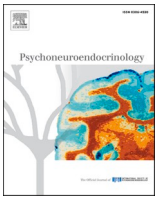
Psychoneuroendocrinology 149 (2023) 106022

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



# Longitudinal association of allostatic load with depressive symptoms among urban adults: Healthy Aging in Neighborhoods of Diversity across the Life Span study

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ARTICLE INFO

*Keywords:*
Allostatic load
Depressive Symptoms
Disparities
Longitudinal study
Race
Sex

ABSTRACT

*Background:* Evidence suggests that lifetime exposure to stressful life events and chronic stressors may be linked to geriatric depression. Allostatic load (AL) is considered a mediator of the stress-health relationship and has been linked to psychosocial factors reflecting health disparities. The purpose of this study was to examine the longitudinal associations of AL with depressive symptoms scores among urban adults, before and after stratifying by sex and race.

*Methods:* Secondary analyses were performed using Visit 1 (2004–2009), Visit 2 (2009–2013) and Visit 3 (2013–2017) data collected on 2298 Healthy Aging in Neighborhoods of Diversity across the Life Span study participants (baseline age: 30–64 y). AL at Visit 1 ($AL_{v1}$) and z-transformed probability of higher AL trajectory ($AL_{traj}$) between Visits 1 and 3 were calculated using cardiovascular, metabolic and inflammatory risk indicators. The 20-item Center for Epidemiologic Studies Depression (CES-D) scale was used to calculate total and domain-specific depressive symptoms scores. Mixed-effects linear models controlled for socio-demographic, lifestyle and health characteristics.

*Results:* In fully adjusted models, a positive cross-sectional relationship was observed between $AL_{v1}$ and "somatic complaints" depressive symptoms ($\beta = 0.21$, $P = 0.006$) score at Visit 1, whereas $AL_{traj}$ was associated with increasing depressive symptoms score ($\beta = 0.086$, $P = 0.003$) between Visits 1 and 3. An inverse relationship was observed between $AL_{traj}$ and "positive affect" depressive symptoms score at Visit 1 among women ($\beta = -0.31$, $P < 0.0001$) and White adults ($\beta = -0.32$, $P = 0.004$). Among women, $AL_{traj}$ was also positively related to change in "somatic complaints" depressive symptoms score between Visits 1 and 3 ($\beta = 0.043$, $P = 0.020$).

*Conclusions:* Among urban adults, AL may be associated with "somatic complaints" depressive symptoms at baseline. Higher AL trajectories may predict increasing depressive symptoms (overall) and increasing "somatic complaints" depressive symptoms (among women). A higher AL trajectory may be associated with lower "positive affect" depressive symptoms at baseline among women and White adults only.

## 1. Introduction

Aging has been linked to a deterioration in physical, cognitive and social functioning, with detrimental implications for quality of life (Obuobi-Donkor et al., 2021). Although often under-diagnosed, depression is a major contributor to the global burden of disease and has been associated with increased morbidity and mortality risks among older adults (Zenebe et al., 2021; Wei et al., 2019). In a recent meta-analysis of 48 studies, Hu et al. estimated the prevalence of depression among older adults to be 28.4% with a 95% confidence interval (CI) ranging between 24.8% and 32.0% (Hu et al., 2022). Personal characteristics that have been linked to geriatric depression include female sex, increasing age, being single or divorced, lower education, unemployment, low income, lack of health insurance, smoking,

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https://doi.org/10.1016/j.psyneuen.2022.106022
Received 3 October 2022; Received in revised form 30 December 2022; Accepted 31 December 2022
Available online 3 January 2023
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childhood traumatic experiences, low self-esteem, social deprivation, loneliness or living alone, bereavement, chronic conditions, cognitive impairment, poor health as well as a history of depression (Zenebe et al., 2021).

A meta-analysis of 61 prospective cohort studies suggested that late-life depression may be associated with > 30% increased all-cause and cardiovascular disease-specific mortality risks (Wei et al., 2019). Evidence suggests that lifetime exposure to stressful life events and chronic stressors may be linked to geriatric depression (Krause, 1986; Rauch et al., 2006; Zannas et al., 2013). Therefore, investigating associations between biomarkers of stress and depressive symptoms in older adults can help identify opportunities for the prevention of late-life depression and its detrimental health outcomes. Allostatic load (AL) is an index that combines cardiovascular, metabolic and inflammatory biomarkers of physiological dysregulation reflecting "wear and tear" from repeated response to stressful situations or from adaptation to chronic stress over the lifespan (Berger et al., 2019; Gillespie et al., 2019; Juster et al., 2016; Kerr et al., 2021; Gale et al., 2016; Ottino-Gonzalez et al., 2019; Chen et al., 2014; Veronesi et al., 2019). AL is considered as a mediator of the effect of stress on health and has been associated with psychosocial factors such as job insecurity (Veronesi et al., 2019; Magnusson Hanson et al., 2020) and racial discrimination (Tomfohr et al., 2016), suggesting that its association with health outcomes may vary according to sex and race. A limited number of studies have thus far examined AL in relation to depression in older populations (Barboza Solis et al., 2016; Berger et al., 2019). These studies were often unable to establish a temporal sequence of events or underpowered to examine disparities according to sex and race. The purpose of this study was to examine the longitudinal association of AL with depressive symptoms among urban adults who participated in the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study. We hypothesized that higher AL will be associated with higher depressive symptoms and that the magnitude of this association may vary according to sex and race.

## 2. Materials and methods

### 2.1. Database

The HANDLS study is an ongoing prospective cohort study initiated in 2004 by the National Institute on Aging (NIA) Intramural Research Program (IRP) to answer research questions pertaining to health disparities in age-related diseases. The HANDLS study recruited a sample of urban adults using an area probability sampling strategy, whereby middle-aged African American and White individuals of both sexes (baseline age: 30–64 years) were selected from thirteen Baltimore city neighborhoods that had widely ranging household incomes (Evans et al., 2010). Moreover, the HANDLS study employs novel research tools and mobile medical research vehicles (MRVs) to improve participation rates and retention among non-traditional research participants. The work described has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The Institutional Review Board of the National Institutes of Health approved the HANDLS study and written informed consent was obtained from HANDLS participants (Evans et al., 2010; Kuczmarski et al., 2015; Wendell et al., 2016; Beydoun et al., 2019b, 2019c, 2020a; Hossain et al., 2019; Wright et al., 2019). The HANDLS study protocols are located at https://handls.nih.gov/02Protocol.htm.

Baseline (Visit 1) data were collected on HANDLS participants in two phases occurring between 2004 and 2009. The first phase consisted of an in-home interview focused on health status, health service utilization, psychosocial factors, nutrition, neighborhood characteristics, and demographics. The second phase covered medical history, physical examination, dietary recall, cognitive evaluation, psychophysiological assessments (*e.g.* heart rate variability, arterial thickness, carotid ultrasonography, assessments of muscle strength, bone density), and laboratory measurements (*e.g.* blood chemistries, hematology, biomarkers of oxidative stress, biomaterials for genetic studies) and was conducted in MRVs. Subsequently, HANDLS participants were followed-up every five years with Visit 2 taking place between 2009 and 2013 and Visit 3 between 2013 and 2017. HANDLS data elements available for analysis can be located at https://handls.nih.gov/06Coll-w00dataDocR.cgi. Whereas different HANDLS study visits included unique types of assessments, several assessments were repeated over time. For the purpose of this study, we analyzed Visit 1, 2 and 3 data on several measures that allowed the computation of depressive symptoms and AL scores. Researchers outside of the NIA IRP submitted a manuscript proposal for committee review and obtained access to restricted HANDLS data after approval and execution of an institutional data sharing agreement. Secondary analyses of existing HANDLS data received exempt status at Fort Belvoir Community Hospital.

### 2.2. Measures

#### 2.2.1. Allostatic load

AL total score was defined using nine risk indicators measured at Visits 1, 2 and 3 of the HANDLS study, and computed using a method described in a previous study (Seeman et al., 2008). Components of the AL total score are displayed in Table A.1. The risk indicators were defined as dichotomous variables and classified as cardiovascular (systolic blood pressure (SBP) (1 = ≥ 140 mm Hg; 0 = < 140 mm Hg), diastolic blood pressure (DBP) (1 = ≥ 90 mm Hg; 0 = < 90 mm Hg), resting heart rate (1 = ≥ 90 beat/min; 0 = < 90 beat/min), metabolic (Total cholesterol (1 = ≥ 240 mg/dl; 0 = < 240 mg/dl), High Density Lipoprotein-Cholesterol (HDL-C) (1 = < 40 mg/dl; 0 = ≥ 40 mg/dl), glycosylated hemoglobin (HbA1c) (1 = ≥ 6.4%; 0 = < 6.4%), sex-specific waist-to-hip ratio (WHR) (1 = > 0.9 (men) and > 0.85 (women); 0 = ≤ 0.9 (men) and ≤ 0.85 (women)) and inflammatory (albumin (1 = < 3.8 g/dl; 0 = ≥ 3.8 g/dl), high-sensitivity C-reactive protein (hsCRP) (1 = ≥ 0.3 mg/dl; 0 = < 0.3 mg/dl)) risk indicators. Group-based trajectory modeling was performed for AL between Visits 1 and 3 using a STATA plugin (*traj* and *trajplot*) adapted from a well-established SAS procedure (Jones et al., 2001; Jones and Nagin, 2007), whereby groups of adults with similar developmental trajectories over time were identified. This group-based approach utilizes a multinomial modeling strategy and maximum likelihood to estimate model parameters, with maximization achieved by the quasi-Newton procedure. We specified a zero-inflated Poisson (*zip*) distribution for the selected outcomes, with intercept (0), linear (1) or quadratic (2) orders for each group trajectory, as appropriate, and displayed group-based trajectories over time with 95% confidence intervals (CI). Subsequently, AL at Visit 1 ($AL_{v1}$) and z-transformed probability of having a high AL trajectory between Visits 1 and 3 ($AL_{traj}$) were defined as exposure variables. Sensitivity analyses were also performed whereby $AL_{traj}$ was replaced with the observed annualized change in AL between Visit 1 and 3.

#### 2.2.2. Depressive symptoms

A depressive symptoms score was calculated using self-reported data from the Center for Epidemiological Studies Depression (CES-D) questionnaire. The CES-D (Nguyen et al., 2004) questionnaire has been shown to have adequate psychometric properties in numerous samples of older adults (Beekman et al., 1997). It consists of 20 items with item scores ranging from '0' to '3' resulting in a CES-D total score that ranges between '0' and '60'. CES-D items focused on the frequency and severity of depressive symptomatology over the past week. HANDLS study participants were asked to indicate whether each item was experienced rarely or none of the time (score=0), some or a little of the time (score=1), occasionally or a moderate amount of time (score=2), or most or all of the time (score=3), with some items requiring reverse coding. Whereas a CES-D total score ≥ 16 suggested significant depressive symptoms, a CES-D total score ≥ 20 suggested a clinically significant amount of depressive symptoms. We also examined

domain-specific CES-D scores, including: (1) *Depressive affect* (*e.g.* feeling sad); (2) *Interpersonal problems* (*e.g.* having trouble in social settings); (3) *Somatic complaints* (*e.g.* poor sleep, poor appetite); and (4) *Positive affect* (*e.g.* having positive thoughts) (Nguyen et al., 2004). We calculated raw domain-specific CES-D sub-scores by adding depressive symptom scores for items that fall under each domain. Described elsewhere are details concerning items used to obtain each domain-specific CES-D sub-score (Nguyen et al., 2004).

#### 2.2.3. Covariates

The hypothesized relationships of various depressive symptoms outcomes (CES-D total and domain-specific scores) with AL at Visit 1 ($AL_{v1}$), z-transformed probability of having a high AL trajectory ($AL_{traj}$) or the observed annualized change in AL between Visits 1 and 3 were examined, taking potential confounders into consideration, including demographic (sex (male, female), age ([in years], continuous), race (White, African American), poverty status (<125% federal poverty line, ≥ 125% federal poverty line), education (less than high school, high school, more than high school), lifestyle (current cigarette smoking [Yes, No]), current drug use [using any of marijuana, opiates, and cocaine] (Yes, No), the 2010 Healthy Eating Index [HEI-2010]) and health (body mass index [BMI; weight/height$^2$ in kg.m$^{-2}$, continuous]) characteristics. Of note, we did not adjust for $AL_{v1}$ when examining $AL_{traj}$ as a predictor of depressive symptoms outcomes as we were mainly interested in the raw change rather than the relative change in AL over time. We analyzed age at baseline (Visit 1) as a continuous variable and used ages at Visits 2 and 3 to calculate the follow-up time durations. Education was defined as a categorical rather than an ordinal variable. Poverty status was operationalized using Department of Health and Human Services poverty thresholds according to household income and total household size (Department of Health and Human Services, 2004). Overall diet quality according to the HEI-2010 (Beydoun et al., 2020b) was based on food and macronutrient-related guidelines for Americans. We also described the relationship of $AL_{v1}$ with multiple comorbidities and self-rated health. Categorical variables were used to define hypertension (Yes, No), diabetes (non-diabetic, pre-diabetic, diabetic), dyslipidemia [or statin use] (Yes, No), and self-reported history of any of several cardiovascular diseases (Yes, No), including atrial fibrillation, angina, coronary artery disease, congestive heart failure, and myocardial infarction, as comorbidities. Finally, self-rated health was categorized as poor/average, good and very good/excellent. Dummy variables were created for each categorical variable that was entered into mixed-effects linear models.

