, >12 years. Race was coded as black or white based on participant self-report. Age was measured in years and restricted to 70–79 (the age range of WHAS II). The following diseases and conditions were established by two physicians based on predefined diagnostic criteria: congestive heart failure, degenerative disc disease, spinal stenosis, hip fracture, and osteoporosis; osteoarthritis of the knee, hip and hand, and rheumatoid arthritis; stroke, Parkinson's disease, pulmonary disease, diabetes mellitus, peripheral arterial disease, and cancer (Guralnik et al., 1995). Number of chronic diseases or conditions was measured as 0, 1, 2, or greater than or equal to 3. Smoking history was measured by whether the participant had ever consistently smoked.

Analysis

Descriptive statistics were compared for participants based on frailty status. Because the frailty measure consists of three ordered categories (nonfrail, prefrail, and frail), we used a weighted ordinal logistic regression model to evaluate differences across frailty categories (Table 3). To test the hypothesis that increased AL is related to increasing likelihood of frailty, we performed multivariable analyses using weighted ordinal logistic regression (a proportional odds model). This approach models cumulative odds as a function of predictors. Based on previous research, we hypothesized that those with higher education might have a higher physiological reserve and differ from those with less education in the association between AL and frailty. To investigate this, we tested an interaction between education group and frailty. We also hypothesized that there might be an interaction between education and race because of the difference in the quality of the education that African American women had access to compared

to white women when this population of 70- to 79-year-old women was educated. This interaction was also tested and was not statistically significant. All models were examined for fit to data using Pearson residual plots and statistics evaluating leverage and collinearity and were found to fit appropriately. The proportional odds assumption was tested using a nested model approach comparing the ordinal model with multinomial logistic regression (Stata Corporation, 1999). All analyses and statistical methods used Stata version 9.0 (College Station, TX).

Results

Baseline characteristics of participants are described in Table 3, categorized by frailty status. In the study, 76% of the women were white, 23% had an eighth grade education or less. At baseline, 44% of women were nonfrail, 46% were prefrail, and 10% were frail.

AL ranged from 0 to 8 out of a possible 11 with 91% of participants scoring between 0 and 4. AL was not significantly related to race, education, or pack-years of smoking using regression models. About 30% of the participants had no chronic diseases, 36% had 1, 18% had 2, and the remaining 16% had 3 or more.

Frailty was more prevalent in those without a high school degree regardless of race (16.7% vs. 5.6%, chi-square p value < .000). In univariable analyses, African Americans were more likely to be frail than whites (13.4% vs. 9.5%, p < .01). However, this relationship was an artifact of differential education in the sample. There was no relationship between race and frailty when education was included in bivariable analyses (OR = 0.86, 95% CI = 0.61–1.32).

In ordered logistic regression analysis, higher AL was associated with increasing frailty across three categories (OR = 1.19, 95% CI = 1.07–1.31, p < .05) controlling for age, race, and education (Table 4). Both smoking status and disease count were associated with frailty but only slightly decreased the association between AL and frailty. The odds ratio for increased frailty for each increment of increase in AL changed to 1.16 (95% CI = 1.04–1.38) after adjustment for smoking status and disease count. Race was not significant in the model but was included because of the previously documented association between race and frailty (Hirsch et al., 2005). Age was not a significant predictor of frailty which may reflect the truncated age range used.

Sensitivity Analyses of Results

We further checked our findings with sensitivity analyses. First, we tested models including only participants with complete AL indicators and found similar results for the relationship between AL and frailty (OR 1.23, 95% CI = 1.10–1.38). Second, we performed an analysis in which missing variables were not allowed to contribute to the overall AL score (OR = 1.22, 95% CI = 1.11–1.34). Third, we assessed the predictive accuracy of the AL summary score by calculating the area under the receiver operating characteristic (ROC) curves for each individual AL factor and frailty, as well as for the summary score and frailty. To do this, we were required to collapse the nonfrail and prefrail together to make a binary frailty categorization. The summary AL score proved slightly more predictive than the individual factors (0.60 for the summary score compared to a range of 0.50–0.59). Sensitivity to our categorization of frailty was assessed by creating a binary frailty variable (grouping nonfrail and prefrail together) to perform an ordinary logistic regression and compare the results with those of the ordinal regressions. This analysis showed similar odds ratios of higher AL to binary frailty (OR 1.21, 95% CI = 1.06–1.40) in the unadjusted model and 1.21 (95% CI = 1.04–1.40) in the full model.

