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Allostatic Load and Cognitive Function Among Urban Adults in the Healthy Aging in Neighborhoods of Diversity across the Life Span Study

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Abstract.
Background: Cross-sectional studies have linked cognition to allostatic load (AL) which reflects multisystem dysregulation from life course exposure to stressors.
Objective: To examine baseline and changes in AL and their relationships with 11 cognitive function test scores, while exploring health disparities according to sex and race.
Methods: Longitudinal [Visit 1 (2004–2009) and Visit 2 (2009–2013)] data were analyzed from 2,223 Healthy Aging in Neighborhoods of Diversity across the Life Span participants. We calculated AL total score using cardiovascular, metabolic, and inflammatory risk indicators, and applied group-based trajectory modeling to define AL change.
Results: Overall and stratum-specific relationships were evaluated using mixed-effects linear regression models that controlled for socio-demographic, lifestyle, and health characteristics. Baseline AL was significantly associated with higher log-transformed Part A Trail Making Test score [Log_e (TRAILS A)] ($\beta = 0.020$, $p = 0.004$) and increasing AL was associated with higher Benton Visual Retention Test score [BVRT] ($\beta = 0.35$, $p = 0.002$) at baseline, in models that controlled for age, sex, race, poverty status, education, literacy, smoking, drug use, the 2010 healthy eating index and body mass index. Baseline AL and AL change were not related to change in cognitive function between visits. There were no statistically significant interaction effects by sex or race in fully-adjusted models.
Conclusion: At baseline, AL was associated with worse attention or executive functioning. Increasing AL was associated with worse non-verbal memory or visuo-constructional abilities at baseline. AL was not related to change in cognitive function over time, and relationships did not vary by sex or race.

Keywords: Adults, allostatic load, cognitive function, health disparities, longitudinal study

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INTRODUCTION

The health impact of the "exposome" is an active area of research with public health implications in which health disparities and lifetime experiences with "wear and tear" are emphasized. In this context, the exposome consists of three domains, namely, the general external environment (e.g., urbanicity, social capital, interpersonal relationships), the specific external environment (e.g., dietary habits, tobacco use), and the internal biological environments (e.g., metabolic factors, inflammation, oxidative stress) [1]. Evidence suggests that acute exposure to stressful situations and chronic stress are associated with an increased risk of a wide range of physical and mental health outcomes including anxiety, depression, autoimmune disorders, cardiovascular disease, certain cancers, and Alzheimer's disease [2]. Chronic stress over the life course is also posited as detrimental to cognition through the "glucocorticoid cascade hypothesis" whereby high cortisol concentration can gradually diminish hippocampal functioning, eventually leading to declines in cognitive function [3]. Circulating levels of cortisol, a hypothalamic-pituitary-adrenal axis hormone, fluctuate daily in response to circadian rhythm and acute environmental changes [3]. Cortisol is a key mediator of allostasis—an individual's capacity to modify their physiological response to changes in the external and internal milieu—and constant fluctuations in cortisol level over time can lead to "wear and tear" or untoward outcomes at the cellular level affecting multiple physiological systems [3]. Allostatic load (AL) is a composite measure reflecting multisystem (cardiovascular, metabolic, and inflammatory) dysregulation that results from cumulative exposure to stressors over the life course and is thought to quantify stress-induced biological risk [3, 4]. AL has been associated with mortality, cardiovascular disease, chronic fatigue, pain, sleep disturbance, and cognitive decline as well as health disparities [4]. To date, published studies focusing on cortisol or AL in relation to cognition [5–7] have often been limited by their inability to establish directionality of associations.

In this longitudinal study, we performed secondary analyses of existing Visit 1 (2004–2009) and Visit 2 (2009–2013) data from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study to examine baseline AL and change in AL total score using cardiovascular, metabolic and inflammatory risk indicators at Visits 1 and 2 and their relationships with cognitive function test scores (at baseline and change between Visits 1 and 2), while examining health disparities according to sex and race. We hypothesized that increasing AL is associated with decreasing cognitive function over time and that the magnitude of this association would vary according to sex and race.

MATERIALS AND METHODS

Sample and study design

Initiated in 2004, the HANDLS study is an ongoing prospective cohort study conducted by the National Institute on Aging (NIA) Intramural Research Program (IRP) and designed to answer research questions focused on health disparities in age-related diseases. The HANDLS study is a unique multidisciplinary project that examines a wide range of parameters among African American and White participants in higher and lower socioeconomic status (SES) groups. It employs novel research tools and mobile medical research vehicles (MRVs) to improve participation rates and retention among non-traditional research participants. The HANDLS study was approved by the Institutional Review Board of the National Institutes of Health, and HANDLS participants provided written informed consent [8–16].

Baseline HANDLS data (Visit 1) were collected between 2004 and 2009 in two phases. The first phase consisted of an in-home interview that included questionnaires about the participant's health status, health service utilization, psychosocial factors, nutrition, neighborhood characteristics, and demographics. The second phase was conducted in MRVs and included medical history, physical examination, dietary recall, cognitive evaluation, psychophysiological assessments (heart rate variability, arterial thickness, carotid ultrasonography, assessments of muscle strength, bone density), and laboratory measurements (blood chemistries, hematology, biomarkers of oxidative stress, biomaterials for genetic studies). Subsequently, HANDLS participants were followed-up every five years, with Visit 2 taking place between 2009 and 2013. The HANDLS visits include repeated as well as unique types of assessments. Researchers outside of the NIA IRP are welcome to submit project proposals. HANDLS data can be shared with these researchers following review and approval of their project proposals and after execution of an institutional data sharing agreement. Secondary analyses

of existing HANDLS data received exempt status at Fort Belvoir Community Hospital. HANDLS data elements available for analysis can be found at https://handls.nih.gov/06Coll-w00dataDocR.cgi.

Measures

Allostatic load

The main exposure variable of interest was AL total score defined using nine risk indicators measured at Visits 1 and 2 of the HANDLS study and computed using a method described in a previous study [17]. As shown in Supplementary Table 1, components of the AL total score 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), glycated 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. We did not incorporate the neuroendocrine dimension into this AL definition since we relied on existing data from the HANDLS study which did not analyze biospecimens for neuroendocrine biomarkers during Visits 1 and 2. As such, this AL definition which covers 3 out of 4 dimensions represents a proxy for AL and may reflect cardiometabolic health predominantly. Change in AL total score between Visit 1 and Visit 2 was defined as δAL, and annualized change in AL between these two visits was used to operationalize δAL [(AL_{v2}-AL_{v1})/(Age_{v2}-Age_{v1})] with complete case analyses. Furthermore, group-based trajectory modeling was performed for δAL using a STATA plugin (traj and trajplot) adapted from a well-established SAS procedure [18, 19], 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). After comparing alternative models, we selected a model with intercept, linear and quadratic terms for two distinct trajectories which had the highest estimated Akaike Information Criterion.

Cognitive function

The main outcome variables were defined using 11 cognitive test scores at Visits 1 and 2 of the HANDLS study. Clinical staff examined cognition with a battery of tests including the Mini-Mental State Examination (MMSE), the California Verbal Learning Test (CVLT) Immediate (List A) and Delayed Free Recall (DFR), the Benton Visual Retention Test (BVRT, # of errors), the Brief Test of Attention (BTA), the Animal Fluency test (AF), the Digit Span Forward and Backwards tests (DS-F and DS-B), the Clock Drawing Test (CDT) and the Trail making test Part A and B (TRAILS A and B, in seconds). A detailed description of each cognitive test is provided in Supplementary Material 1. Cognitive domains spanned global mental status, verbal memory, verbal fluency, attention, visual memory, visuo-spatial abilities, and executive function, which includes working memory. Total MMSE was normalized using previously described methods [20], while Trails A and B scores (in seconds) were Log_e transformed to achieve pseudo-normality. With the exception of BVRT, Trails A and B, all cognitive test scores were in the direction of higher values reflecting better performance at Visits 1 and 2.