### 2.3. Statistical methods

Descriptive, bivariate and multivariable analyses were performed using STATA version 16 (StataCorp, College Station, TX). Measures of central tendency (mean, median) and dispersion (standard deviation, interquartile range) were used to describe continuous variables whereas counts and percentages were used to describe categorical variables. Bivariate associations were evaluated using Chi-square test, Fisher's exact test, independent samples t-test, Wilcoxon's rank sum test, one-way ANOVA, Kruskal-Wallis test, Pearson's or Spearman-rank correlation, as appropriate. Linear regression (mixed-effects and ordinary least squares [OLS]) models were constructed, whereby socio-demographic, lifestyle and health characteristics were examined as potential confounders (Appendix B). Model-building strategies involved testing for multicollinearity among variables included within mixed-effects models. Given that each covariate had on average < 5% missing data, we ensured sample sizes were constant between distinct adjusted models by conducting multiple imputations (5 imputations, 10 iterations) using the chained equations methodology. All covariates were used simultaneously during this estimation process, and, similar to previous studies (Beydoun et al., 2019a, 2016a), continuous covariates were centered on their means. First, Visit 1 socio-demographic, lifestyle and health characteristics, CES-D test scores (at Visit 1 and change between Visit 1 and Visit 3) as well as $AL_{v1}$ and the probability of having a higher AL trajectory between Visits 1 and 3 were described before and after stratifying according to $AL_{v1}$ tertiles, using the largest sample after exclusion of HANDLS subjects with missing data on the CES-D scale. Second, a series of mixed-effects linear regression models were constructed separately for $AL_{v1}$ as a predictor of CES-D test scores (at Visit 1 and change between Visit 1 and Visit 3) and $AL_{traj}$ as a predictor of CES-D test scores (at Visit 1 and change between Visit 1 and Visit 3), adjusting for distinct sets of covariates. The time variable used was time on study, in years, between Visits 1 and 3. *Models 1* were a series of mixed-effects linear models that were adjusted for age, sex, race, poverty status, inverse mills ratio (IMR) as well as time on study and its interaction with $AL_{v1}$ or $AL_{traj}$ and covariates. *Models 2* were a series of mixed-effects linear models that were adjusted for age, sex, race, poverty status, education, smoking, drug use, the HEI-2010, BMI, IMR as well as time on study and its interaction with $AL_{v1}$ or $AL_{traj}$ and covariates. As a sensitivity analysis, we replaced $AL_{traj}$ with the observed annualized change in AL between Visit 1 and Visit 3, within mixed-effects linear models. Also, as a sensitivity analysis, interaction effects of $AL_{v1}$ or $AL_{traj}$ with sex and race were evaluated for *Models 1* and *2*, and stratified analyses were conducted separately for men, women, as well as White and African American HANDLS participants. As such, we applied *Models 1–2* to two exposures ($AL_{v1}$ and $AL_{traj}$), five CES-D test scores (one total score and four domain-specific scores) with up to two repeats (effect on Visit 1 CES-D test scores and effect on change in CES-D test scores between Visits 1 and 3) and two stratifying variables (sex, race). In all models, we adjusted for sample selectivity due to missing data using a two-stage Heckman selection strategy. After predicting an indicator of selection with sex, age at Visit 1, race and poverty status using a probit regression model, which yielded an IMR (a function of the probability of being selected given these characteristics), we estimated linear regression models adjusted for the IMR in addition to aforementioned covariates (Beydoun et al., 2013). Type I error rate was set *a priori* for main and interactive effects before correction for multiple testing to 0.05 and 0.10, respectively (Selvin, 2004). We accounted for outcome multiplicity (*i.e.*, 5 CES-D test scores) using the approach of familywise Bonferroni correction (Hochberg, 1987), specifically for *Model 1*. Subsequently, *Model 2* was considered as a sensitivity model in which potentially confounding and/or mediating variables were included. As such, we adjusted significance levels for main effects to $p \leq 0.010$ (0.05/5), and for two-way interaction terms to $p \leq 0.10/5 = 0.020$, similar to previous work (Beydoun et al., 2016b).

#### 2.3.1. Sample size calculations

Based on simulations performed using STATA IPDPOWER for the main effect size of 0.1 and a two-way interaction term between time and baseline exposure, a sample size of ~1700 HANDLS participants with approximately 1.7 observations per participant is sufficient to obtain > 80% power at alpha = 0.05.

## 3. Results

As shown in Fig. 1, a total of 3720 participants were enrolled in the HANDLS study at baseline, of whom 2321 participants had complete data on risk indicators used to calculate AL at Visit 1, 2 and/or 3. The analytic sample consists of subsets of 2298 HANDLS study participants with available AL and CES-D test scores at Visit 1, 2 and/or 3. As shown in Table A.2, HANDLS study participants with Visit 1 AL and CES-D total scores differed significantly according to whether or not they were included in the final analytic sample on AL, CES-D total score or risk of dying by the end of the follow-up period. Table 1 presents socio-demographic, lifestyle and health characteristics at Visit 1, $AL_{v1}$, non-standardized $AL_{traj}$ and CES-D total scores (at Visit 1 and change between Visit 1 and Visit 3), overall, and according to tertiles of $AL_{v1}$. The mean ( ± standard error [SEM]) for $AL_{v1}$ and CES-D total score at Visit 1

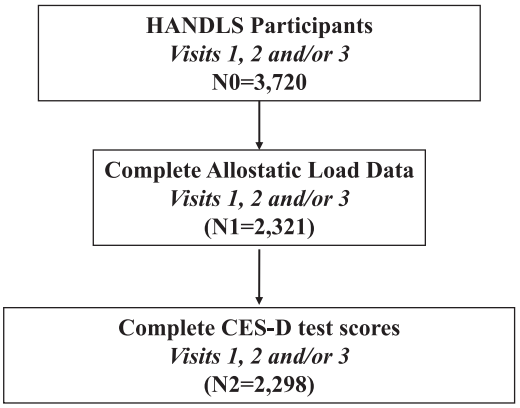


**Fig. 1.** Study Flowchart – HANDLS (2004–2017).

were 1.95 ( ± 0.03) and 15.06 ( ± 0.24), respectively. Similarly, the mean ( ± SEM) for probability of higher AL trajectory and change in CES-D total score between Visit 1 and Visit 3 were estimated at 0.77 ± 0.01 and − 0.12 ± 0.0023, respectively. $AL_{v1}$ tertiles differed significantly according to baseline age, education, drug use, BMI, comorbidities and self-rated health, but not according to sex, race, poverty status, cigarette smoking or HEI-2010 score at Visit 1. In particular, an increasing prevalence of HANDLS participants with poor or average self-reported health status, hypertension, diabetes, dyslipidemia or cardiovascular disease was observed with increasing $AL_{v1}$ tertiles. Conversely, there were no significant differences among $AL_{v1}$ tertiles on CES-D total and domain-specific scores (Table 1). As shown in Table A.3, the CES-D total score at Visit 1 as well as change in CES-D total score between Visits 1 and 3 also differed according to most of the selected socio-demographic, lifestyle and health characteristics at Visit 1.

The relationships of $AL_{v1}$ with CES-D total and domain-specific scores (at Visit 1 and change between Visit 1 and Visit 3) are displayed in Table 2, overall, and according to sex and race. Overall, a positive cross-sectional relationship was observed between $AL_{v1}$ and CES-D total score in *Model 1* (β (standard error [SE])= 0.56 (0.18), P = 0.001) but not in *Model 2* (β (SE)= 0.45 (0.19), P = 0.022). In terms of domain-specific CES-D scores, $AL_{v1}$ was significantly associated with "somatic complaints" CES-D sub-domain score in *Models 1* (β (SE)= 0.24 (0.068), P < 0.0001) and *2* (β (SE)= 0.21 (0.076), P = 0.006), but not with other CES-D sub-domains. When the analytic sample was restricted to men or African American participants, there were no significant relationships between $AL_{v1}$ and CES-D scores. Among women, $AL_{v1}$ and CES-D total scores were positively associated in *Model 1* (β (SE)= 0.64 (0.25), P = 0.009), but not in *Model 2* (β (SE)= 0.44 (0.27), P = 0.11). Similarly, $AL_{v1}$ and "somatic complaints" CES-D sub-domain score were positively associated among women in *Model 1* (β (SE) = 0.28 (0.094), p = 0.003), but not in *Model 2* (β (SE)= 0.23 (0.10), P = 0.028). Among White participants, a significant cross-sectional relationship was observed between $AL_{v1}$ and CES-D total score in *Model 1* (β (SE)= 0.89 (0.29), P = 0.002) but not in *Model 2* (β (SE)= 0.66 (0.33), P = 0.048). Similarly, "somatic symptoms" CES-D sub-domain score was directly related (β (SE)= 0.31 (0.11), P = 0.004) and "positive affect" CES-D sub-domain score was inversely related (β (SE)= −0.22 (0.072), P = 0.002) to $AL_{v1}$, among White participants in *Model 1* alone. $AL_{v1}$ was not related to changes in CES-D total and sub-domain scores between Visits 1 and 3 in *Models 1–2*. As shown in Table A.4, there were no significant interaction effects by sex or race, except for the relationship of $AL_{v1}$ with "positive affect" CES-D sub-domain score, which differed according to race in *Model 1* (P = 0.015).

As shown in Fig. 2, two distinct groups were identified using group-based trajectory modeling. Specifically, trajectories in AL were examined among 2545 HANDLS participants, of whom 78.1% belonged to trajectory 2 (high) and 21.9% belonged to trajectory 1 (low). The socio-

**Table 1**
Summary statistics for depressive symptoms (Visit 1 and change between Visit 1 and Visit 3), socio-demographic, lifestyle and health characteristics at Visit 1 and allostatic load (at Visit and change between Visit 1 and Visit 3), overall, and according to tertiles of allostatic load at Visit 1 (n = 2298).*.