Discussion

Increased AL was moderately associated with increased odds of frailty in this study of older women across the full spectrum of physical function in the community. This is the first time, to the authors' knowledge, that the association between AL and frailty has been examined empirically. In previous research, both AL and frailty have predicted morbidity and mortality in older adults (Bandein-Roche et al., 2006; Fried et al., 2001; Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002; Seeman et al., 2001). The observation here that they are related has implications for the health of the burgeoning geriatric population. AL may represent the body's response to common environmental demands as well as intrinsic changes with aging and superimposed diseases. Testing that distinction is out-side the scope of this article.

There is a growing body of work on the role of multi-system dysregulation in the health of older adults (Cappola et al., 2003; Seplaki, Goldman, Gleib, & Weinstein, 2005; Seplaki, Goldman, Weinstein, & Lin, 2006). This article extends that work to include the range of factors involved in AL. If it is possible to identify a common pathway to decrease patients' multiple dysregulations, then nurses and other clinicians may be able to intervene on this pathway and consequently decrease the prevalence of frailty.

There is significant work on frailty, which suggests that deficit accumulation (e.g., decreased cognition, incontinence, hypertension) is the important phenomenon in the onset of frailty (Rockwood & Mitnitski, 2007). According to this work, the relationship between AL and the syndrome of frailty might be because of the accumulation of deficits rather than the physiologic changes underlying AL, or perhaps even some combination of such precipitating factors.

There are several limitations to the current study. This analysis was cross sectional, so we cannot infer that increased AL caused the propensity to be frail. Although hypothesized to be temporally first, it is possible that the frailty in itself has increased the AL. Longitudinal studies are needed to rule out such reverse causation. Second, this measure of AL was limited by variable availability. Measures included in prior studies (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997; Seeman et al., 2001; Seeman et al., 2004; Szanton et al., 2005) that were absent from the WHAS included primary indicators of the HPA-axis and sympathetic nervous system, specifically cortisol, norepinephrine, and epinephrine. Third, although the participants were drawn from a population-sampling frame, not every person approached consented to be in the study. The people who declined study participation could have been those most likely to be frail; if so, these results may be conservative. Finally, like most observational studies, because the WHAS studies are observational and frailty is multi-factorial in etiology, it is possible that participants with higher AL were more likely to be frail for other unmeasured reasons.

To our knowledge, this is the first study that empirically examines the relationship between the dysregulation constructs theorized to underlie both AL and frailty. Second, our data come from a population-based study with strictly standardized measures. A third strength was rigorous statistical methods and multiple sensitivity analyses.

Summary

In community-dwelling older women, AL, a measure of cumulative dysregulation, was associated with frailty, independent of chronic disease. Whether the association between AL and frailty is causal is unproven. However, this study provides some support for the hypothesis that accumulation of dysregulation may be associated with the loss of reserve characterized by frailty.

Acknowledgments

This work was supported by National Institutes of Health grants 1F31NR009470-01, 1-T32 NR07968-01, R01 AG11703, 1R37AG1990502, the John A. Hartford Foundation Building Academic Geriatric Nursing Capacity Scholars Program and by the Johns Hopkins Older Americans Independence Center (1P50AG 021334-01).

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Table 1

Quartile Cutpoints for Measured Components of Allostatic Load in Women's Health and Aging Studies at Baseline

Table of Cutpoints	Variable Min/Max	Quartile Cutpoint	<i>M (SD)</i>
Body mass index	14/49	30.5	27.5 (0.2)
Low creatinine clearance (ml/min)	13/113	46.2	57.3 (0.6)
High glycosolated hemoglobin (%)	4.4/15.6	7.9	7.2 (0.1)
High triglycerides (mg/dl)	34/584	205	163.9 (3.8)
Low DHEA-S (μg/dl)	0.9/2.2	0.24	.52 (0.01)
High interleukin-6	0.55/52.8	3.95	2.73 (4.87)
Low insulin-like growth factor (ng/ml)	12.8/446	91	126.0 (2.2)
Ratio of total cholesterol/HDL	2.01/10.6	5.39	4.5 (0.06)
High diastolic blood pressure (mm/Hg)	47/129	81	73.4 (0.5)
High systolic blood pressure (mm/Hg)	91/215	161	147.0 (0.9)

NOTES: DHEA-S = dihydroepiandrosterone sulphate; HDL = high density lipoprotein.

Table 2**Frailty Classification Criteria**

Criterion	Operational Definition
Weight loss/underweight	Unintentional weight loss $\geq 10\%$ since age of 60, or BMI < 18.5
Slowness	Time to walk 4 m at usual pace, according to height: ≤ 0.65 m/s for height ≤ 1.59 m; ≤ 0.76 m/s for height > 1.59m
Weakness	Grip strength of the dominant hand, categorized by BMI: ≤ 17 kg for BMI ≤ 23 ; ≤ 17.3 kg for those with BMI > 23 and ≤ 26 ; ≤ 18 kg for those with BMI > 26 and ≤ 29 ; ≤ 21 kg for BMI > 29
Exhaustion	Any of the following during the previous month: Low usual energy level (≤ 3) ^a ; felt unusually tired in past month; felt unusually weak in past month
Low physical activity	Self-reported, estimated energy expenditure in kcal based on participation in six activities in the Minnesota Leisure Time Activity Scale: <90 kcal/week

NOTE: BMI = body mass index.