Covariates The hypothesized relationships between AL and cognitive function were examined, taking potential confounders into consideration, including demographic (sex (male, female), age (years), 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), literacy (Wide Range Achievement Test, third edition [WRAT-3] (Supplementary Material 1)), 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], comorbidities, depression symptoms score, self-rated health) characteristics. Age at Visit 1 was analyzed as a continuous variable and age at Visit 2 was used to compute time between Visits 1 and 2, a measure relevant to our modeling approach.

Poverty status was operationalized using Department of Health and Human Services poverty thresholds based on household income and total household size for the entire HANDLS cohort [21]. The HEI-2010 [22] measures overall diet quality based on food and macronutrient-related guidelines for Americans. Comorbidities were defined as 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. Depressive symptoms were evaluated using the 20-item Center for Epidemiological Studies Depression Scale described in Supplementary Material 2. Finally, self-rated health was categorized as poor/average, good and very good/excellent.

Statistical methods

All statistical analyses were performed using STATA version 16 (StataCorp, College Station, TX). Summary statistics consisted of measures of central tendency and dispersion for continuous variables as well as counts and percentages for categorical variables. Bivariate associations were examined 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 (Supplementary Material 3). Model-building strategies involved testing for multicollinearity among variables included within mixed-effects models. Given that each covariate had <5% missing data, on average, 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 [23, 24], continuous covariates were centered on their means. Multiple imputations were performed for missing data on socio-demographic, lifestyle, and health characteristics. Mixed-effects models were conducted on samples with available Visits 1 and/or Visit 2 data and imputations of each cognitive function test assumed missingness at random. Given the sampling strategy of the HANLDS study, multiple imputations, but not design effects, were taken into consideration in the context of estimation.

First, baseline socio-demographic, lifestyle and health characteristics, cognitive test scores (at baseline and change over time) as well as baseline AL and δAL were described before and after stratifying according to baseline AL tertiles, using the largest sample after exclusion of HANDLS subjects with missing data on MMSE. Second, a series of mixed-effects linear regression models were constructed separately for baseline AL as a predictor of cognitive test scores (at baseline and change over time) and AL change as a predictor of cognitive test scores (at baseline and change over time), adjusting for distinct sets of covariates. The time variable used was time on study, in years, between Visit 1 and Visit 2. *Models 1* were adjusted for age, sex, race, poverty status, inverse mills ratio (IMR) as well as time on study between visits 1 and 2 and its interaction with AL or AL change and covariates. *Models 2* were adjusted for age, sex, race, poverty status, education, literacy, smoking, drug use, the 2010 HEI, BMI, IMR as well as time on study between visits 1 and 2 and its interaction with AL or AL change and covariates. As a sensitivity analysis, *Models 3* were adjusted for age, sex, race, poverty status, education, literacy, smoking, drug use, 2010 HEI, BMI, hypertension, diabetes, dyslipidemia, cardiovascular disease, depressive symptoms, self-rated health, IMR as well as time on study between visits 1 and 2 and its interaction with AL or AL change and covariates. Although hypertension, diabetes, dyslipidemia, and cardiovascular disease can overlap substantially with AL, we used *Models 3* as a sensitivity analysis to assess whether it was indeed AL that was associated with cognitive function or a chronic condition linked to AL. Interaction effects of AL or AL change 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 and AL change), 11 cognitive test scores with up to two repeats (effect on baseline cognitive test and effect on change in cognitive test) 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 [25]. 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 [26]. We accounted for outcome multiplicity (i.e., 11 cognitive test scores) using the approach of familywise Bonferroni correction [27], specifically for *Model 1*. Subsequently, *Models 2* and *3* were considered sensitivity models in which potentially confounding and/or mediating variables were included. As such, we adjusted significance levels for main effects to $p < 0.00455$ (0.05/11), and for two-way interaction terms to $0.10/11 = 0.00910$, similar to previous work [28].

RESULTS

As shown in Fig. 1, the initial HANDLS sample consisted of 3,720 subjects (54.7% female, mean age: 48.3 years, 59.1% African Americans, 58.7% ≥125% federal poverty line) at Visit 1. A total of 2,468 subjects also completed Visit 2 of the HANDLS study; among them, 2,321 had complete data on Visit 1 AL and AL change between visits 1 and 2. A cognitive test was considered credible if the tag filters assigned to its score suggest that it can be used to reflect cognitive functioning rather than another cause of poor performance (e.g., very low literacy, vision problems, other disabilities). After restricting the study sample to HANDLS participants with complete and credible cognitive test scores at Visits 1 and/or Visit 2, the number of study-eligible Visit 1 HANDLS participants ranged between 2,066 and 2,253, whereas the number of study-eligible Visit 2 HANDLS participants ranged between 1,702 and 1,794. Further analyses were performed on subsets of these participants with non-missing data on AL, AL change, and each of the 11 cognitive function tests performed at Visit 1 and/or Visit 2, ranging between 2,270 and 1,753.

Table 1 presents summary statistics for baseline socio-demographic, lifestyle and health characteristics, AL, cognitive test scores as well as AL change and changes in cognitive test scores, overall, and according to tertiles of baseline AL, among 2,223 study-eligible HANDLS participants (56.9% female, mean age: 48.6 years, 59.3% African Americans, 60.9% ≥ 125% federal poverty line) with complete and credible MMSE test scores at baseline. The mean baseline AL and AL change were 1.9 and 0.8, respectively. Baseline AL tertiles did not differ significantly according to race, poverty status, cigarette smok-

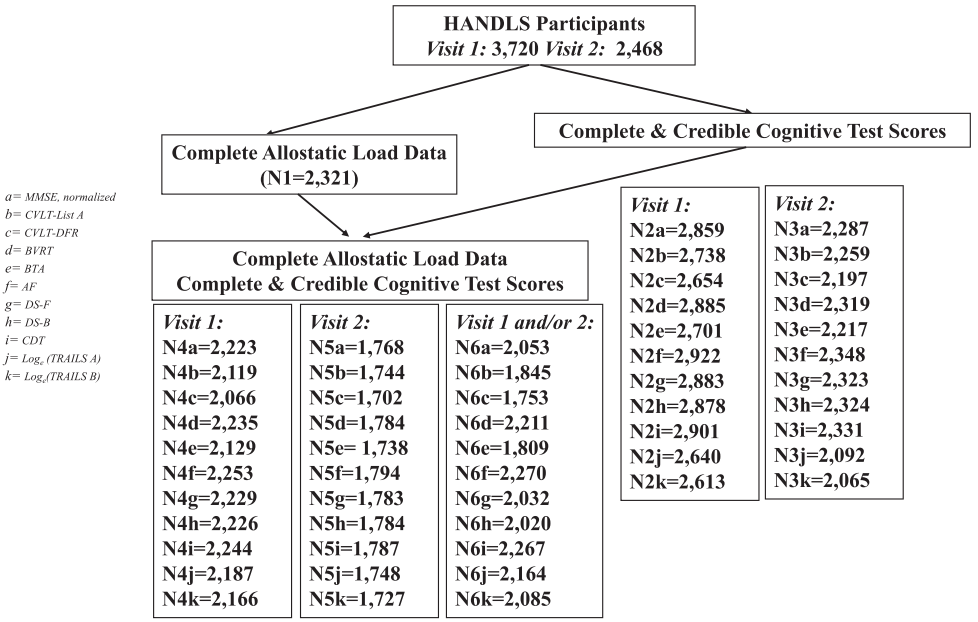


Fig. 1. Study Flowchart – HANDLS (2004–2013). HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; Cognitive tests include the Mini-Mental State Examination (MMSE), the California Verbal Learning Test (CVLT) Immediate (List A) and Delayed Free Recall (DFR), the Benton Visual Retention Test (BVRT, # of errors), the Brief Test of Attention (BTA), the Animal Fluency test (AF), the Digit Span Forward and Backwards tests (DS-F and DS-B), the Clock Drawing Test (CDT), the Trail making test Part A and B (TRAILS A and B, in seconds).