| | % or Mean ± SEM | AL tertiles at Visit 1 | | |
|---|---|---|---|---|
| | | 1st (0–1) | 2nd (2) | 3rd (3–7) |
| **ALLOSTATIC LOAD:** | | P < 0.0001 | | |
| $AL_{v1}$ (n = 2298) | 1.95 ± 0.03 | 0.68 ± 0.02 | 2.00 ± 0.00 | 3.54 ± 0.03 |
| | | P < 0.0001 | | |
| $AL_{traj}$ (raw score) (n = 1953) | 0.77 ± 0.01 | 0.56 ± 0.009 | 0.88 ± 0.005 | 0.97 ± 0.002 |
| **SOCIO-DEMOGRAPHIC** (n = 2298): | | | | |
| ***Sex:*** | | P = 0.55 | | |
| Male | 43.2 | 44.59 | 42.70 | 42.02 |
| Female | 56.7 | 55.41 | 57.29 | 57.97 |
| ***Age (years):*** | | P < 0.0001 | | |
| Continuous | 48.59 ± 0.19 | 46.44 ± 0.29 | 49.31 ± 0.37 | 50.76 ± 0.33 |
| ***Race:*** | | P = 0.24 | | |
| White | 40.86 | 39.55 | 39.91 | 43.41 |
| African American | 59.14 | 60.45 | 60.09 | 56.59 |
| ***Poverty status:*** | | P = 0.86 | | |
| < 125% federal poverty line | 39.38 | 39.87 | 38.51 | 39.53 |
| ≥ 125% federal poverty line | 60.62 | 60.13 | 61.49 | 60.47 |
| ***Education:*** | | P < 0.0001 | | |
| Less than high school | 6.15 | 4.22 | 5.87 | 8.90 |
| High school | 58.86 | 55.97 | 60.31 | 61.33 |
| More than high school | 34.98 | 39.81 | 33.82 | 29.76 |
| **LIFESTYLE** (n = 2298): | | | | |
| ***Cigarette smoking:*** | | P = 0.31 | | |
| Yes | 47.10 | 49.09 | 46.18 | 45.40 |
| No | 52.89 | 50.91 | 53.88 | 54.59 |
| ***Drug use:*** | | P = 0.0001 | | |
| Yes | 17.54 | 21.76 | 16.18 | 13.31 |
| No | 82.45 | 78.24 | 83.82 | 86.68 |
| ***HEI-2010 score:*** | | P = 0.33 | | |
| | 42.75 ± 0.31 | 43.21 ± 0.41 | 42.58 ± 0.49 | 42.30 ± 0.55 |
| **HEALTH** (n = 2298): | | | | |
| ***Body mass index (kg/m$^2$):*** | | P < 0.0001 | | |
| | 30.02 ± 0.16 | 26.44 ± 0.20 | 30.90 ± 0.28 | 33.84 ± 0.31 |
| ***Self-rated health:*** | | P < 0.0001 | | |
| Poor/Average | 26.69 | 20.57 | 22.83 | 38.05 |
| Good | 39.48 | 36.01 | 42.08 | 41.66 |
| Very good/Excellent | 33.82 | 43.41 | 35.09 | 20.28 |
| ***Hypertension:*** | | P < 0.0001 | | |
| Yes | 48.01 | 26.07 | 51.21 | 73.54 |
| No | 51.99 | 73.93 | 48.79 | 26.46 |
| ***Diabetes:*** | | P < 0.0001 | | |
| None | 64.09 | 81.52 | 62.76 | 42.72 |
| Pre-diabetes | 18.33 | 13.39 | 22.67 | 20.83 |
| Diabetes | 17.58 | 5.08 | 14.56 | 36.44 |
| ***Dyslipidemia:*** | | P < 0.0001 | | |
| Yes | 26.78 | 16.08 | 29.07 | 38.59 |
| No | 73.22 | 83.92 | 70.93 | 61.41 |
| ***Cardiovascular disease:*** | | P < 0.0001 | | |
| Yes | 18.14 | 11.92 | 18.44 | 25.94 |
| No | 81.85 | 88.08 | 81.55 | 74.06 |
| **DEPRESSIVE SYMPTOMS:** | | | | |
| *Visit 1* | | | | |
| | | P = 0.077 | | |
| ***CES-D total score (n = 2264)*** | 15.06 ± 0.24 | 14.52 ± 0.37 | 15.02 ± 0.44 | 15.79 ± 0.42 |
| | | P = 0.21 | | |

(*continued on next page*)

**Table 1** (*continued*)

| | % or Mean ± SEM | AL tertiles at Visit 1 | | |
|---|---|---|---|---|
| ***CES-D domain 1 score (n = 2282) [depressive affect]*** | 4.68 ± 0.10 | 4.51 ± 0.16 | 4.63 ± 0.19 | 4.94 ± 0.19 |
| | | P = 0.35 | | |
| ***CES-D domain 2 score (n = 2282) [interpersonal problems]*** | 1.01 ± 0.03 | 0.97 ± 0.04 | 1.07 ± 0.06 | 1.00 ± 0.051 |
| | | P = 0.018 | | |
| ***CES-D domain 3 score (n = 2282) [somatic complaints]*** | 6.77 ± 0.092 | 6.50 ± 0.14 | 6.77 ± 0.17 | 7.11 ± 0.16 |
| | | P = 0.34 | | |
| ***CES-D domain 4 score (n = 2282) [positive affect]*** | 9.42 ± 0.058 | 9.48 ± 0.093 | 9.47 ± 0.11 | 9.29 ± 0.10 |
| *Visit 1 to Visit 3* | | | | |
| | | P = 0.26 | | |
| ***CES-D total score (n = 2298)*** | -0.12 ± 0.0023 | -0.12 ± 0.0037 | -0.12 ± 0.0043 | -0.13 ± 0.0041 |
| | | P = 0.28 | | |
| ***CES-D domain 1 score (n = 2298) [depressive affect]*** | -0.075 ± 0.0012 | -0.074 ± 0.0019 | -0.076 ± 0.0023 | -0.078 ± 0.0022 |
| | | P = 0.39 | | |
| ***CES-D domain 2 score (n = 2298) [interpersonal problems]*** | -0.014 ± 0.0002 | -0.014 ± 0.00035 | -0.015 ± 0.00047 | -0.014 ± 0.00041 |
| | | P = 0.15 | | |
| ***CES-D domain 3 score (n = 2298) [somatic complaints]*** | -0.080 ± 0.00087 | -0.079 ± 0.0014 | -0.080 ± 0.0016 | -0.083 ± 0.0015 |
| | | P = 0.19 | | |
| ***CES-D domain 4 score (n = 2298) [positive affect]*** | -0.049 ± 0.0011 | -0.046 ± 0.002 | -0.051 ± 0.0022 | -0.050 ± 0.0019 |

* P values are based on bivariate associations between tertiles of allostatic load at Visit 1 and each of the variables presented within the table. *Abbreviations:* $AL_{v1}$ = Allostatic Load at Visit 1; $AL_{traj}$ = Probability of belonging to a group with higher allostatic load between Visit 1 and Visit 3 according to group-based trajectory modeling; CES-D = Center for Epidemiological Studies Depression; HEI = Healthy Eating Index; n = Sample size; SEM = Standard error of the mean.

demographic characteristics of 1953 HANDLS participants were compared between these two groups (343 from trajectory 1 and 2003 from trajectory 2) suggesting differences by sex, age and education, but not by race or poverty status (Table A.5). We examined $AL_{traj}$ (z-transformed probability of belonging to a group with higher AL over time according to group-based trajectory modeling) in relation to CES-D test scores. Table 3 displays the relationship of $AL_{traj}$ with CES-D total and domain-specific scores (baseline and between-visit change), overall, as well as by sex and race. Overall, higher $AL_{traj}$ was associated with higher CES-D total score at Visit 1 for *Model 1* (β (SE)= 0.88 (0.23), $P < 0.0001$) and with increasing CES-D total score between Visits 1 and 3 for both *Models 1* (β (SE)= 0.076 (0.026), $P = 0.004$) and *2* (β (SE)= 0.086 (0.029), $P = 0.003$). Furthermore, "somatic complaints" CES-D sub-domain score at Visit 1 was directly associated with higher $AL_{traj}$ in *Models 1* and *2*. There were no significant associations when the analytic sample was restricted to men or African American participants. Among women and White participants, significant results were observed for the overall CES-D score as well as the "somatic symptoms" and "positive affect" sub-domain scores in *Models 1*. In *Models 2*, $AL_{traj}$ was inversely related to Visit 1 "positive affect" CES-D sub-domain score among women (β (SE)= −0.31 (0.089), $P < 0.0001$) and White participants (β (SE)= −0.32 (0.11), $P = 0.004$). In *Model 2*, $AL_{traj}$ was directly associated with change between Visits 1 and 3 in "somatic complaints" CES-D

**Table 2**
Relationship of allostatic load at Visit 1 with depressive symptoms total and domain-specific scores (Visit 1 and change between Visit 1 and Visit 3), overall, and by stratifying variables (n = 2298).

| | Allostatic Load | | | |
|---|---|---|---|---|
| | Model 1[1] | | Model 2[2] | |
| OVERALL:[3] | β (SE) | P value | β (SE) | P value |
| *CES-D total score:* | N = 2298, K= 2.4 | | N = 2298, K= 2.4 | |
| $AL_{v1}$ | 0.56 (0.18) | 0.001 | 0.45 (0.19) | 0.022 |
| $AL_{v1}$ × Time | 0.012 (0.022) | 0.59 | 0.0068 (0.025) | 0.79 |
| *CES-D domain 1 score:* | N = 2298, K= 2.4 | | N = 2298, K= 2.4 | |
| $AL_{v1}$ | 0.18 (0.078) | 0.016 | 0.15 (0.086) | 0.081 |
| $AL_{v1}$ × Time | -0.0019 (0.0096) | 0.84 | -0.0039 (0.011) | 0.72 |
| *CES-D domain 2 score:* | N = 2298, K= 2.4 | | N = 2298, K= 2.4 | |
| $AL_{v1}$ | 0.032 (0.021) | 0.13 | 0.022 (0.024) | 0.35 |
| $AL_{v1}$ × Time | -0.0018 (0.0031) | 0.57 | -0.0034 (0.0035) | 0.33 |
| *CES-D domain 3 score:* | N = 2298, K= 2.4 | | N = 2298, K= 2.4 | |
| $AL_{v1}$ | 0.24 (0.068) | < 0.0001 | 0.21 (0.076) | 0.006 |
| $AL_{v1}$ × Time | 0.0048 (0.0094) | 0.61 | 0.0034 (0.010) | 0.75 |
| *CES-D domain 4 score:* | N = 2298, K= 2.4 | | N = 2298, K= 2.4 | |
| $AL_{v1}$ | -0.093 (0.043) | 0.031 | -0.063 (0.048) | 0.19 |
| $AL_{v1}$ × Time | -0.0093 (0.0068) | 0.17 | -0.0072 (0.0077) | 0.35 |
| **MEN:** | | | | |
| *CES-D total score:* | N = 994, K=2.3 | | N = 994, K=2.3 | |
| $AL_{v1}$ | 0.54 (0.25) | 0.032 | 0.50 (0.28) | 0.078 |
| $AL_{v1}$ × Time | -0.012 (0.034) | 0.73 | -0.0021 (0.038) | 0.96 |
| *CES-D domain 1 score:* | N = 994, K= 2.3 | | N = 994, K= 2.3 | |
| $AL_{v1}$ | 0.20 (0.11) | 0.064 | 0.18 (0.12) | 0.12 |
| $AL_{v1}$ × Time | -0.019 (0.014) | 0.17 | -0.012 (0.016) | 0.44 |
| *CES-D domain 2 score:* | N = 994, K= 2.3 | | N = 994, K= 2.3 | |
| $AL_{v1}$ | 0.047 (0.033) | 0.16 | 0.042 (0.038) | 0.28 |
| $AL_{v1}$ × Time | -0.0013 (0.0049) | 0.78 | -0.0033 (0.0056) | 0.56 |
| *CES-D domain 3 score:* | N = 994, K= 2.3 | | N = 994, K= 2.3 | |
| $AL_{v1}$ | 0.22 (0.099) | 0.026 | 0.19 (0.11) | 0.079 |
| $AL_{v1}$ × Time | -0.00085 (0.014) | 0.95 | 0.0053 (0.016) | 0.75 |
| *CES-D domain 4 score:* | N = 994, K= 2.3 | | N = 994, K= 2.3 | |
| $AL_{v1}$ | -0.069 (0.064) | 0.28 | -0.072 (0.073) | 0.32 |
| $AL_{v1}$ × Time | -0.0044 (0.011) | 0.67 | -0.0015 (0.012) | 0.90 |
| **WOMEN:** | | | | |
| *CES-D total score:* | N = 1304, K=2.5 | | N = 1304, K=2.5 | |
| $AL_{v1}$ | 0.64 (0.25) | 0.009 | 0.44 (0.27) | 0.11 |
| $AL_{v1}$ × Time | 0.018 (0.029) | 0.53 | 0.0079 (0.034) | 0.82 |
| *CES-D domain 1 score:* | N = 1304, K= 2.5 | | N = 1304, K= 2.5 | |
| $AL_{v1}$ | 0.19 (0.11) | 0.073 | 0.13 (0.12) | 0.29 |
| $AL_{v1}$ × Time | 0.0069 (0.013) | 0.60 | 0.0019 (0.015) | 0.90 |
| *CES-D domain 2 score:* | N = 1304, K= 2.5 | | N = 1304, K= 2.5 | |
| $AL_{v1}$ | 0.019 (0.028) | 0.48 | 0.0027 (0.031) | 0.93 |
| $AL_{v1}$ × Time | -0.0012 (0.0040) | 0.76 | -0.0027 (0.0045) | 0.55 |
| *CES-D domain 3 score:* | N = 1304, K= 2.5 | | N = 1304, K= 2.5 | |
| $AL_{v1}$ | 0.28 (0.094) | 0.003 | 0.23 (0.10) | 0.028 |
| $AL_{v1}$ × Time | 0.0065 (0.013) | 0.60 | 0.0016 (0.014) | 0.91 |
| *CES-D domain 4 score:* | N = 1304, K= 2.5 | | N = 1304, K= 2.5 | |
| $AL_{v1}$ | -0.12 (0.058) | 0.032 | -0.072 (0.065) | 0.27 |
| $AL_{v1}$ × Time | -0.0088 (0.0088) | 0.32 | -0.0076 (0.0099) | 0.45 |

(*continued on next page*)