^a 10-point Likert scale with 0 = no energy and 10 = the most energy you ever had. Participants were considered: frail, if ≥ 3 criteria present; prefrail, if 1–2 of the criteria present; nonfrail, if none.

Table 3
Sample Characteristics: Comparison by Frailty Categorization

	Total (N = 728)	Nonfrail (N = 303)	Prefrail (N = 350)	Frail (N = 76)	p Value for trend [*]
Mean age (SD)	74.2 (0.1)	74.0 (2.8)	74.3 (2.7)	74.7 (3.0)	.03
Mean years in school (SD)	11.3 (3.6)	12.6 (0.2)	11.2 (0.4)	9.5 (0.4)	.03
White %	76	80	75	70	.08
Allostatic load (SD)	2.5 (0.1)	2.22 (0.09)	2.59 (0.09)	2.87 (0.17)	<.001
Body mass index (SD)	27.5 (0.2)	26.6 (0.31)	28.1 (0.38)	29.6 (0.98)	.05
Creatinine clearance, ml/min (SD)	57.3 (0.6)	54.9 (0.9)	58.6 (1.0)	62.78 (2.8)	<.001
Glycosolated hemoglobin, % (SD)	7.2 (0.1)	6.7 (0.08)	7.5 (0.11)	8.0 (0.22)	<.001
Triglycerides (mg/dl)	163.9 (3.8)	150.8 (4.9)	173.3 (6.1)	194.0 (15.5)	<.001
Dihydroepiandrosterone-sulphate, ug/dl (SD)	.52 (0.01)	.57 (0.02)	.48 (0.02)	.41 (0.04)	<.001
Interleukin-6 (SD)	2.73 (0.19)	3.18 (0.13)	3.78 (0.34)	4.86 (1.01)	<.002
Insulin-like growth factor 1, ng/mL (SD)	126.0 (2.2)	124.9 (2.9)	127.0 (3.7)	118.7 (7.4)	.85
Ratio of total to high density lipoprotein cholesterol (SD)	4.50 (.06)	4.4 (.08)	4.6 (.09)	4.7 (.17)	.02
Systolic blood pressure, mmHg (SD)	147.0 (.9)	150.6 (1.3)	143.4 (1.3)	142.2 (2.76)	<.001
Diastolic blood pressure, mm Hg (SD)	73.4 (.5)	75.6 (.9)	71.6 (.72)	68.4 (1.77)	<.001

NOTE: DHEA-S = dihydroepiandrosterone sulphate.

Nonfrail, prefrail, and frail are categorized based on unintentional weight loss/underweight, slow walking speed, weakness, self-reported exhaustion, and low physical activity. Greater than or equal to 3 characteristics is frail, 1–2 of the same characteristics is prefrail and nonfrail is none. Creatinine clearance was calculated by the Cockcroft-Gault equation.

* p-Value for trend was tested by ologit and represents the T of the ologit test of differences in means between the 3 groups.

Table 4Adjusted Odds Ratios of Increasing Frailty Level for Allostatic Load, Age, Race, and Education, $N = 728$

	Point Estimate of Odds Ratio (95% Confidence Interval)	
	Model A	Model B
Allostatic load ^a	1.19 (1.07–1.31)	1.16 (1.04–1.28)
Age in years ^b	1.05 (0.99–1.11)	1.06 (1.00–1.12)
Race ^c	0.97 (0.65–1.43)	.95 (.65–1.40)
Education ^d	1.64 (1.42–1.89)	1.60 (1.39–1.85)
Disease count ^e		1.47 (1.26–1.71)
Smoking status ^f		1.38 (1.10–1.73)

NOTE: Numbers in bold are statistically significant. Each odds ratio is adjusted for the other predictors. All predictors were included in one multivariable ordinal logistic regression model ($N = 728$).

^a Odds ratio per unit increment in score. Range of scores in sample: 0–8.

^b Odds ratio per year increment in age. Age range in sample: 70–79.

^c Odds ratio for black versus white.

^d Odds ratio in ordinal measure of <8, 9–11, 12, >12 years of educational attainment.

^e Odds ratio for one, two, or three or more diseases.

^f Odds ratio for smoking status: current versus ex-smoking versus never smoked.