Table 1
Summary statistics for baseline socio-demographic, lifestyle and health characteristics, allostatic load, and cognitive test scores as well as between-visit change in allostatic load and cognitive test scores, overall, and according to tertiles of baseline allostatic load ($n = 2,223$)[1]

	% or Mean ± SEM	AL tertiles		
		1st	2nd	3rd
ALLOSTATIC LOAD:		N = 2,223; $p < 0.0001$		
AL	1.9 ± 0.03	0.7 ± 0.02	2.0 ± 0.0	3.5 ± 0.03
		N = 1,768; $p < 0.0001$		
δ AL	0.8 ± 0.005	0.6 ± 0.007	0.8 ± 0.003	0.9 ± 0.003
SOCIO-DEMOGRAPHIC:		N = 2,223		
Sex:			$p = 0.049$	
Male	43.1	44.4	42.4	42.1
Female	56.9	55.6	57.6	57.8
Age (y):			$p < 0.0001$	
Continuous	48.6 ± 0.2	46.5 ± 0.3	49.3 ± 0.4	50.7 ± 0.3
Race:		$p = 0.095$		
White	40.7	39.2	39.7	43.4
African American	59.3	60.8	60.3	56.5
Poverty status:		$p = 0.73$		
<125% federal poverty line	39.1	39.9	37.9	39.1
≥125% federal poverty line	60.9	60.1	62.1	60.9
Education:			$p < 0.0001$	
Less than high school	5.9	3.8	5.9	8.6
High school	59.3	56.3	60.4	62.1
More than high school	34.9	39.9	33.7	29.3
Literacy:			$p = 0.020$	
WRAT-3 score	42.2 ± 0.2	42.7 ± 0.3	41.9 ± 0.3	41.8 ± 0.3
LIFESTYLE:		N = 2,223		
Cigarette smoking:		$p = 0.18$		
Yes	52.9	48.9	46.0	45.5
No	47.1	51.1	54.0	54.4
Drug use:			$p < 0.0001$	
Yes	17.9	22.2	16.3	13.8
No	82.1	77.7	83.7	86.2
HEI-2010 score:		$p = 0.067$		
	42.8 ± 0.3	43.4 ± 0.4	42.3 ± 0.5	42.3 ± 0.5
HEALTH:		N = 2,223		
Body mass index (kg/m^2):			$p < 0.0001$	
	30.1 ± 0.2	26.4 ± 0.2	31.0 ± 0.3	33.9 ± 0.3
Self-rated health:			$p < 0.0001$	
Poor/Average	26.5	20.6	22.6	37.6
Good	39.8	36.0	42.4	42.2
Very good/Excellent	33.8	43.4	35.0	20.1
CES-D:			$p = 0.024$	
	14.9 ± 0.2	14.4 ± 0.4	14.9 ± 0.4	15.8 ± 0.4
Hypertension:			$p < 0.0001$	
Yes	47.9	26.7	51.1	72.9
No	52.0	73.3	48.9	27.1
Diabetes:			$p < 0.0001$	
None	63.9	81.3	62.4	42.5
Pre-diabetes	18.5	13.5	23.0	20.9
Diabetes	17.6	5.2	14.6	36.5
Dyslipidemia:			$p < 0.0001$	
Yes	26.9	15.8	29.5	39.3
No	73.0	84.2	70.5	60.7
Cardiovascular disease:			$p < 0.0001$	
Yes	18.2	12.0	18.3	26.1
No	81.8	88.0	81.7	73.9

(*Continued*)

Table 1
(*Continued*)

	% or Mean ± SEM	AL tertiles 1st	2nd	3rd
COGNITIVE TESTS: [2]				
Visit 1				
MMSE total score:				
Normalized	75.7 ± 0.4	76.8 ± 0.6	75.8 ± 0.6 N = 2,206; $p = 0.002$	74.2 ± 0.6
CVLT-List A	24.1 ± 0.2	24.3 ± 0.2	23.9 ± 0.3 N = 1,813; $p = 0.36$	23.9 ± 0.3
CVLT-DFR	7.1 ± 0.07	7.2 ± 0.1	7.1 ± 0.1 N = 1,768; $p = 0.58$	7.1 ± 0.1
BVRT	6.6 ± 0.1	5.9 ± 0.2	6.7 ± 0.2 N = 2,228; $p < 0.0001$	7.4 ± 0.2
BTA	6.6 ± 0.05	6.8 ± 0.08	6.6 ± 0.09 N = 1,849; $p < 0.0001$	6.3 ± 0.09
AF	18.7 ± 0.1	19.0 ± 0.2	18.4 ± 0.2 N = 2,212; $p = 0.028$	18.5 ± 0.2
DS-F	7.2 ± 0.05	7.3 ± 0.08	7.2 ± 0.09 N = 2,166; $p = 0.001$	6.9 ± 0.08
DS-B	5.6 ± 0.05	5.7 ± 0.07	5.6 ± 0.09 N = 2,155; $p = 0.038$	5.5 ± 0.08
CDT	8.7 ± 0.03	8.8 ± 0.04	8.8 ± 0.05 N = 2,216; $p = 0.15$	8.7 ± 0.05
Log_e (TRAILS A)	3.5 ± 0.009	3.4 ± 0.01	3.5 ± 0.02 N = 2,154; $p < 0.0001$	3.6 ± 0.01
Log_e (TRAILS B)	4.7 ± 0.02	4.6 ± 0.02	4.7 ± 0.03 N = 2,137; $p < 0.0001$	4.7 ± 0.03
Visit 1 to Visit 2				
MMSE total score:				
Normalized	–0.2 ± 0.00	–0.006 ± 0.004	–0.004 ± 0.005 N = 2,223; $p = 0.02$	0.01 ± 0.005
CVLT-List A	–1.1 ± 0.0009	–1.1 ± 0.001	–1.14 ± 0.002 N = 2,119; $p = 0.02$	–1.1 ± 0.001
CVLT-DFR	–0.4 ± 0.0003	–0.4 ± 0.0005	–0.4 ± 0.0005 N = 2,066; $p = 0.08$	–0.3 ± 0.0005
BVRT	0.4 ± 0.009	0.5 ± 0.01	0.4 ± 0.02 N = 2,235; $p = 0.06$	0.4 ± 0.02
BTA	–0.06 ± 0.0004	–0.06 ± 0.0006	–0.06 ± 0.0007 N = 2,129; $p = 0.002$	–0.06 ± 0.0007
AF	0.03 ± 0.002	0.03 ± 0.002	0.03 ± 0.003 N = 2,253; $p = 0.8$	0.03 ± 0.003
DS-F	–0.01 ± 0.0003	–0.01 ± 0.0004	–0.01 ± 0.0005 N = 2,229; $p = 0.001$	–0.01 ± 0.0005
DS-B	–0.02 ± 0.0002	–0.02 ± 0.0004	–0.02 ± 0.0004 N = 2,226; $p = 0.014$	–0.02 ± 0.0004
CDT	–0.02 ± 0.0005	–0.01 ± 0.0008	–0.02 ± 0.0009 N = 2,244; $p = 0.1$	–0.02 ± 0.0009
Log_e (TRAILS A)	0.006 ± 0.0001	0.005 ± 0.0002	0.006 ± 0.0002 N = 2,187; $p < 0.0001$	0.007 ± 0.0002
Log_e (TRAILS B)	0.003 ± 0.0006	0.005 ± 0.0009	0.001 ± 0.001 N = 2,166; $p < 0.0001$	0.002 ± 0.001

AL, allostatic load; CESD, Center for Epidemiologic Studies Depression scale; HEI, Healthy Eating Index; N, sample size; WRAT, Wide Range Achievement Test; SEM, standard error of the mean. [1]Interpretation of uncorrected p values takes into account multiple testing for analyses focused on cognitive tests only, whereby familywise Bonferroni correction is made for 11 cognitive tests; [2]Cognitive tests include the Mini-Mental State Examination (MMSE), the California Verbal Learning Test (CVLT) Immediate (List A) and Delayed Free Recall (DFR), the Benton Visual Retention Test (BVRT, # of errors), the Brief Test of Attention (BTA), the Animal Fluency test (AF), the Digit Span Forward and Backwards tests (DS-F and DS-B), the Clock Drawing Test (CDT), the Trail making test Part A and B (TRAILS A and B, in seconds).

ing or HEI-2010 score. The proportion female, with high school education or better, hypertension, diabetes, dyslipidemia, and cardiovascular disease were higher, whereas the proportion of drug users was lower with higher baseline AL tertiles. Similarly, the mean age, BMI and depression symptoms score were higher while the mean literacy score were lower with higher baseline AL tertiles. Differences in baseline and changes in cognitive test scores between visits observed by baseline AL tertiles were in the expected direction, suggesting an inverse bivariate relationship between the two constructs.