**Table 2** (*continued*)

| | Allostatic Load | | | |
|---|---|---|---|---|
| | Model 1[1] | | Model 2[2] | |
| OVERALL:[3] | β (SE) | P value | β (SE) | P value |
| **WHITE:** | | | | |
| *CES-D total score:* | N = 939, K=2.4 | | N = 939, K=2.4 | |
| $AL_{v1}$ | 0.89 (0.29) | 0.002 | 0.66 (0.33) | 0.048 |
| $AL_{v1}$ × Time | 0.024 (0.039) | 0.54 | -0.043 (0.047) | 0.37 |
| *CES-D domain 1 score:* | N = 939, K= 2.4 | | N = 939, K= 2.4 | |
| $AL_{v1}$ | 0.25 (0.13) | 0.049 | 0.21 (0.15) | 0.16 |
| $AL_{v1}$ × Time | 0.0052 (0.017) | 0.76 | -0.019 (0.020) | 0.35 |
| *CES-D domain 2 score:* | N = 939, K= 2.4 | | N = 939, K= 2.4 | |
| $AL_{v1}$ | 0.037 (0.033) | 0.26 | -0.000079 (0.039) | 0.99 |
| $AL_{v1}$ × Time | 0.0025 (0.0050) | 0.62 | 0.0034 (0.0061) | 0.57 |
| *CES-D domain 3 score:* | N = 939, K= 2.4 | | N = 939, K= 2.4 | |
| $AL_{v1}$ | 0.31 (0.11) | 0.004 | 0.22 (0.13) | 0.082 |
| $AL_{v1}$ × Time | 0.028 (0.016) | 0.077 | -0.0012 (0.019) | 0.95 |
| *CES-D domain 4 score:* | N = 939, K= 2.4 | | N = 939, K= 2.4 | |
| $AL_{v1}$ | -0.22 (0.072) | 0.002 | -0.17 (0.084) | 0.044 |
| $AL_{v1}$ × Time | 0.0035 (0.011) | 0.75 | 0.021 (0.013) | 0.11 |
| **AFRICAN AMERICAN:** | | | | |
| *CES-D total score:* | N = 1359, K=2.4 | | N = 1359, K=2.4 | |
| $AL_{v1}$ | 0.38 (0.22) | 0.099 | 0.36 (0.24) | 0.14 |
| $AL_{v1}$ × Time | 0.0031 (0.027) | 0.91 | 0.016 (0.030) | 0.60 |
| *CES-D domain 1 score:* | N = 1359, K= 2.4 | | N = 1359, K= 2.4 | |
| $AL_{v1}$ | 0.16 (0.10) | 0.099 | 0.14 (0.10) | 0.18 |
| $AL_{v1}$ × Time | -0.0069 (0.012) | 0.56 | -0.00084 (0.013) | 0.95 |
| *CES-D domain 2 score:* | N = 1359, K= 2.4 | | N = 1359, K= 2.4 | |
| $AL_{v1}$ | 0.025 (0.028) | 0.38 | 0.029 (0.031) | 0.35 |
| $AL_{v1}$ × Time | -0.0029 (0.0040) | 0.47 | -0.0058 (0.0044) | 0.19 |
| *CES-D domain 3 score:* | N = 1359, K= 2.4 | | N = 1359, K= 2.4 | |
| $AL_{v1}$ | 0.20 (0.089) | 0.022 | 0.22 (0.096) | 0.019 |
| $AL_{v1}$ × Time | -0.0082 (0.012) | 0.49 | -0.0010 (0.013) | 0.94 |
| *CES-D domain 4 score:* | N = 1359, K= 2.4 | | N = 1359, K= 2.4 | |
| $AL_{v1}$ | -0.0064 (0.053) | 0.91 | -0.00033 (0.058) | 0.99 |
| $AL_{v1}$ × Time | -0.016 (0.0085) | 0.054 | -0.018 (0.0093) | 0.055 |

*Abbreviations:* $AL_{v1}$ = Allostatic Load at Visit 1; CES-D = Center for Epidemiological Studies Depression; K = Mean number of visits per subject; n = Sample size; SE = Standard error. [1] Model 1 is a series of mixed effects linear models adjusted for age, sex, race, poverty status, inverse mills ratio as well as time on study between visits 1 and 3 (in years) and its interaction with allostatic load and covariates. [2] Model 2 is a series of mixed effects linear models adjusted for age, sex, race, poverty status, education, smoking, drug use, 2010 healthy eating index, body mass index, inverse mills ratio as well as time on study between visits 1 and 3 (in years) and its interaction with allostatic load and covariates. [3] Depressive symptoms scores include the CES-D total score, the CES-D domain 1 score [depressive affect], the CES-D domain 2 score [interpersonal problems], the CES-D domain 3 score [somatic complaints] and the CES-D domain 4 score [positive affect].

sub-domain score (β (SE)= 0.043 (0.018), P = 0.020) among women. As shown in Table A.6, there were no significant interaction effects by sex or race, except for the relationship of $AL_{traj}$ with "positive affect" CES-D sub-domain score at Visit 1 which differed according to sex in *Models 1* and *2* and according to race in *Model 1* only. Similar results were obtained with observed annualized change in AL as a predictor of CESD at baseline or change in CESD between Visit 1 and 3. Specifically, annualized change in AL was associated with change in the CESD total score as well as the "somatic symptoms" sub-domain scores between Visit 1 and 3 in both *Models 1* and *2* (Table A.7).

## 4. Discussion

In this prospective cohort study of > 2000 urban adults, 30–64 years of age at baseline, we examined the longitudinal association of AL with depressive symptoms over three waves of data collection that span the time period between 2004 and 2017. Study findings implied a direct cross-sectional relationship between AL and the "somatic complaints" sub-domain of depressive symptoms at baseline, whereas higher AL trajectory was directly associated with between-visit change in depressive symptoms total score in fully adjusted models involving all eligible HANDLS participants. Stratum-specific analyses suggested an inverse relationship between AL trajectory and the "positive affect" sub-domain of depressive symptoms at baseline among women and White participants only, whereas AL trajectory was directly associated with between-visit change in "somatic complaints" depressive symptoms among women only. There were no statistically significant associations among men or African American populations.

Study findings are, for the most part, consistent with previously conducted cohort and cross-sectional studies linking AL to psychosocial stress and a wide range of health outcomes including depression (Barboza Solis et al., 2016; Berg et al., 2017; Berger et al., 2019; Gillespie et al., 2019; Juster et al., 2013, 2016; Kerr et al., 2021; Magnusson Hanson et al., 2020; Ong et al., 2017). Barboza Solis et al. analyzed data on 7573 adults from the 1958 British birth cohort and found that AL at age 44 years defined using 14 biomarkers representing 4 physiological systems was associated with worse subjective health based on sleep patterns, physical and mental health at 50 years of age (Barboza Solis et al., 2016). Relationships of the hair cortisol, AL, and depressive symptoms were examined by Berger et al. in a cross-sectional study of 329 Aboriginal and Torres Strait Islander individuals recruited at two health screening programs in north Queensland (Berger et al., 2019). Their results suggested that depressive symptoms determined using the Patient Health Questionnaire-9 scale were not related to hair cortisol or AL, controlling for age, gender and smoking, whereas anhedonia and insomnia sub-scores were associated with AL at one study site (Berger et al., 2019). Gillespie et al. examined the role of AL in the association of depressive symptoms based on the CES-D scale with incident coronary heart disease (CHD) using Jackson Heart Study data on 2670 African American men and women (Gillespie et al., 2019). A direct relationship was observed between CES-D score and AL (metabolic, cardiovascular, immune and overall), with results driven mainly by women (Gillespie et al., 2019). Whereas neuroendocrine and overall AL predicted incident CHD among men, the association of CES-D score with incident CHD was partly mediated by metabolic AL among women (Gillespie et al., 2019). Distinct findings reported in the existing literature are likely due to methodological differences in study design, sample size as well as AL and depressive symptoms definitions. Particularly, distinct findings by study design (cross-sectional or cohort) may suggest the need to perform longitudinal analyses, whereby baseline levels of both AL and depressive symptoms are evaluated in order to establish the temporal sequence of events.

Study findings are also consistent with hypothesized biological mechanisms linking late-life or geriatric depression to neuroplasticity (Ho and King, 2021), neuronal homeostasis (Andreescu et al., 2019), neuro-inflammation (Jeon and Kim, 2018; Walker et al., 2014), neurovascular dysfunction (Jeon and Kim, 2018), as well as early-life adversity (Ho and King, 2021), childhood trauma (Murphy et al., 2022), stress and its sequelae which include AL (Arnaldo et al., 2022; Walker et al., 2014; Murphy et al., 2022). According to Ho et al., exposure to early life psychosocial adversity – including childhood abuse and neglect – is among the strongest predictors of depression which is frequently initiated during a highly dynamic developmental period that precedes

A

| | β | SE | P |
|---|---|---|---|
| **Group 1** | | | |
| Intercept | -3.77 | 1.27 | 0.0028 |
| Linear Age | +0.111 | 0.05 | 0.016 |
| Quadratic Age | -0.0008 | 0.0004 | 0.071 |
| **Group 2** | | | |
| Intercept | -0.495 | 0.289 | 0.086 |
| Linear Age | +0.042 | 0.011 | 0.0001 |
| Quadratic Age | -0.0003 | 0.0001 | 0.0017 |

B

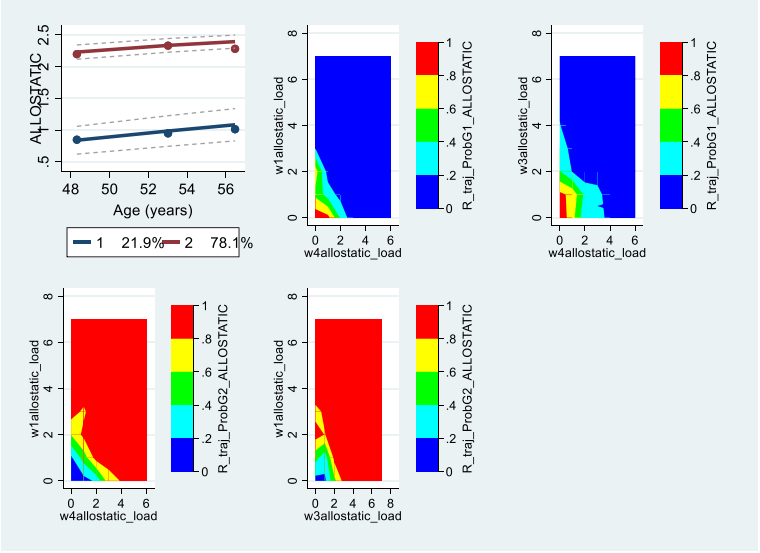


**Fig. 2.** Group-based trajectories for allostatic load – HANDLS (2004–2017).

adulthood, whereby environmental inputs can still shape brain function as a result of neuroplasticity and AL is a key mediator between early life adversity and depression (Ho and King, 2021). According to Walker et al., characterizing risk factors, biomarkers (*e.g.* stress hormones, inflammatory markers, AL) and symptoms can enhance our understanding of neuro-adaptive and neuro-degenerative mechanisms that underlie the development of mood disorders and help clinicians in their efforts to identify, prevent and intervene against these disorders (Walker et al., 2014).

To our knowledge, this study is among few to apply a cohort design or to examine sub-domains of depressive symptoms in relation to AL. Despite these strengths, interpretation of study findings should take into account several limitations. First, hypothesized relationships between AL and depressive symptoms were evaluated using sub-samples of the original HANDLS participants possibly leading to selection bias. Second, measurement errors are likely since many aspects of exposure, outcome and covariate assessments were self-reported, potentially leading to biased measures of association. Third, a wide range of AL definitions have been reported which depend on biomarker availability, and this may have limited our ability to compare study findings with the published literature. Fourth, the duration of follow-up between HANDLS Visits 1 and 3 may not have been sufficient to observe clinically meaningful changes in AL or depressive symptoms. Therefore, future studies should examine hypothesized relationships over longer follow-up times. Fifth, HANDLS is an observational study, and, therefore, we could not establish causal relationships and residual confounding is likely despite adjustment for multiple characteristics. Sixth, examination of interaction effects by sex and race may have been underpowered when evaluating AL in relation to depressive symptoms. Although differences by sex and race in the relationship between AL and depressive symptoms may reflect different degrees of resilience among distinct groups, Type I error is a concern, and, therefore, these findings should be interpreted with caution. Finally, given the sampling strategy employed by the HANDLS study, study findings are primarily generalizable to the target population of middle-aged and older adults in an urban setting. However, given the biopsychosocial nature of hypothesized relationships, there is no reason for these findings not to be generalized to suburban or rural settings as well as adults at any age.