Table 2 presents the relationship of AL at Visit 1 with 11 cognitive test scores (baseline and between-visit change). Overall, baseline AL was significantly associated with BVRT ($\beta = 0.31$, $p < 0.0001$), BTA ($\beta = -0.12$, $p = 0.001$), Log_e (TRAILS A) ($\beta = 0.026$, $p < 0.0001$) and Log_e (TRAILS B) ($\beta = 0.042$, $p < 0.0001$) at baseline in *Model 1* and with Log_e (TRAILS A) ($\beta = 0.020$, $p = 0.004$) at baseline in *Model 2*. These relationships were in the expected direction of worse cognitive function with increasing AL total score. As shown in Supplementary Table 2, a significant AL-by-sex interaction effect was observed in *Model 1* for Log_e (TRAILS A) ($p = 0.001$) at baseline and a significant AL-by-race interaction effect was observed in *Model 1* for normalized MMSE ($p = 0.006$) at baseline, with no significant AL-by-sex and AL-by-race interaction effects observed in *Model 2*. As presented in Table 2, among men, baseline AL was not significantly related to cognitive test scores within *Models 1* and *2*. Among women, baseline AL was significantly related to BVRT, BTA, DS-F, DS-B, Log_e (TRAILS A) and Log_e (TRAILS B) at baseline within *Model 1*, but only to BVRT at baseline within *Model 2*. Among White participants, baseline AL was significantly related to normalized MMSE, BVRT, BTA, Log_e (TRAILS A) and Log_e (TRAILS B) at baseline within *Model 1*, but was not related to cognitive test scores within *Model 2*. Among African American participants, baseline AL was not significantly related to cognitive test scores within *Models 1* or *2*. Taking multiple testing into consideration, baseline AL was not related to between-visit change in cognitive test scores for *Models 1* or *2* (Table 2).

Figure 2 graphically displays group-based trajectory modeling, whereby AL is plotted against age for each of the two distinct trajectory groups identified, i.e., Group 1 and Group 2. In addition, a table of intercept, linear and quadratic terms for the two trajectory groups is displayed. Of note, group-based trajectory modeling generates the probability of belonging to each group namely, Group 1 and Group 2, for each study participant. As such, we calculated the z-transformed probability of belonging to Group 2 for each of the study participants, since Group 2 increased significantly with linear age ($\beta = +0.047$, $p = 0.003$), whereas Group 1 did not increase significantly with linear age ($\beta = +0.092$, $p = 0.16$). Additional details are provided in the Supplementary Materials. Subsequently, we examined the z-transformed probability of belonging to Group 2 in relation to cognitive function tests. Table 3 presents the relationship of AL change with 11 cognitive test scores (baseline and between-visit change). Overall, increasing AL was associated with MMSE (normalized) ($\beta = -1.08$, $p = 0.002$), BVRT ($\beta = 0.48$, $p < 0.0001$), BTA ($\beta = -0.20$, $p < 0.0001$), DS-F ($\beta = -0.14$, $p = 0.003$), DS-B ($\beta = -0.13$, $p = 0.004$), and Log_e (TRAILS B) ($\beta = 0.062$, $p < 0.0001$) at baseline within *Model 1*, but only with BVRT ($\beta = 0.35$, $p = 0.002$) at baseline within *Model 2*. These relationships were in the expected direction of worse cognitive function at baseline with higher z-transformed probability of belonging to the increasing AL group. No statistically significant interaction effects by sex or race were observed, as shown in Supplementary Table 3. Stratified analyses by sex revealed no significant associations for *Model 2*, with a significant association between increasing AL and Log_e (TRAILS A) at baseline among men and between increasing AL and several cognitive tests (BVRT, BTA, AF, DS-F, DS-B, Log_e (TRAILS B)) at baseline among women within *Model 1*. Similarly, stratified analyses by race revealed no significant associations in *Model 2* or among African American participants. Among White participants, increasing AL was associated with several cognitive tests (BVRT, BTA, AF, DS-F, Log_e (TRAILS A), Log_e (TRAILS B)) at baseline in *Model 1*. Taking multiple testing into consideration, AL change was not related to between-visit change in cognitive test scores for *Models 1* or *2* (Table 3).

The relationships of AL and AL trajectories with cognitive test scores after controlling for *Models 1* and *2* covariates along with comorbidities (hypertension, diabetes, dyslipidemia, and cardiovascular disease), depressive symptoms score and self-rated health are presented in Supplementary Table 4. Given the role of comorbidities, depressive symptoms and self-rated health as potential mediators between AL, AL change, and cognitive function, it was expected that controlling for these characteristics would reduce the magnitude of hypothesized relationships.

Table 2
Relationship of allostatic load at baseline with 11 cognitive test scores (baseline and between-visit change), overall, and by stratifying variables

	Allostatic Load			
	Model 1[1]		Model 2[2]	
OVERALL:[3,4]	β (SE)	*p*	β (SE)	*p*
MMSE, normalized:	N = 2,223, K = 1.6		N = 2,223, K = 1.6	
AL	–0.69 (0.26)	0.007	–0.23 (0.25)	0.36
AL × Time	0.015 (0.061)	0.80	–0.0021 (0.068)	0.97
CVLT-List A:	N = 2,119, K = 1.6		N = 2,119, K = 1.6	
AL	–0.084 (0.11)	0.45	–0.03 (0.12)	0.78
AL × Time	–0.037 (.025)	0.14	–0.012 (0.028)	0.67
CVLT-DFR:	N = 2,066, K = 1.5		N = 2,066, K = 1.5	
AL	0.0044 (0.052)	0.08	–0.038 (0.06)	0.49
AL × Time	–0.019 (0.013)	0.13	–0.0047 (.014)	0.74
BVRT:	N = 2,235, K = 1.7		N = 2,235, K = 1.7	
AL	0.31 (0.08)	<0.0001	0.20 (0.09)	0.023
AL × Time	–0.015 (0.019)	0.40	–0.0078 (0.021)	0.70
BTA:	N = 2,129, K = 1.6		N = 2,129, K = 1.6	
AL	–0.12 (0.038)	0.001	–0.057 (0.040)	0.16
AL × Time	–0.0099 (0.0091)	0.28	–0.013 (0.010)	0.21
AF:	N = 2,253, K = 1.7		N = 2,253, K = 1.7	
AL	–0.14 (0.09)	0.11	–0.077 (0.092)	0.40
AL × Time	0.012 (0.018)	0.48	0.0089 (0.019)	0.65
DS-F:	N = 2,229, K = 1.6		N = 2,229, K = 1.6	
AL	–0.088 (0.035)	0.013	–0.027 (.036)	0.45
AL × Time	0.0047 (0.0075)	0.53	0.011 (0.0084)	0.19
DS-B:	N = 2,226, K = 1.6		N = 2,226, K = 1.6	
AL	–0.087 (0.035)	0.013	–0.030 (0.035)	0.39
AL × Time	0.0023 (0.0075)	0.75	0.0092 (0.0085)	0.28
CDT:	N = 2,244, K = 1.7		N = 2,244, K = 1.7	
AL	–0.031 (0.020)	0.12	–0.026 (0.022)	0.23
AL × Time	–0.011 (0.0055)	0.031	–0.0087 (0.0062)	0.16
Log_e (TRAILS A):	N = 2,187, K = 1.7		N = 2,187, K = 1.7	
AL	0.026 (0.0063)	<0.0001	0.020 (0.0070)	0.004
AL × Time	–0.00095 (.0016)	0.54	–0.00035 (0.0017)	0.84
Log_e (TRAILS B):	N = 2,166, K = 1.6		N = 2,166, K = 1.6	
AL	0.042 (0.011)	<0.0001	0.031 (0.011)	0.008
AL × Time	–0.0028 (0.0023)	0.22	–0.0012 (0.0026)	0.64
MEN:				
MMSE, normalized:	N = 959, K = 1.6		N = 959, K = 1.6	
AL	–0.31 (0.43)	0.47	–0.067 (0.40)	0.87
AL × Time	0.073 (0.10)	0.47	–0.0053 (0.11)	0.96
CVLT-List A:	N = 903, K = 1.5		N = 903, K = 1.5	
AL	0.10 (.17)	0.54	0.089 (0.17)	0.62
AL × Time	0.0085 (0.040)	0.83	–0.021 (0.046)	0.65
CVLT-DFR:	N = 873, K = 1.5		N = 873, K = 1.5	
AL	0.098 (0.079)	0.22	0.023 (0.084)	0.79
AL × Time	–0.014 (0.020)	0.47	–0.021 (0.024)	0.38
BVRT:	N = 965, K = 1.6		N = 965, K = 1.6	
AL	0.024 (0.13)	0.85	–0.044 (0.14)	0.74
AL × Time	–0.036 (.028)	0.19	–0.024 (0.032)	0.45
BTA:	N = 917, K = 1.5		N = 917, K = 1.5	
AL	–0.013 (0.058)	0.83	0.0033 (0.063)	0.96
AL × Time	–0.0093 (0.014)	0.52	–0.024 (0.017)	0.15
AF:	N = 972, K = 1.7		N = 972, K = 1.7	
AL	0.089 (0.14)	0.51	0.074 (0.15)	0.61
AL × Time	–0.0027 (0.029)	0.93	–0.032 (0.034)	0.34
DS-F:	N = 964, K = 1.6		N = 964, K = 1.6	
AL	–0.018 (0.056)	0.74	–0.0016 (0.058)	0.97
AL × Time	–0.0015 (0.012)	0.89	–0.0055 (0.014)	0.69

(*Continued*)

Table 2
(*Continued*)

	Allostatic Load			
	Model 1[1]		Model 2[2]	
DS-B:	N = 963, K = 1.6		N = 963, K = 1.6	
AL	–0.0074 (0.056)	0.89	0.038 (0.056)	0.49
AL × Time	0.0026 (.012)	0.82	–0.0047 (0.013)	0.73
CDT:	N = 968, K = 1.7		N = 968, K = 1.7	
AL	0.015 (0.031)	0.64	0.0081 (0.035)	0.82
AL × Time	–0.0067 (.0088)	0.45	–0.0095 (0.010)	0.35
Log_e (TRAILS A):	N = 933, K = 1.6		N = 933, K = 1.6	
AL	0.027 (0.010)	0.006	0.029 (0.011)	0.009
AL × Time	–0.0023 (0.0024)	0.34	–0.0028 (0.0028)	0.32
Log_e (TRAILS B):	N = 923, K = 1.6		N = 923, K = 1.6	
AL	0.033 (0.017)	0.060	0.024 (0.018)	0.18
AL × Time	–0.0029 (0.0035)	0.41	0.0072 (0.016)	0.66
WOMEN:				
MMSE, normalized:	N = 1,264, K = 1.7		N = 1,264, K = 1.7	
AL	–0.97 (0.32)	0.002	–0.30 (0.31)	0.33
AL × Time	–0.010 (0.077)	0.89	–0.0055 (0.086)	0.95
CVLT-List A:	N = 1,216, K = 1.6		N = 1,216, K = 1.6	
AL	–0.19 (0.15)	0.20	–0.060 (0.16)	0.70
AL × Time	–0.066 (.033)	0.047	–0.022 (0.037)	0.56
CVLT-DFR:	N = 1,193, K = 1.5		N = 1,193, K = 1.5	
AL	–0.054 (0.069)	0.43	–0.063 (0.073)	0.39
AL × Time	–0.019 (0.016)	0.23	0.0015 (0.017)	0.93
BVRT:	N = 1,270, K = 1.7		N = 1,270, K = 1.7	
AL	0.48 (0.11)	<0.0001	0.35 (0.12)	0.003
AL × Time	–0.0038 (0.025)	0.88	–0.00040 (0.027)	0.99
BTA:	N = 1,212, K = 1.6		N = 1,212, K = 1.6	
AL	–0.19 (0.049)	<0.0001	–0.11 (0.055)	0.052
AL × Time	–0.011 (0.011)	0.34	–0.0077 (0.013)	0.55
AF:	N = 1,281, K = 1.7		N = 1,281, K = 1.7	
AL	–0.28 (0.11)	0.012	–0.17 (0.12)	0.15
AL × Time	0.026 (0.022)	0.23	0.035 (0.024)	0.16
DS-F:	N = 1,265, K = 1.6		N = 1,265, K = 1.6	
AL	–0.14 (0.04)	0.001	–0.056 (0.047)	0.24
AL × Time	0.0078 (0.0096)	0.41	0.017 (0.010)	0.11
DS-B:	N = 1,263, K = 1.6		N = 1,263, K = 1.6	
AL	–0.15 (0.05)	0.001	–0.068 (.045)	0.13
AL × Time	0.0017 (0.0098)	0.86	0.012 (0.010)	0.24
CDT:	N = 1,276, K = 1.7		N = 1,276, K = 1.7	
AL	–0.060 (0.026)	0.021	–0.049 (0.029)	0.088
AL × Time	–0.014 (0.0070)	0.043	–0.0089 (0.0078)	0.26
Log_e (TRAILS A):	N = 1,254, K = 1.7		N = 1,254, K = 1.7	
AL	0.026 (0.0083)	0.001	0.015 (0.0091)	0.092
AL × Time	–0.00027 (0.0020)	0.89	0.00083 (0.0022)	0.71
Log_e (TRAILS B):	N = 1,243, K = 1.7		N = 1,243, K = 1.7	
AL	0.052 (0.014)	<0.0001	0.034 (0.015)	0.024
AL × Time	–0.0027 (0.0030)	0.37	–0.0016 (0.0034)	0.64
WHITE:				
MMSE, normalized:	N = 904, K = 1.6		N = 904, K = 1.6	
AL	–1.45 (0.41)	<0.0001	–0.39 (0.38)	0.30
AL × Time	–0.0077 (0.10)	0.94	–0.037 (0.11)	0.75
CVLT-List A:	N = 863, K = 1.5		N = 863, K = 1.5	
AL	–0.13 (0.19)	0.48	0.0079 (0.19)	0.97
AL × Time	–0.10 (0.045)	0.025	–0.037 (0.052)	0.48
CVLT-DFR:	N = 836, K = 1.5		N = 836, K = 1.5	
AL	–0.071 (0.087)	0.42	–0.039 (0.094)	0.68
AL × Time	–0.025 (0.022)	0.26	0.0076 (0.026)	0.76
BVRT:	N = 913, K = 1.7		N = 913, K = 1.7	
AL	0.52 (0.12)	<0.0001	0.28 (0.12)	0.022
AL × Time	–0.018 (.027)	0.49	–0.027 (0.032)	0.39
BTA:	N = 866, K = 1.6		N = 866, K = 1.6	
AL	–0.18 (0.058)	0.002	–0.067 (0.063)	0.29
AL × Time	0.0012 (0.015)	0.94	–0.0065 (0.018)	0.72

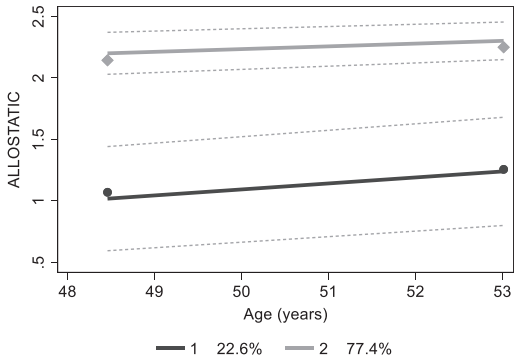
(*Continued*)