## 5. Conclusions

Among urban adults, AL may be directly associated with the "somatic complaints" sub-domain of depressive symptoms at baseline. Similarly, a higher AL trajectory may predict an increasing depressive symptoms score between visits in the general population and an increasing between-visit "somatic complaints" sub-domain score among women only. Baseline "positive affect" depressive symptoms score may be inversely related to the probability of higher AL trajectory among women and White subjects only. These results suggest a bi-directional relationship between AL and depressive symptoms, and implicate specific sub-domains ("somatic complains" and "positive affect") of depressive symptoms as predictors or outcomes of AL. These results also suggest that women and White subjects exhibit stronger relationships between AL and depressive symptoms highlighting health disparities by

**Table 3**
Relationship of allostatic load trajectory between Visit 1 and Visit 3 with depressive symptoms total and domain-specific scores (at Visit 1 and change between Visit 1 and 3), overall, and by stratifying variables.

| | Allostatic Load Trajectory | | | |
|---|---|---|---|---|
| | Model 1[1] | | Model 2[2] | |
| | β (SE) | P | β (SE) | P |
| **OVERALL:**[3] | | | | |
| *CES-D total score:* | N = 1953, K=2.6 | | N = 1953, K=2.6 | |
| $AL_{traj}$ | 0.88 (0.23) | < 0.0001 | 0.59 (0.25) | 0.020 |
| $AL_{traj}$ × Time | 0.076 (0.026) | 0.004 | 0.086 (0.029) | 0.003 |
| *CES-D domain 1 score:* | N = 1953, K= 2.6 | | N = 1953, K= 2.6 | |
| $AL_{traj}$ | 0.26 (0.10) | 0.012 | 0.15 (0.11) | 0.18 |
| $AL_{traj}$ × Time | 0.024 (0.012) | 0.045 | 0.029 (0.013) | 0.026 |
| *CES-D domain 2 score:* | N = 1953, K= 2.6 | | N = 1953, K= 2.6 | |
| $AL_{traj}$ | 0.087 (0.028) | 0.002 | 0.077 (0.030) | 0.013 |
| $AL_{traj}$ × Time | 0.00089 (0.0038) | 0.81 | -0.000030 (0.0041) | 0.99 |
| *CES-D domain 3 score:* | N = 1953, K= 2.6 | | N = 1953, K= 2.6 | |
| $AL_{traj}$ | 0.31 (0.091) | 0.001 | 0.21 (0.098) | 0.033 |
| $AL_{traj}$ × Time | 0.033 (0.011) | 0.003 | 0.038 (0.013) | 0.003 |
| *CES-D domain 4 score:* | N = 1953, K= 2.6 | | N = 1953, K= 2.6 | |
| $AL_{traj}$ | -0.20 (0.056) | < 0.0001 | -0.16 (0.063) | 0.010 |
| $AL_{traj}$ × Time | -0.017 (0.0082) | 0.034 | -0.017 (0.0092) | 0.065 |
| **MEN:** | | | | |
| *CES-D total score:* | N = 819, K=2.6 | | N = 819, K=2.6 | |
| $AL_{traj}$ | 0.42 (0.32) | 0.19 | 0.21 (0.35) | 0.55 |
| $AL_{traj}$ × Time | 0.059 (0.038) | 0.12 | 0.079 (0.042) | 0.061 |
| *CES-D domain 1 score:* | N = 819, K= 2.6 | | N = 819, K= 2.6 | |
| $AL_{traj}$ | 0.13 (0.14) | 0.35 | 0.029 (0.15) | 0.85 |
| $AL_{traj}$ × Time | 0.013 (0.016) | 0.43 | 0.027 (0.018) | 0.13 |
| *CES-D domain 2 score:* | N = 819, K= 2.6 | | N = 819, K= 2.6 | |
| $AL_{traj}$ | 0.094 (0.042) | 0.023 | 0.090 (0.046) | 0.052 |
| $AL_{traj}$ × Time | 0.000015 (0.0056) | 0.99 | -0.0017 (0.0062) | 0.78 |
| *CES-D domain 3 score:* | N = 819, K= 2.6 | | N = 819, K= 2.6 | |
| $AL_{traj}$ | 0.18 (0.12) | 0.16 | 0.078 (0.14) | 0.57 |
| $AL_{traj}$ × Time | 0.021 (0.016) | 0.21 | 0.029 (0.018) | 0.11 |
| *CES-D domain 4 score:* | N = 819, K= 2.6 | | N = 819, K= 2.6 | |
| $AL_{traj}$ | -0.042 (0.081) | 0.60 | -0.027 (0.089) | 0.76 |
| $AL_{traj}$ × Time | -0.022 (0.011) | 0.057 | -0.022 (0.013) | 0.090 |
| **WOMEN:** | | | | |
| *CES-D total score:* | N = 1134, K=2.7 | | N = 1134, K=2.7 | |
| $AL_{traj}$ | 1.35 (0.34) | < 0.0001 | 0.99 (0.37) | < 0.0001 |
| $AL_{traj}$ × Time | 0.078 (0.038) | 0.039 | 0.082 (0.043) | 0.057 |
| *CES-D domain 1 score:* | N = 1134, K= 2.7 | | N = 1134, K= 2.7 | |
| $AL_{traj}$ | 0.38 (0.15) | 0.012 | 0.24 (0.17) | 0.14 |
| $AL_{traj}$ × Time | 0.030 (0.017) | 0.075 | 0.031 (0.019) | 0.10 |
| *CES-D domain 2 score:* | N = 1134, K= 2.7 | | N = 1134, K= 2.7 | |
| $AL_{traj}$ | 0.075 (0.039) | 0.052 | 0.056 (0.043) | 0.19 |
| $AL_{traj}$ × Time | 0.0031 (0.0052) | 0.55 | 0.0027 (0.0058) | 0.65 |
| *CES-D domain 3 score:* | N = 1134, K= 2.7 | | N = 1134, K= 2.7 | |
| $AL_{traj}$ | 0.48 (0.13) | < 0.0001 | 0.36 (0.14) | 0.012 |
| $AL_{traj}$ × Time | 0.041 (0.016) | 0.012 | 0.043 (0.018) | 0.020 |
| *CES-D domain 4 score:* | N = 1134, K= 2.7 | | N = 1134, K= 2.7 | |
| $AL_{traj}$ | -0.36 (0.080) | < 0.0001 | -0.31 (0.089) | < 0.0001 |
| $AL_{traj}$ × Time | -0.0076 (0.011) | 0.51 | -0.0039 (0.013) | 0.76 |
| **WHITE:** | | | | |
| *CES-D total score:* | N = 770, K=2.7 | | N = 770, K=2.7 | |
| $AL_{traj}$ | 1.38 (0.38) | < 0.0001 | 1.09 (0.44) | 0.012 |
| $AL_{traj}$ × Time | 0.11 (0.045) | 0.012 | 0.072 (0.054) | 0.18 |
| *CES-D domain 1 score:* | N = 770, K= 2.7 | | N = 770, K= 2.7 | |
| $AL_{traj}$ | 0.40 (0.17) | 0.016 | 0.31 (0.19) | 0.10 |
| $AL_{traj}$ × Time | 0.039 (0.020) | 0.047 | 0.029 (0.023) | 0.22 |
| *CES-D domain 2 score:* | N = 770, K= 2.7 | | N = 770, K= 2.7 | |
| $AL_{traj}$ | 0.099 (0.043) | 0.022 | 0.063 (0.050) | 0.21 |
| $AL_{traj}$ × Time | 0.0057 (0.0059) | 0.34 | 0.0085 (0.0071) | 0.23 |
| *CES-D domain 3 score:* | N = 770, K= 2.7 | | N = 770, K= 2.7 | |
| $AL_{traj}$ | 0.48 (0.14) | 0.001 | 0.38 (0.16) | 0.021 |
| $AL_{traj}$ × Time | 0.063 (0.019) | 0.001 | 0.040 (0.02) | 0.070 |
| *CES-D domain 4 score:* | N = 770, K= 2.7 | | N = 770, K= 2.7 | |
| $AL_{traj}$ | -0.35 (0.094) | < 0.0001 | -0.32 (0.11) | 0.004 |
| $AL_{traj}$ × Time | -0.0089 (0.013) | 0.50 | 0.0081 (0.016) | 0.61 |
| **AFRICAN AMERICAN:** | | | | |
| *CES-D total score:* | N = 1183, K=2.6 | | N = 1183, K=2.6 | |
| $AL_{traj}$ | 0.58 (0.31) | 0.059 | 0.38 (0.32) | 0.23 |
| $AL_{traj}$ × Time | 0.052 (0.034) | 0.13 | 0.075 (0.037) | 0.041 |
| *CES-D domain 1 score:* | N = 1183, K= 2.6 | | N = 1183, K= 2.6 | |
| $AL_{traj}$ | 0.19 (0.14) | 0.17 | 0.080 (0.14) | 0.57 |
| $AL_{traj}$ × Time | 0.014 (0.014) | 0.36 | 0.024 (0.016) | 0.14 |
| *CES-D domain 2 score:* | N = 1183, K= 2.6 | | N = 1183, K= 2.6 | |
| $AL_{traj}$ | 0.073 (0.038) | 0.053 | 0.073 (0.040) | 0.072 |
| $AL_{traj}$ × Time | -0.00024 (0.0050) | 0.96 | -0.0025 (0.0054) | 0.64 |
| *CES-D domain 3 score:* | N = 1183, K= 2.6 | | N = 1183, K= 2.6 | |
| $AL_{traj}$ | 0.22 (0.12) | 0.062 | 0.17 (0.13) | 0.18 |
| $AL_{traj}$ × Time | 0.015 (0.015) | 0.31 | 0.027 (0.016) | 0.087 |
| *CES-D domain 4 score:* | N = 1183, K= 2.6 | | N = 1183, K= 2.6 | |
| $AL_{traj}$ | -0.097 (0.072) | 0.18 | -0.072 (0.076) | 0.35 |
| $AL_{traj}$ × Time | -0.022 (0.011) | 0.034 | -0.025 (0.011) | 0.028 |

*Abbreviations:* $AL_{traj}$ = z-transformed probability of belonging to a group with higher allostatic load over time according to group-based trajectory modeling; CES-D = Center for Epidemiological Studies Depression; K = Mean number of visits per subject; n = Sample size; SE = Standard error. [1] Model 1 is a series of mixed effects linear models adjusted for age, sex, race, poverty status, inverse mills ratio as well as time on study in years between visits 1 and 3 and its interaction with allostatic load trajectory and covariates. [2] Model 2 is a series of mixed effects linear models adjusted for age, sex, race, poverty status, education, smoking, drug use, 2010 healthy eating index, body mass index, inverse mills ratio as well as time on study in years between visits 1 and 3 and its interaction with allostatic load trajectory and covariates. [3] Depressive symptoms scores include the CES-D total score, the CES-D domain 1 score [depressive affect], the CES-D domain 2 score [interpersonal problems], the CES-D domain 3 score [somatic complaints] and the CES-D domain 4 score [positive affect].

sex and race. Further studies using longitudinal designs with larger sample sizes and longer follow-up times are required to confirm and extend these findings. The link between AL and "positive affect" is consistent with the extant literature focused on anhedonia (Carbone, 2021; Berger et al., 2019; Ravi et al., 2021). Although expected the finding that AL which was defined as a combination of cardiovascular, metabolic, and inflammatory risk indicators is more strongly associated with somatic as opposed to non-somatic domains of depression has implications for future research. Specifically, it is important to recognize that the somatic and non-somatic aspects of depression should be examined separately when attempting to use AL to further our understanding of the aging process.

## Funding

This research was supported entirely by the Intramural Research Program of the NIH, National Institute on Aging (Z01-AG000513). The funding source did not play a role in study design, data collection, analysis and interpretation, or in the writing of the report and decision to submit the article for publication.

## Declaration of Interest

None.

## Acknowledgements

The authors would like to thank staff, investigators and participants in HANDLS and NIA internal reviewers.

*Disclaimer*

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*Notes:* CES-D=Center for Epidemiological Studies Depression scale; HANDLS=Healthy Aging in Neighborhoods of Diversity across the Life Span.

*Notes:* HANDLS=Healthy Aging in Neighborhoods of Diversity across the Life Span; A=Table display of intercept, linear and quadratic terms for the two trajectories in allostatic load identified using group-based trajectories, whereby Group 1 allostatic load has a lower y-intercept than Group 2, and both Group 1 and 2 have significant and positive linear terms; B=A graphical display of the two groups identified using group-based trajectory modeling is shown, whereby ALLOSTATIC represents allostatic load total score and Age (years) represents the time variable. Also, HANDLS wave 1 (Visit 1) allostatic load total score [w1allostatic_load], HANDLS wave 3 (Visit 2) allostatic load total score [w3allostatic_load], and HANLDS wave 4 (Visit 3) allostatic load total score [w4allostatic_load] are displayed graphically to estimate the distributions of probabilities of belonging to Group 1 and Group 2.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.106022.