Table 2
(*Continued*)

	Allostatic Load			
	Model 1[1]		Model 2[2]	
AF:	N = 923, K = 1.7		N = 923, K = 1.7	
AL	–0.29 (.15)	0.046	–0.077 (0.16)	0.62
AL × Time	–0.019 (0.032)	0.55	–0.015 (0.038)	0.69
DS-F:	N = 905, K = 1.6		N = 905, K = 1.6	
AL	–0.16 (0.059)	0.008	–0.0035 (0.061)	0.95
AL × Time	–0.0021 (0.013)	0.87	0.0055 (0.015)	0.71
DS-B:	N = 905, K = 1.6		N = 905, K = 1.6	
AL	–0.13 (0.061)	0.034	0.032 (0.062)	0.59
AL × Time	–0.0014 (0.013)	0.92	0.0028 (0.015)	0.85
CDT:	N = 918, K = 1.7		N = 918, K = 1.7	
AL	–0.031 (0.030)	0.31	–0.015 (0.035)	0.68
AL × Time	–0.018 (0.0088)	0.040	–0.018 (0.010)	0.088
Log_e (TRAILS A):	N = 895, K = 1.7		N = 895, K = 1.7	
AL	0.032 (0.0088)	<0.0001	0.026 (0.010)	0.012
AL × Time	–0.00012 (0.0021)	0.96	–00.0027 (0.0024)	0.27
Log_e (TRAILS B):	N = 885, K = 1.6		N = 885, K = 1.6	
AL	0.057 (0.016)	<0.0001	0.032 (0.016)	0.053
AL × Time	–0.0034 (0.0031)	0.27	–0.0052 (0.0036)	0.16
AFRICAN AMERICAN:				
MMSE, normalized:	N = 1,319, K = 1.6		N = 1,319, K = 1.6	
AL	–0.11 (0.33)	0.74	–0.052 (0.32)	0.87
AL × Time	0.017 (0.078)	0.83	0.0064 (0.084)	0.94
CVLT-List A:	N = 1,256, K = 1.6		N = 1,256, K = 1.6	
AL	–0.0045 (0.14)	0.97	–0.018 (0.14)	0.89
AL × Time	–0.0027 (0.031)	0.93	0.0027 (0.034)	0.94
CVLT-DFR:	N = 1,230, K = 1.5		N = 1,230, K = 1.5	
AL	0.069 (.065)	0.28	–0.019 (0.068)	0.77
AL × Time	–0.013 (0.015)	0.37	–0.0078 (0.017)	0.64
BVRT:	N = 1,322, K = 1.7		N = 1,322, K = 1.7	
AL	0.090 (0.11)	0.43	0.084 (0.12)	0.48
AL × Time	–0.0089 (0.025)	0.72	0.0050 (0.027)	0.85
BTA:	N = 1,263, K = 1.6		N = 1,263, K = 1.6	
AL	–0.075 (0.050)	0.14	–0.041 (0.054)	0.45
AL × Time	–0.019 (0.011)	0.094	–0.018 (0.013)	0.15
AF:	N = 1,330, K = 1.7		N = 1,330, K = 1.7	
AL	0.030 (0.10)	0.77	–0.0049 (0.11)	0.97
AL × Time	0.027 (0.021)	0.19	0.024 (0.023)	0.30
AL	–0.036 (0.044)	0.41	–0.033 (0.046)	0.47
AL × Time	0.0064 (0.0094)	0.49	0.013 (0.010)	0.19
DS-B:	N = 1,321, K = 1.6		N = 1,321, K = 1.6	
AL	–0.051 (0.043)	0.23	–0.053 (0.042)	0.21
AL × Time	0.0039 (0.0094)	0.68	0.011 (0.010)	0.24
CDT:	N = 1,326, K = 1.7		N = 1,326, K = 1.7	
AL	–0.022 (0.027)	0.41	–0.027 (0.029)	0.35
AL × Time	–0.0086 (0.0072)	0.23	–0.0052 (0.0079)	0.50
Log_e (TRAILS A):	N = 1,292, K = 1.7		N = 1,292, K = 1.7	
AL	0.022 (0.0089)	0.015	0.016 (0.0097)	0.090
AL × Time	–0.00097 (0.0021)		0.00075 (0.0024)	0.75
Log_e (TRAILS B):	N = 1,281, K = 1.6		N = 1,281, K = 1.6	
AL	0.030 (0.016)	0.057	0.028 (0.016)	0.078
AL × Time	–0.0019 (0.0032)	0.56	0.00084 (0.0035)	0.81

AL, allostatic load; K, mean number of visits per subject; N, sample size; SE, standard error. [1]Model 1 is adjusted for age, sex, race, poverty status, inverse mills ratio as well as time on study between visits 1 and 2 (in years) and its interaction with allostatic load and covariates. [2]Model 2 is 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 between visits 1 and 2 (in years) and its interaction with allostatic load and covariates. [3]Cognitive tests include the Mini-Mental State Examination (MMSE), the California Verbal Learning Test (CVLT) Immediate (List A) and Delayed Free Recall (DFR), the Benton Visual Retention Test (BVRT, # of errors), the Brief Test of Attention (BTA), the Animal Fluency test (AF), the Digit Span Forward and Backwards tests (DS-F and DS-B), the Clock Drawing Test (CDT), the Trail making test Part A and B (TRAILS A and B, in seconds); [4]Interpretation of uncorrected *p* values takes into account multiple testing, whereby familywise Bonferroni correction is made for 11 cognitive tests.

A



B

	β	SE	P
Group 1			
Intercept	-3.318	1.769	0.061
Linear Age	0.092	0.066	0.16
Quadratic Age	-0.0005	0.0006	0.43
Group 2			
Intercept	-0.618	0.402	0.12
Linear Age	**+0.047**	**0.016**	**0.003**
Quadratic Age	**-0.0004**	**0.0002**	**0.019**

Fig. 2. Group-based trajectories for allostatic load – HANDLS (2004–2013). A) Graphical display of two groups identified using group-based trajectory modeling, whereby ALLOSTATIC represents allostatic load total score and Age (years) represents the time variable. B) Table display of intercept, linear and quadratic terms for the two trajectories in allostatic load identified using group-based trajectories; Group-based trajectory modeling generates the probability of belonging to each group namely, Group 1 and Group 2, for each study participant. As such, we calculated the z-transformed probability of belonging to Group 2 for each of the study participants, since Group 2 increased significantly with linear age ($\beta = +0.047$, $p = 0.003$), whereas Group 1 did not increase significantly with linear age ($\beta = +0.092$, $p = 0.16$). Subsequently, we examined the z-transformed probability of belonging to Group 2 in relation to cognitive function tests. HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span.

DISCUSSION

In this longitudinal study involving a diverse population of adults in an urban setting, baseline AL as well as AL change were examined as predictors of cognitive function at baseline and over time, before and after stratifying according to sex and race. In general, baseline AL and AL change were inversely related to specific domains of cognitive function, but unrelated to others. In linear models that controlled for sex, race and poverty status, a cross-sectional relationship was observed between AL and worse cognitive function based on BVRT, BTA, Log_e (TRAILS A) and Log_e (TRAILS B). Similarly, in linear models that controlled for sex, race, and poverty status, AL change was associated with worse cognitive function based on normalized MMSE, BVRT, BTA, DS-F, DS-B, and Log_e (TRAILS B) at baseline, suggesting that cognitive function at baseline may predict change in AL over time. Furthermore, baseline AL was significantly related to baseline Log_e (TRAILS A), whereas AL change was significantly related to baseline BVRT, after controlling for age, sex, race, poverty status, education, literacy, smoking, drug use, the 2010 HEI, and BMI. Although distinct patterns of associations emerged according to sex and race, no statistically significant interaction effects were observed in fully adjusted models. Finally, baseline AL and AL change were not related to between-visit change in cognitive function.

Study results were consistent with published cross-sectional studies on AL and cognitive function. In a cross-sectional analysis of clinical data among 103 healthy and overweight adults, aged 21–40 years, Ottino-González et al. found that AL was negatively associated with cognitive flexibility, with a stronger association in the overweight group [7]. In another cross-sectional study, Dargél et al. examined 1,072 bipolar disorder outpatients, aged 18–65 years, and found that higher AL was associated with

lower cognitive functioning [29]. Karlamangla et al. performed a cross-sectional evaluation of 1,076 individuals of both sexes (mean age: 57 years) and found a strong inverse relationship between multi-system AL and cognitive function (episodic memory and executive function) [5]. Conversely, Narbutas et al. examined the cross-sectional relationships of AL and cognitive reserve with cognitive function (episodic memory, executive function, attention) among 101 healthy individuals (mean age: 59.4 years) with no evidence of Alzheimer's disease pathology, and found that higher cognitive reserve was the main correlate of better cognitive performance across all domains, whereas sympathetic functioning and lipid metabolism, two specific measures of AL, were not related to domain-specific cognition [30]. A cross-sectional study by Charles et al. examined the relationships of daily output and change in cortisol levels with physiological and cognitive functioning among 1,001 individuals, aged 28–84 years, and found that a greater range in cortisol throughout the day was associated with both lower AL and higher cognitive functioning [3]. Although AL definition varies among studies, many of the risk indicators used to define AL overlap with those used to define metabolic syndrome, and several systematic reviews have also identified cross-sectional relationships between metabolic syndrome and cognitive function [31–35].

To date, few studies have examined the longitudinal relationship between AL and cognitive function. Gale et al. examined childhood intelligence and social class in childhood and adulthood as predictors of frailty and AL in a longitudinal study involving 876 members of the Lothian birth cohort (mean age: 70 years) and found that lower intelligence, but not socioeconomic disadvantage, in childhood was associated with higher AL at age 70 [36]. According to the theory on allostasis and AL, the brain is a primary mediator of the stress response [37]. As such, the brain is one potential biological mechanism that links AL to cognitive function. Specifically, AL is associated with several brain changes, e.g., structural atrophy/hypertrophy [38], especially in the hippocampus, hypothalamus, amygdala and prefrontal cortex [39]. These brain regions are in turn associated with cognitive function [40, 41]. We were able to identify one study that examined brain structures, i.e., total brain volume, gray matter volume (GM), white matter volume (WM) and hippocampal volume, as potential mediators in the link between AL and cognitive function, i.e., general intelligence, processing speed and knowledge [42]. Notably, the indirect effects were not tested for significance. However, GM and WM had the largest attenuation effects between AL and the following two cognitive functions, namely, intelligence and processing speed. Further research, especially longitudinal research, is needed to test potential mechanisms in the link between AL and cognitive functioning.

Study findings should be interpreted in light of several limitations. First, hypothesized relationships were examined using sub-samples of the original HANDLS participants, potentially leading to selection bias. Second, although psychometric properties of cognitive tests were taken into account, measurement error may have persisted, potentially leading to biased measures of association. Third, there are multiple definitions for AL, limiting our ability to compare study findings with the published literature. We applied a definition of the AL index using nine AL indicators defined using dichotomous variables based on cutoffs previously validated by other researchers, covering cardiovascular, metabolic, and inflammatory dimensions. Although cortisol may be a key feature of the AL, its daily fluctuation and its unavailability in the HANDLS study precluded its inclusion as an AL indicator. Fourth, the duration of follow-up between Visits 1 and 2 of the HANDLS study may not have been sufficient to observe a clinically meaningful change in cognitive function. Therefore, future studies should examine hypothesized relationships over longer follow-up times. Fifth, because the HANDLS project is a prospective cohort study and is therefore observational in nature, causality could not be established and residual confounding is likely despite an effort to control for a wide range of socio-demographic, lifestyle, and health characteristics. Sixth, although nearly equal numbers of men and women as well as White and African American participants enrolled in the HANDLS study, examination of interaction effects by sex and race may have been underpowered in the context of AL and cognitive function. Seventh, consistent with prior research, effect sizes were relatively small suggesting limited impact of AL on cognition from a clinical and population health perspective. Finally, our results can only be generalized to adults in an urban setting, given the sampling strategy employed by the HANDLS project.

Despite these limitations, this study is among few that have examined both cross-sectional and longitudinal relationships between AL and cognitive function using an established cohort of urban adults with extensive data collection at baseline and

Table 3
Relationship of allostatic load change with 11 cognitive test scores (baseline and between-visit change), overall, and by stratifying variables

	Allostatic Load Trajectory			
	Model 1[1]		Model 2[2]	
	β (SE)	*p*	β (SE)	*p*
OVERALL: [3,4]				
MMSE, normalized:	N = 1,768, K = 1.8		N = 1,768, K = 1.8	
AL_{traj}	–1.08 (0.34)	0.002	–0.17 (0.33)	0.59
AL_{traj} × Time	0.045 (0.074)	0.54	0.020 (0.081)	0.80
CVLT-List A:	N = 1,744, K = 1.7		N = 1,744, K = 1.7	
AL_{traj}	–0.26 (0.15)	0.079	–0.061 (0.15)	0.69
AL_{traj} × Time	–0.061 (0.030)	0.047	–0.044 (0.034)	0.19
CVLT-DFR:	N = 1,702, K = 1.6		N = 1,702, K = 1.6	
AL_{traj}	–0.0047 (0.069)	0.95	0.011 (0.07)	0.87
AL_{traj} × Time	–0.031 (0.015)	0.036	–0.020 (0.016)	0.22
BVRT:	N = 1,784, K = 1.8		N = 1,784, K = 1.8	
AL_{traj}	0.48 (0.11)	<0.0001	0.35 (0.11)	0.002
AL_{traj} × Time	–0.020 (0.021)	0.34	–0.018 (.024)	0.45
BTA:	N = 1,738, K = 1.7		N = 1,738, K = 1.7	
AL_{traj}	–0.20 (0.049)	<0.0001	–0.11 (0.053)	0.041
AL_{traj} × Time	–0.0053 (0.010)	0.62	–0.0069 (0.012)	0.57
AF:	N = 1,794, K = 1.9		N = 1,794, K = 1.9	
AL_{traj}	–0.28 (0.12)	0.015	–0.10 (0.12)	0.40
AL_{traj} × Time	0.0084 (0.021)	0.69	–0.0019 (0.024)	0.94
DS-F:	N = 1,783, K = 1.8		N = 1,783, K = 1.8	
AL_{traj}	–0.14 (0.047)	0.003	–0.029 (0.048)	0.55
AL_{traj} × Time	0.0041 (0.0087)	0.64	0.0099 (0.0098)	0.31
DS-B:	N = 1,784, K = 1.8		N = 1,784, K = 1.8	
AL_{traj}	–0.13 (0.046)	0.004	–0.014 (0.047)	0.76
AL_{traj} × Time	0.0014 (0.0088)	0.87	0.0069 (0.0099)	0.48
CDT:	N = 1,787, K = 1.9		N = 1,787, K = 1.9	
AL_{traj}	–0.067 (0.027)	0.013	–0.052 (0.029)	0.079
AL_{traj} × Time	–0.013 (0.0066)	0.049	–0.010 (.0075)	0.16
Log_e (TRAILS A):	N = 1,748, K = 1.8		N = 1,748, K = 1.8	
AL_{traj}	0.033 (0.0085)	<0.0001	0.022 (0.0094)	0.016
AL_{traj} × Time	–0.00067 (0.0018)	0.71	–0.00035 (0.0020)	0.86
Log_e (TRAILS B):	N = 1,727, K = 1.8		N = 1,727, K = 1.8	
AL_{traj}	0.062 (0.014)	<0.0001	0.040 (0.015)	0.009
AL_{traj} × Time	–0.0039 (0.0027)	0.15	–0.0025 (0.0030)	0.40
MEN:				
MMSE, normalized:	N = 738, K = 1.8		N = 738, K = 1.8	
AL_{traj}	–0.53 (0.57)	0.35	0.14 (0.53)	0.78
AL_{traj} × Time	0.086 (0.11)	0.47	0.0084 (0.13)	0.95
CVLT-List A:	N = 722, K = 1.7		N = 722, K = 1.7	
AL_{traj}	0.13 (0.22)	0.57	0.16 (0.23)	0.49
AL_{traj} × Time	–0.010 (0.046)	0.83	–0.044 (0.051)	0.39
CVLT-DFR:	N = 698, K = 1.6		N = 698, K = 1.6	
AL_{traj}	0.15 (0.10)	0.14	0.089 (0.11)	0.40
AL_{traj} × Time	0.021 (0.023)	0.37	–0.023 (0.026)	0.37
BVRT:	N = 741, K = 1.8		N = 741, K = 1.8	
AL_{traj}	0.28 (0.17)	0.09	0.21 (0.18)	0.23
AL_{traj} × Time	–0.033 (0.032)	0.31	–0.019 (0.036)	0.59
BTA:	N = 724, K = 1.7		N = 724, K = 1.7	
AL_{traj}	–0.11 (0.08)	0.15	–0.11 (0.08)	0.17
AL_{traj} × Time	–0.011 (0.017)	0.52	–0.022 (0.019)	0.23
AF:	N = 746, K = 1.9		N = 746, K = 1.9	
AL_{traj}	0.029 (0.19)	0.87	0.052 (0.19)	0.79
AL_{traj} × Time	–0.015 (0.034)	0.67	–0.046 (0.038)	0.23
DS-F:	N = 743, K = 1.8		N = 743, K = 1.8	
AL_{traj}	–0.049 (0.074)	0.50	–0.00018 (0.076)	0.99
AL_{traj} × Time	–0.0072 (0.014)	0.60	–0.011 (0.015)	0.45
DS-B:	N = 744, K = 1.8		N = 744, K = 1.8	