## References

Andreescu, C., Ajilore, O., Aizenstein, H.J., Albert, K., Butters, M.A., Landman, B.A., Karim, H.T., Krafty, R., Taylor, W.D., 2019. Disruption of neural homeostasis as a model of relapse and recurrence in late-life depression. Am. J. Geriatr. Psychiatry 27, 1316–1330.

Arnaldo, I., Corcoran, A.W., Friston, K.J., Ramstead, M.J.D., 2022. Stress and its sequelae: an active inference account of the etiological pathway from allostatic overload to depression. Neurosci. Biobehav Rev. 135, 104590.

Barboza Solis, C., Fantin, R., Kelly-Irving, M., Delpierre, C., 2016. Physiological wear-and-tear and later subjective health in mid-life: findings from the 1958 British birth cohort. Psychoneuroendocrinology 74, 24–33.

Beekman, A.T., Deeg, D.J., Limbeek, V.A.N., Braam, J., De Vries, A.W., M. Z, Van Tilburg, W., 1997. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. Psychol. Med 27, 231–235.

Berg, C.J., Haardorfer, R., Mcbride, C.M., Kilaru, V., Ressler, K.J., Wingo, A.P., Saba, N. F., Payne, J.B., Smith, A., 2017. Resilience and biomarkers of health risk in Black smokers and nonsmokers. Health Psychol. 36, 1047–1058.

Berger, M., Taylor, S., Harriss, L., Campbell, S., Thompson, F., Jones, S., Sushames, A., Amminger, G.P., Sarnyai, Z., Mcdermott, R., 2019. Hair cortisol, allostatic load, and depressive symptoms in Australian Aboriginal and Torres Strait Islander people. Stress 22, 312–320.

Beydoun, H.A., Huang, S., Beydoun, M.A., Hossain, S., Zonderman, A.B., 2019a. Mediating-moderating effect of allostatic load on the association between dietary approaches to stop hypertension diet and all-cause and cause-specific mortality: 2001-2010 national health and nutrition examiNATION SURveys. Nutrients 11.

Beydoun, M.A., Beydoun, H.A., Kitner-Triolo, M.H., Kaufman, J.S., Evans, M.K., Zonderman, A.B., 2013. Thyroid hormones are associated with cognitive function: moderation by sex, race, and depressive symptoms. J. Clin. Endocrinol. Metab. 98, 3470–3481.

Beydoun, M.A., Beydoun, H.A., Mode, N., Dore, G.A., Canas, J.A., Eid, S.M., Zonderman, A.B., 2016a. Racial disparities in adult all-cause and cause-specific mortality among us adults: mediating and moderating factors. BMC Public Health 16, 1113.

Beydoun, M.A., Canas, J.A., Dore, G.A., Beydoun, H.A., Rostant, O.S., Fanelli-Kuczmarski, M.T., Evans, M.K., Zonderman, A.B., 2016b. Serum uric acid and its association with longitudinal cognitive change among urban adults. J. Alzheimers Dis. 52, 1415–1430.

Beydoun, M.A., Nkodo, A., Fanelli-Kuczmarski, M.T., Maldonado, A.I., Beydoun, H.A., Popkin, B.M., Evans, M.K., Zonderman, A.B., 2019b. Longitudinal associations between monetary value of the diet, DASH diet score and the allostatic load among middle-aged urban adults. Nutrients 11.

Beydoun, M.A., Weiss, J., Obhi, H.K., Beydoun, H.A., Dore, G.A., Liang, H., Evans, M.K., Zonderman, A.B., 2019c. Cytokines are associated with longitudinal changes in cognitive performance among urban adults. Brain Behav. Immun. 80, 474–487.

Beydoun, M.A., Canas, J.A., Fanelli-Kuczmarski, M.T., Maldonado, A.I., Shaked, D., Kivimaki, M., Evans, M.K., Zonderman, A.B., 2020a. Association of antioxidant VITAmins A, C, E and carotenoids with cognitive performance over time: a cohort study of middle-aged adults. Nutrients 12.

Beydoun, M.A., Hossain, S., Beydoun, H.A., Shaked, D., Weiss, J., Evans, M.K., Zonderman, A.B., 2020b. Red cell distribution width is directly associated with poor cognitive performance among nonanemic, middle-aged, urban adults. J. Nutr. 150, 128–139.

Carbone, J.T., 2021. Allostatic load and mental health: a latent class analysis of physiological dysregulation. Stress 24, 394–403.

Chen, X., Redline, S., Shields, A.E., Williams, D.R., Williams, M.A., 2014. Associations of allostatic load with sleep apnea, insomnia, short sleep duration, and other sleep disturbances: findings from the National Health and Nutrition Examination Survey 2005 to 2008. Ann. Epidemiol. 24, 612–619.

Department O.F. HEALTH AND HUMAN SERVICES. 2004. Annual Update of the HHS Poverty Guidelines; Notice [Online]. Available: ⟨https://aspe.hhs.gov/sites/default/files/documents/ff1ac67af87462a031279a1a462bcd13/HHS-Poverty-Guidelines-Fed-Register-2004.pdf⟩ [Accessed 69].

Evans, M.K., Lepkowski, J.M., Powe, N.R., Laveist, T., Kuczmarski, M.F., Zonderman, A. B., 2010. Healthy aging in neighborhoods of diversity across the life span (HANDLS): overcoming barriers to implementing a longitudinal, epidemiologic, urban study of health, race, and socioeconomic status. Ethn. Dis. 20, 267–275.

Gale, C.R., Booth, T., Starr, J.M., Deary, I.J., 2016. Intelligence and socioeconomic position in childhood in relation to frailty and cumulative allostatic load in later life: the Lothian Birth Cohort 1936. J. Epidemiol. Community Health 70, 576–582.

Gillespie, S.L., Anderson, C.M., Zhao, S., Tan, Y., Kline, D., Brock, G., Odei, J., O'brien, E., Sims, M., Lazarus, S.A., Hood, D.B., Williams, K.P., Joseph, J.J., 2019. Allostatic load in the association of depressive symptoms with incident coronary heart disease: The Jackson Heart Study. Psychoneuroendocrinology 109, 104369.

Ho, T.C., King, L.S., 2021. Mechanisms of neuroplasticity linking early adversity to depression: developmental considerations. Transl. Psychiatry 11, 517.

Hochberg, Y., Tamhane, A.C., 1987. Multiple Comparison Procedures. Wiley, New York.

Hossain, S., Beydoun, M.A., Kuczmarski, M.F., Tajuddin, S., Evans, M.K., Zonderman, A. B., 2019. The interplay of diet quality and Alzheimer's disease genetic risk score in relation to cognitive performance among urban African Americans. Nutrients 11.

Hu, T., Zhao, X., Wu, M., Li, Z., Luo, L., Yang, C., Yang, F., 2022. Prevalence of depression in older adults: a systematic review and meta-analysis. Psychiatry Res. 311, 114511.

Jeon, S.W., Kim, Y.K., 2018. The role of neuroinflammation and neurovascular dysfunction in major depressive disorder. J. Inflamm. Res. 11, 179–192.

Jones, B., Nagin, D., 2007. Advances in group-based trajectory modeling and an SAS procedure for estimating them. Sociol. Methods Res. 35, 542–571.

Jones, B., Nagin, D., Roeder, K., 2001. A SAS procedure based on mixture models for estimating developmental trajectories. Sociol. Methods Res. 29, 374–393.

Juster, R.P., Moskowitz, D.S., Lavoie, J., D'antono, B., 2013. Sex-specific interaction effects of age, occupational status, and workplace stress on psychiatric symptoms and allostatic load among healthy Montreal workers. Stress 16, 616–629.

Juster, R.P., Pruessner, J.C., Desrochers, A.B., Bourdon, O., Durand, N., Wan, N., Tourjman, V., Kouassi, E., Lesage, A., Lupien, S.J., 2016. Sex and gender roles in relation to mental health and allostatic load. Psychosom. Med. 78, 788–804.

Kerr, P., Barbosa Da Torre, M., Giguere, C.E., Lupien, S.J., Juster, R.P., 2021. Occupational gender roles in relation to workplace stress, allostatic load, and mental health of psychiatric hospital workers. J. Psychosom. Res. 142, 110352.

Krause, N., 1986. Life stress as a correlate of depression among older adults. Psychiatry Res. 18, 227–237.

Kuczmarski, A.V., Cotugna, N., Mason, M.A., Evans, M.K., Zonderman, A.B., 2015. Depression and cognitive impairment are associated with low education and literacy status and smoking but not caffeine consumption in urban African Americans and white adults. J. Caffeine Res. 5, 31–41.

Magnusson Hanson, L.L., Rod, N.H., Vahtera, J., Virtanen, M., Ferrie, J., Shipley, M., Kivimaki, M., Westerlund, H., 2020. Job insecurity and risk of coronary heart disease: mediation analyses of health behaviors, sleep problems, physiological and psychological factors. Psychoneuroendocrinology 118, 104706.

Murphy, F., Nasa, A., Cullinane, D., Raajakesary, K., Gazzaz, A., Sooknarine, V., Haines, M., Roman, E., Kelly, L., O'neill, A., Cannon, M., Roddy, D.W., 2022. Childhood trauma, the HPA axis and psychiatric illnesses: a targeted literature synthesis. Front Psychiatry 13, 748372.

Nguyen, H.T., Kitner-Triolo, M., Evans, M.K., Zonderman, A.B., 2004. Factorial invariance of the CES-D in low socioeconomic status African Americans compared with a nationally representative sample. Psychiatry Res. 126, 177–187.

Obuobi-Donkor, G., Nkire, N., Agyapong, V.I.O., 2021. Prevalence of major depressive disorder and correlates of thoughts of death, suicidal behaviour, and death by suicide in the geriatric population-a general review of literature. Behav. Sci. (Basel) 11.

Ong, A.D., Williams, D.R., Nwizu, U., Gruenewald, T.L., 2017. Everyday unfair treatment and multisystem biological dysregulation in African American adults. Cult. Divers Ethn. Minor Psychol. 23, 27–35.

Ottino-Gonzalez, J., Jurado, M.A., Garcia-Garcia, I., Caldu, X., Prats-Soteras, X., Tor, E., Sender-Palacios, M.J., Garolera, M., 2019. Allostatic load and executive functions in overweight adults. Psychoneuroendocrinology 106, 165–170.

Rauch, S.A., Morales, K.H., Zubritsky, C., Knott, K., Oslin, D., 2006. Posttraumatic stress, depression, and health among older adults in primary care. Am. J. Geriatr. Psychiatry 14, 316–324.

Ravi, M., Miller, A.H., Michopoulos, V., 2021. The immunology of stress and the impact of inflammation on the brain and behavior. BJPsych Adv. 27, 158–165.

Seeman, T., Merkin, S.S., Crimmins, E., Koretz, B., Charette, S., Karlamangla, A., 2008. Education, income and ethnic differences in cumulative biological risk profiles in a national sample of US adults: NHANES III (1988-1994). Soc. Sci. Med 66, 72–87.

Selvin, S., 2004. Statistical Analysis of Epidemiologic Data. Oxford University Press.

Tomfohr, L.M., Pung, M.A., Dimsdale, J.E., 2016. Mediators of the relationship between race and allostatic load in African and White Americans. Health Psychol. 35, 322–332.

Veronesi, G., Cavicchiolo, M., Ferrario, M.M., 2019. Allostatic load as a mediator of the association between psychosocial risk factors and cardiovascular diseases. Recent evidence and indications for prevention. G Ital. Med Lav. Erg. 41, 333–336.

Walker, A.J., Kim, Y., Price, J.B., Kale, R.P., Mcgillivray, J.A., Berk, M., Tye, S.J., 2014. Stress, inflammation, and cellular vulnerability during early stages of affective disorders: biomarker strategies and opportunities for prevention and intervention. Front Psychiatry 5, 34.

Wei, J., Hou, R., Zhang, X., Xu, H., Xie, L., Chandrasekar, E.K., Ying, M., Goodman, M., 2019. The association of late-life depression with all-cause and cardiovascular mortality among community-dwelling older adults: systematic review and meta-analysis. Br. J. Psychiatry 215, 449–455.

Wendell, C.R., Waldstein, S.R., Evans, M.K., Zonderman, A.B., 2016. Subclinical carotid atherosclerosis and neurocognitive function in an urban population. Atherosclerosis 249, 125–131.

Wright, R.S., Waldstein, S.R., Gerassimakis, C.S., Sprung, M.R., Moody, D.L.B., Taylor, A. D., Al'najjar, E., Mcneely, J.M., Zhang, Z., Evans, M.K., Zonderman, A.B., 2019. Multiple influences on cognitive function among urban-dwelling African Americans. J. Racial Ethn. Health Disparities 6, 851–860.

Zannas, A.S., Mcquoid, D.R., Payne, M.E., Steffens, D.C., Macfall, J.R., Ashley-Koch, A., Taylor, W.D., 2013. Negative life stress and longitudinal hippocampal volume changes in older adults with and without depression. J. Psychiatr. Res 47, 829–834.

Zenebe, Y., Akele, B., M, W.S., Necho, M., 2021. Prevalence and determinants of depression among old age: a systematic review and meta-analysis. Ann. Gen. Psychiatry 20, 55.

# Appendices

## Appendix A – Tables

**Table A.1.** Allostatic load criteria (Seeman et al., 2008).

| | **High-risk clinical** |
|---|---|
| Waist-to-Hip Ratio | >0.9 for men; > 0.85 for women (Alberti and Zimmet, 1998) |
| Albumin (g/dL) | < 3.8 (Visser et al., 2005) |
| C-reactive protein (mg/dL) | ≥ 0.3 (Ridker, 2003) |
| Total cholesterol (mg/dL) | ≥240 (Expert Panel on Detection and Treatment of High Blood Cholesterol in, 2001) |
| HDL (mg/dL) | <40 (Expert Panel on Detection and Treatment of High Blood Cholesterol in, 2001) |
| Glycated hemoglobin (%) | ≥6.4 (Golden et al., 2003, Osei et al., 2003) |
| Resting heart rate (beat/min) | ≥90 (Seccareccia et al., 2001) |
| Systolic BP | ≥140 (Lenfant et al., 2003) |
| Diastolic BP | ≥90 (Lenfant et al., 2003) |

*Abbreviations:* HDL = High Density Lipoprotein; BP = Blood pressure.

**Table A.2.** Comparisons of HANDLS participants with available allostatic load and depressive symptoms score at Visit 1 that are not in the analytic sample (Group A) with those in the analytic sample (Group B)

| | **Group A** | **Group B** | **P** |
|---|---|---|---|
| $AL_{v1}$ | | | |
| N | 23 | 2,298 | < 0.0001 |
| Mean ± SD | 2.52 ± 0.33 | 1.95 ± 0.028 | |
| $CESD_{v1}$ | | | |
| N | 472 | 2,264 | < 0.0001 |
| Mean ± SD | 15.64 ± 0.56 | 15.06 ± 0.24 | |
| Died by end of follow-up | | | |
| N | 1,422 | 2,298 | < 0.0001 |
| % | 20.11% | 15.49% | |

*Abbreviations:* $AL_{v1}$ = Allostatic load at Visit 1; $CESD_{v1}$ = Center for Epidemiological Studies Depression scale score at Visit 1; SD = Standard deviation.

**Table A.3.** Summary statistics for depressive symptoms total score (Visit 1 and change between Visit 1 and Visit 3) by socio-demographic, lifestyle and health characteristics at Visit 1 (n=2,298) *

| | CESD total score Mean ± SEM or β (SE) | |
|---|---|---|
| | **Visit 1** | **Change between Visit 1 and Visit 3** |
| **OVERALL:** | | |
| **SOCIO-DEMOGRAPHIC:** | 15.06 ± 0.24 | -0.12 ± 0.0023 |
| ***Sex:*** | P<0.0001 | P<0.0001 |
| Male | 13.87 ± 0.32 | -0.12 ± 0.0033 |
| Female | 15.97 ± 0.33 | -0.13 ± 0.0032 |
| ***Age (years):*** | P<0.0001 | P=0.019 |
| Continuous | β (SE) = -0.090 (0.025) | β (SE) = 0.00058 (0.00025) |
| ***Race:*** | P=0.035 | P=0.034 |
| White | 15.66 ± 0.39 | -0.13 ± 0.0036 |
| African American | 14.64 ± 0.29 | -0.12 ± 0.0030 |
| ***Poverty status:*** | P<0.0001 | P<0.0001 |
| <125% federal poverty line | 13.66 ± 0.29 | 17.24 ± 0.38 |
| ≥ 125% federal poverty line | -0.12 ± 0.0028 | -0.14 ± 0.0039 |
| ***Education:*** | P<0.0001 | P<0.0001 |
| Less than high school | 18.10 ± 1.03 | -0.14 ± 0.010 |
| High school | 16.24 ± 0.32 | -0.13 ± 0.0031 |
| More than high school | 12.56 ± 0.38 | -0.11 ± -0.11 |
| **LIFESTYLE:** | | |
| ***Cigarette smoking:*** | P<0.0001 | P<0.0001 |
| Yes | 16.82 ± 0.35 | -0.13 ± 0.0035 |
| No | 13.50 ± 0.32 | -0.11 ± 0.0031 |
| ***Drug use:*** | P<0.0001 | P=0.0002 |
| Yes | 17.49 ± 0.57 | -0.14 ± 0.0059 |
| No | 14.54 ± 0.26 | -0.12 ± 0.0025 |
| ***HEI-2010 score:*** | P<0.0001 | P<0.0001 |
| | β (SE) = -0.15 (0.021) | β (SE) = 0.0011 (0.00021) |
| **HEALTH:** | | |
| ***Body mass index (kg/m$^2$):*** | P=0.56 | P=0.86 |
| | β (SE) = 0.017 (0.030) | β (SE) = -0.000050 (0.00029) |
| ***Self-rated health:*** | P<0.0001 | P<0.0001 |
| Poor/Average | 20.78 ± 0.50 | -0.17 ± 0.0050 |
| Good | 14.59 ± 0.35 | -0.12 ± 0.0035 |
| Very good/Excellent | 11.10 ± 0.33 | -0.095 ± 0.0033 |
| ***Hypertension:*** | P=0.034 | P=0.066 |
| Yes | 15.59 ± 0.34 | -0.13 ± 0.0033 |
| No | 14.57 ± 0.32 | -0.12 ± 0.0032 |
| ***Diabetes:*** | P= 0.82 | P=0.91 |
| None | 14.97 ± 0.30 | -0.13 ± 0.0029 |
| Pre-diabetes | 15.06 ± 0.55 | -0.12 ± 0.0054 |
| Diabetes | 15.38 ± 0.55 | -0.12 ± 0.0056 |
| ***Dyslipidemia:*** | P=0.26 | P=0.46 |
| Yes | 15.56 ± 0.51 | -0.13 ± 0.0048 |
| No | 14.87 ± 0.28 | -0.12 ± 0.0028 |

| | | |
|---|---|---|
| ***Cardiovascular disease:*** | P=0.006 | P=0.028 |
| Yes | 16.47 ± 0.58 | -0.14 ± 0.0055 |
| No | 14.75 ± 0.26 | -0.12 ± 0.0026 |

***** P values are based on bivariate associations between depressive symptoms total score at Visit 1 or change between Visit 1 and Visit 3 and each of the variables presented within the table. *Abbreviations:* β = Slope of linear regression model; CES-D = Center for Epidemiological Studies Depression; HEI = Healthy Eating Index; n=Sample size; SE = Standard error.

**Table A.4.** Interaction effects by sex and race for the effects of allostatic load at Visit 1 on depressive symptoms total and domain-specific scores (Visit 1 and change between Visit 1 and Visit 3) [3]

| | Model 1 [1] | | Model 2 [2] | |
|---|---|---|---|---|
| | β (SE) | P value | β (SE) | P value |
| **SEX** | | | | |
| CES-D total [$AL_{v1}$] | -0.058 (0.35) | 0.87 | 0.072 (0.34) | 0.83 |
| CES-D total [$AL_{v1}$ × Time] | -0.014 (0.044) | 0.75 | -0.0086 (0.044) | 0.84 |
| CES-D domain 1 [$AL_{v1}$] | 0.040 (0.15) | 0.79 | 0.091 (0.15) | 0.55 |
| CES-D domain 1 [$AL_{v1}$ × Time] | -.021 (0.019) | 0.27 | -0.020 (0.019) | 0.29 |
| CES-D domain 2 [$AL_{v1}$] | 0.025 (0.043) | 0.55 | 0.033 (0.043) | 0.43 |
| CES-D domain 2 [$AL_{v1}$ × Time] | 0.00067 (0.0062) | 0.91 | 0.0011 (0.0062) | 0.86 |
| CES-D domain 3 [$AL_{v1}$] | -0.061 (0.14) | 0.66 | -0.016 (0.13) | 0.90 |
| CES-D domain 3 [$AL_{v1}$ × Time] | -0.0018 (0.018) | 0.92 | 0.00072 (0.019) | 0.97 |
| CES-D domain 4 [$AL_{v1}$] | 0.044 (0.086) | 0.60 | 0.023 (0.085) | 0.79 |
| CES-D domain 4 [$AL_{v1}$ × Time] | -0.000036 (0.014) | 0.99 | -0.0018 (0.014) | 0.89 |
| **RACE** | | | | |
| CES-D total [$AL_{v1}$] | -0.56 (0.36) | 0.11 | -0.19 (0.35) | 0.57 |
| CES-D total [$AL_{v1}$ × Time] | -0.0032 (0.045) | 0.94 | 0.0024 (0.046) | 0.96 |
| CES-D domain 1 [$AL_{v1}$] | -0.11 (0.15) | 0.49 | 0.031 (0.15) | 0.84 |
| CES-D domain 1 [$AL_{v1}$ × Time] | -0.0068 (0.019) | 0.73 | -0.0068 (0.020) | 0.74 |
| CES-D domain 2 [$AL_{v1}$] | -0.018 (0.043) | 0.66 | 0.0087 (0.043) | 0.84 |
| CES-D domain 2 [$AL_{v1}$ × Time] | -0.0025 (0.0064) | 0.69 | -0.0024 (0.0064) | 0.71 |
| CES-D domain 3 [$AL_{v1}$] | -0.13 (0.14) | 0.33 | 0.0019 (0.14) | 0.99 |
| CES-D domain 3 [$AL_{v1}$ × Time] | -0.026 (0.019) | 0.17 | -0.023 (0.019) | 0.24 |
| CES-D domain 4 [$AL_{v1}$] | 0.21 (0.086) | 0.015 | 0.14 (0.086) | 0.091 |
| CES-D domain 4 [$AL_{v1}$ × Time] | -0.024 (0.013) | 0.085 | -0.028 (0.014) | 0.043 |

*Abbreviations:* $AL_{v1}$ = Allostatic load at Visit 1; CES-D = Center for Epidemiological Studies Depression scale; SE = Standard error; [1] Model 1 represents a series of mixed-effects linear models adjusted for age, sex, race, poverty status, inverse mills ratio as well as time on study in years between visits 1 and 3 and its interaction with allostatic load and covariates. [2] Model 2 represents a series of mixed-effects linear models adjusted for age, sex, race, poverty status, education, smoking, drug use, 2010 healthy eating index, body mass index, inverse mills ratio as well as time on study in years between visits 1 and 3 and its interaction with allostatic load and covariates. [3] Depressive symptoms scores include the CES-D total score, the CES-D domain 1 score [depressive affect], the CES-D domain 2 score [interpersonal problems], the CES-D domain 3 score [somatic complaints] and the CES-D domain 4 score [positive affect].

**Table A.5.** Socio-demographic characteristics of the two groups defined by group-based trajectory modeling (n=1,953)

| | **Group 1 [Low Trajectory] (n=343)** | **Group 2 [High Trajectory] (n=1,610)** | **P *** |
|---|---|---|---|
| ***Sex:*** | | | < 0.0001 |
| Male | 53.6 % | 39.4 % | |
| Female | 46.4 % | 60.6 % | |
| ***Age (years):*** | | | |
| Mean (SEM) | 46.04 (0.47) | 48.77 (0.22) | < 0.0001 |
| ***Race:*** | | | 0.93 |
| White | 39.6 % | 39.4 % | |
| African American | 60.3 % | 60.6 % | |
| ***Poverty status:*** | | | 0.13 |
| <125% federal poverty line | 65.6% | 61.2% | |
| ≥ 125% federal poverty line | 34.4% | 38.8% | |
| ***Education:*** | | | |
| Less than high school | 2.18 % | 6.8 % | Ref. |
| High school | 51.7 % | 60.4 % | 0.04 |
| More than high school | 45.5 % | 32.8 % | < 0.0001 |

*Abbreviations:* SEM = Standard error of the mean. * P values are based on Chi-square tests of design-based F tests.

**Table A.6.** Interaction effects by sex and race for the effects of allostatic load trajectory on depressive symptoms total and domain-specific scores (Visit 1 and change between Visit 1 and Visit 3) [3]

| | Model 1 [1] | | Model 2 [2] | |
|---|---|---|---|---|
| | β (SE) | P value | β (SE) | P value |
| **SEX** | | | | |
| CES-D total [$AL_{traj}$] | -0.92 (0.47) | 0.053 | -0.74 (0.46) | 0.11 |
| CES-D total [$AL_{traj} \times$ Time] | -0.015 (0.053) | 0.78 | -0.012 (0.054) | 0.82 |
| CES-D domain 1 [$AL_{traj}$] | -0.24 (0.21) | 0.26 | -0.17 (0.21) | 0.41 |
| CES-D domain 1 [$AL_{traj} \times$ Time] | -0.017 (0.023) | 0.48 | -0.018 (0.024) | 0.45 |
| CES-D domain 2 [$AL_{traj}$] | 0.019 (0.056) | 0.73 | 0.028 (0.056) | 0.63 |
| CES-D domain 2 [$AL_{traj} \times$ Time] | -0.0025 (0.0076) | 0.74 | -0.0019 (0.0077) | 0.80 |
| CES-D domain 3 [$AL_{traj}$] | -0.32 (0.18) | 0.077 | -0.26 (0.18) | 0.15 |
| CES-D domain 3 [$AL_{traj} \times$ Time] | -0.019 (0.023) | 0.42 | -0.017 (0.023) | 0.45 |
| CES-D domain 4 [$AL_{traj}$] | 0.32 (0.11) | 0.006 | 0.29 (0.11) | 0.009 |
| CES-D domain 4 [$AL_{traj} \times$ Time] | -0.017 (0.017) | 0.30 | -0.021 (0.016) | 0.20 |
| **RACE** | | | | |
| CES-D total [$AL_{traj}$] | -0.89 (0.48) | 0.062 | -0.42 (0.47) | 0.38 |
| CES-D total [$AL_{traj} \times$ Time] | -0.044 (0.055) | 0.43 | -0.046 (0.056) | 0.41 |
| CES-D domain 1 [$AL_{traj}$] | -0.23 (0.21) | 0.27 | -0.046 (0.21) | 0.83 |
| CES-D domain 1 [$AL_{traj} \times$ Time] | -0.019 (0.024) | 0.42 | -0.024 (0.024) | 0.33 |
| CES-D domain 2 [$AL_{traj}$] | -0.022 (0.057) | 0.70 | 0.0088 (0.057) | 0.88 |
| CES-D domain 2 [$AL_{traj} \times$ Time] | -.0052 (0.0078) | 0.51 | -0.0055 (0.0079) | 0.48 |
| CES-D domain 3 [$AL_{traj}$] | -0.31 (0.19) | 0.094 | -0.12 (0.18) | 0.49 |
| CES-D domain 3 [$AL_{traj} \times$ Time] | -0.042 (0.024) | 0.077 | -0.042 (0.024) | 0.079 |
| CES-D domain 4 [$AL_{traj}$] | 0.28 (0.12) | 0.014 | 0.21 (0.11) | 0.070 |
| CES-D domain 4 [$AL_{traj} \times$ Time] | -0.020 (0.017) | 0.24 | -0.025 (0.017) | 0.15 |

*Abbreviations:* $AL_{traj}$ = z-transformed probability of belonging to a group with higher allostatic load between Visit 1 and Visit 3 according to group-based trajectory modeling; CES-D = Center for Epidemiological Studies Depression; SE = Standard error; [1] Model 1 represents a series of mixed-effects linear models adjusted for age, sex, race, poverty status, inverse mills ratio as well as time on study in years between visits 1 and 3 and its interaction with trajectory in allostatic load and covariates. [2] Model 2 represents a series of mixed-effects linear models adjusted for age, sex, race, poverty status, education, literacy, smoking, drug use, 2010 healthy eating index, body mass index, inverse mills ratio as well as time on study in years between visits 1 and 3 and its interaction with trajectory in allostatic load and covariates. [3] Depressive symptoms scores include the CES-D total score, the CES-D domain 1 score [depressive affect], the CES-D domain 2 score [interpersonal problems], the CES-D domain 3 score [somatic complaints] and the CES-D domain 4 score [positive affect].

**Table A.7.** Relationship of observed annualized change in allostatic load between Visit 1 and Visit 3 with depressive symptoms total and domain-specific scores (at Visit 1 and change between Visit 1 and 3)

| | **Model 1** [1] | | **Model 2** [2] | |
|---|---|---|---|---|
| | β (SE) | P value | β (SE) | P value |
| | N=1,611, K=2.8 | | N=1,611, K=2.8 | |
| CES-D total [$AL_{ac}$] | -0.030 (0.27) | 0.91 | -0.083 (0.26) | 0.75 |
| CES-D total [$AL_{ac}$ × Time] | 0.087 (0.033) | **0.008** | 0.086 (0.033) | **0.011** |
| | N=1,611, K=2.8 | | N=1,611, K=2.8 | |
| CES-D domain 1 [$AL_{ac}$] | 0.055 (0.11) | 0.65 | 0.0330 (0.11) | 0.77 |
| CES-D domain 1 [$AL_{ac}$ × Time] | 0.026 (0.014) | 0.072 | 0.026 (0.015) | 0.072 |
| | N=1,611, K=2.8 | | N=1,611, K=2.8 | |
| CES-D domain 2 [$AL_{ac}$] | 0.0021 (0.032) | 0.95 | -0.0018 (0.032) | 0.95 |
| CES-D domain 2 [$AL_{ac}$ × Time] | 0.0072 (0.0047) | 0.12 | 0.0075 (0.0047) | 0.11 |
| | N=1,611, K=2.8 | | N=1,611, K=2.8 | |
| CES-D domain 3 [$AL_{ac}$] | -0.12 (0.10) | 0.23 | -0.15 (0.10) | 0.14 |
| CES-D domain 3 [$AL_{ac}$ × Time] | 0.042 (0.014) | **0.003** | 0.040 (0.014) | **0.005** |
| | N=1,611, K=2.8 | | N=1,611, K=2.8 | |
| CES-D domain 4 [$AL_{ac}$] | -0.036 (0.063) | 0.57 | -0.028 (0.063) | 0.66 |
| CES-D domain 4 [$AL_{ac}$ × Time] | -0.013 (0.010) | 0.19 | -0.012 (0.010) | 0.23 |

*Abbreviations:* $AL_{ac}$ = Observed annualized change in allostatic load between Visit 1 and Visit 3; CES-D = Center for Epidemiological Studies Depression; K = Mean number of visits per subject; n = Sample size; SE = Standard error. [1] Model 1 is a series of mixed effects linear models adjusted for age, sex, race, poverty status, inverse mills ratio as well as time on study in years between visits 1 and 3 and its interaction with allostatic load trajectory and covariates. [2] Model 2 is a series of mixed effects linear models adjusted for age, sex, race, poverty status, education, smoking, drug use, 2010 healthy eating index, body mass index, inverse mills ratio as well as time on study in years between visits 1 and 3 and its interaction with allostatic load trajectory and covariates. [3] Depressive symptoms scores include the CES-D total score, the CES-D domain 1 score [depressive affect], the CES-D domain 2 score [interpersonal problems], the CES-D domain 3 score [somatic complaints] and the CES-D domain 4 score [positive affect].

**Appendix B – Mixed-effects linear regression models**

The main multiple mixed-effects regression models can be summarized as follows:

**Multi-level models vs. Composite models**

**Eq. 1.1-1.4**

$$Y_{ij} = \pi_{0i} + \pi_{1i} Time_{ij} + \varepsilon_{ij}$$

$$\pi_{0i} = \gamma_{00} + \gamma_{0a} X_{aij} + \sum_{k=1}^{l} \gamma_{0k} Z_{ik} + \zeta_{0i}$$

$$\pi_{1i} = \gamma_{10} + \gamma_{1a} X_{aij} + \sum_{m=1}^{n} \gamma_{1m} Z_{im} + \zeta_{1i}$$

$$Y_{ij} = \gamma_{00} + \gamma_{0a} X_{aij} + \sum_{k=1}^{l} \gamma_{0k} Z_{ik} + \gamma_{10} Time_{ij} + \gamma_{1a} X_{aij} Time_{ij} + \sum_{m=1}^{n} \gamma_{1m} Z_{im} Time_{ij} + (\zeta_{0i} + \zeta_{1i} Time_{ij} + \varepsilon_{ij})$$

Where $Y_{ij}$ is the outcome (5 depressive symptoms test scores measured at $v_1$, $v_2$, and/or $v_3$) for each individual "i" and visit "j"; $\pi_{0i}$ is the level-1 intercept for individual i; $\pi_{1i}$ is the level-1 slope for individual i; $\gamma_{00}$ is the level-2 intercept of the random intercept $\pi_{0i}$; $\gamma_{10}$ is the level-2 intercept of the slope $\pi_{1i}$; $Z_{ik}$ is a vector of fixed covariates for each individual *i* that are used to predict level-1 intercepts and slopes, which can include socio-demographic variables among others. In this analysis, mixed-effects regression models included AL exposure measured at $v_1$ or as a trajectory exposure (Probability of belonging to "High increasing" group, z-scored) ($X_{ij}$), along with covariates ($Z_{ij}$). $\zeta_{0i}$ and $\zeta_{1i}$ are level-2 disturbances; $\varepsilon_{ij}$ is the within-person level-1 disturbance (Blackwell et al., 2006).

It is worth noting that the models were fit using the entire HANDLS study cohort with complete data on either $v_1$, $v_2$ or $v_3$ for each depressive symptoms test score, those models were used to improve reliability of predicted estimates. Empirical Bayes estimators for annual rate of change in each depressive symptoms test score were also predicted from time-interval mixed-effects models, with up to 3 repeats on each outcome, without adding any covariates in the model aside from *TIME*.

**REFERENCES:**

ALBERTI, K. G. & ZIMMET, P. Z. 1998. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med,* 15**,** 539-53.

BLACKWELL, E., DE LEON, C. F. & MILLER, G. E. 2006. Applying mixed regression models to the analysis of repeated-measures data in psychosomatic medicine. *Psychosom Med,* 68**,** 870-8.

EXPERT PANEL ON DETECTION, E. & TREATMENT OF HIGH BLOOD CHOLESTEROL IN, A. 2001. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA,* 285**,** 2486-97.

GOLDEN, S., BOULWARE, L. E., BERKENBLIT, G., BRANCATI, F., CHANDER, G., MARINOPOULOS, S., PAASCHE-ORLOW, M., POWE, N. & RAMI, T. 2003. Use of glycated hemoglobin and microalbuminuria in the monitoring of diabetes mellitus. *Evid Rep Technol Assess (Summ)***,** 1-6.

LENFANT, C., CHOBANIAN, A. V., JONES, D. W., ROCCELLA, E. J., JOINT NATIONAL COMMITTEE ON THE PREVENTION, D. E. & TREATMENT OF HIGH BLOOD, P. 2003. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. *Hypertension,* 41**,** 1178-9.

OSEI, K., RHINESMITH, S., GAILLARD, T. & SCHUSTER, D. 2003. Is glycosylated hemoglobin A1c a surrogate for metabolic syndrome in nondiabetic, first-degree relatives of African-American patients with type 2 diabetes? *J Clin Endocrinol Metab,* 88**,** 4596-601.

RIDKER, P. M. 2003. Cardiology Patient Page. C-reactive protein: a simple test to help predict risk of heart attack and stroke. *Circulation,* 108**,** e81-5.

SECCARECCIA, F., PANNOZZO, F., DIMA, F., MINOPRIO, A., MENDITTO, A., LO NOCE, C., GIAMPAOLI, S. & MALATTIE CARDIOVASCOLARI ATEROSCLEROTICHE ISTITUTO

SUPERIORE DI SANITA, P. 2001. Heart rate as a predictor of mortality: the MATISS project. *Am J Public Health,* 91**,** 1258-63.

SEEMAN, T., MERKIN, S. S., CRIMMINS, E., KORETZ, B., CHARETTE, S. & KARLAMANGLA, A. 2008. Education, income and ethnic differences in cumulative biological risk profiles in a national sample of US adults: NHANES III (1988-1994). *Soc Sci Med,* 66**,** 72-87.

VISSER, M., KRITCHEVSKY, S. B., NEWMAN, A. B., GOODPASTER, B. H., TYLAVSKY, F. A., NEVITT, M. C. & HARRIS, T. B. 2005. Lower serum albumin concentration and change in muscle mass: the Health, Aging and Body Composition Study. *Am J Clin Nutr,* 82**,** 531-7.