(*Continued*)

Table 3
(Continued)

	Allostatic Load Trajectory			
	Model 1[1]		Model 2[2]	
	β (SE)	*p*	β (SE)	*p*
AL_{traj}	–0.018 (0.073)	0.80	0.065 (0.074)	0.38
AL_{traj} × Time	–0.0037 (0.014)	0.79	–0.014 (0.015)	0.35
CDT:	N = 742, K = 1.9		N = 742, K = 1.9	
AL_{traj}	–0.018 (0.042)	0.66	–0.0088 (0.046)	0.85
AL_{traj} × Time	–0.013 (0.010)	0.23	–0.018 (0.011)	0.12
Log_e (TRAILS A):	N = 720, K = 1.8		N = 720, K = 1.8	
AL_{traj}	0.038 (0.013)	0.004	0.039 (0.015)	0.007
AL_{traj} × Time	–0.0022 (0.0028)	0.42	–0.0029 (0.0031)	0.36
Log_e (TRAILS B):	N = 710, K = 1.8		N = 710, K = 1.8	
AL_{traj}	0.060 (0.023)	0.008	0.059 (0.023)	0.010
AL_{traj} × Time	–0.0051 (0.0039)	0.20	–0.0039 (0.0043)	0.36
WOMEN:				
MMSE, normalized:	N = 1,030, K = 1.8		N = 1,030, K = 1.8	
AL_{traj}	–1.41 (0.42)	0.001	–0.31 (0.42)	0.47
AL_{traj} × Time	0.0054 (0.095)	0.96	0.0058 (0.10)	0.96
CVLT-List A:	N = 1,022, K = 1.7		N = 1,022, K = 1.7	
AL_{traj}	–0.49 (0.20)	0.014	–0.15 (0.21)	0.49
AL_{traj} × Time	–0.096 (0.041)	0.020	–0.057 (0.046)	0.20
CVLT-DFR:	N = 1,004, K = 1.6		N = 1,004, K = 1.6	
AL_{traj}	–0.089 (0.096)	0.35	–0.0054 (0.10)	0.96
AL_{traj} × Time	–0.037 (0.019)	0.057	–0.022 (0.021)	0.29
BVRT:	N = 1,043, K = 1.9		N = 1,043, K = 1.9	
AL_{traj}	0.56 (0.14)	<0.0001	0.38 (0.15)	0.016
AL_{traj} × Time	–0.0086 (0.029)	0.77	–0.014 (0.034)	0.68
BTA:	N = 1,014, K = 1.7		N = 1,014, K = 1.7	
AL_{traj}	–0.26 (0.066)	<0.0001	–0.11 (0.072)	0.10
AL_{traj} × Time	–0.0026 (0.014)	0.85	0.0042 (0.015)	0.79
AF:	N = 1,048, K = 1.9		N = 1,048, K = 1.9	
AL_{traj}	–0.47 (0.15)	0.002	–0.19 (0.16)	0.24
AL_{traj} × Time	0.029 (0.027)	0.27	0.034 (0.030)	0.27
DS-F:	N = 1,040, K = 1.8		N = 1,040, K = 1.8	
AL_{traj}	–0.21 (0.06)	0.001	–0.056 (.064)	0.38
AL_{traj} × Time	0.0094 (0.011)	0.41	0.019 (0.013)	0.13
DS-B:	N = 1,040, K = 1.8		N = 1,040, K = 1.8	
AL_{traj}	–0.22 (0.061)	<0.0001	–0.057 (0.062)	0.36
AL_{traj} × Time	0.0041 (0.011)	0.73	0.017 (0.013)	0.19
CDT:	N = 1,045, K = 1.9		N = 1,045, K = 1.9	
AL_{traj}	–0.095 (0.036)	0.008	–0.073 (0.04)	0.065
AL_{traj} × Time	–0.012 (0.0087)	0.17	–0.0041 (0.0099)	0.68
Log_e (TRAILS A):	N = 1,028, K = 1.8		N = 1,028, K = 1.8	
AL_{traj}	0.031 (0.011)	0.006	0.014 (0.013)	0.27
AL_{traj} × Time	–0.00033 (0.0024)	0.89	0.00027 (0.0027)	0.92
Log_e (TRAILS B):	N = 1,017, K = 1.8		N = 1,017, K = 1.8	
AL_{traj}	0.062 (0.019)	0.002	0.023 (0.021)	0.27
AL_{traj} × Time	–0.0029 (0.0037)	0.42	–0.0014 (0.0041)	0.74
WHITE:				
MMSE, normalized:	N = 698, K = 1.8		N = 698, K = 1.8	
AL_{traj}	–1.67 (0.54)	0.002	0.31 (0.52)	0.55
AL_{traj} × Time	0.038 (0.12)	0.75	–0.015 (0.13)	0.91
CVLT-List A:	N = 693, K = 1.6		N = 693, K = 1.6	
AL_{traj}	–0.38 (0.26)	0.14	0.067 (0.28)	0.81
AL_{traj} × Time	–0.10 (0.055)	0.063	–0.045 (0.065)	0.48
CVLT-DFR:	N = 670, K = 1.6		N = 670, K = 1.6	
AL_{traj}	–0.045 (0.12)	0.71	0.094 (0.13)	0.47
AL_{traj} × Time	–0.053 (0.027)	0.049	–0.025 (0.031)	0.43

(*Continued*)

Table 3
(Continued)

	Allostatic Load Trajectory			
	Model 1[1]		Model 2[2]	
	β (SE)	*p*	β (SE)	*p*
BVRT:	N = 704, K = 1.9		N = 704, K = 1.9	
AL_{traj}	0.67 (0.16)	<0.0001	0.30 (0.17)	0.073
AL_{traj} × Time	–0.040 (0.032)	0.19	–0.054 (0.038)	0.16
BTA:	N = 688, K = 1.7		N = 688, K = 1.7	
AL_{traj}	–0.33 (0.07)	<0.0001	–0.18 (0.084)	0.032
AL_{traj} × Time	0.011 (0.018)	0.52	0.0082 (0.021)	0.69
AF:	N = 713, K = 1.9		N = 713, K = 1.9	
AL_{traj}	–0.63 (0.20)	0.002	–0.17 (0.21)	0.44
AL_{traj} × Time	–0.042 (0.038)	0.27	–0.055 (0.045)	0.22
DS-F:	N = 705, K = 1.8		N = 705, K = 1.8	
AL_{traj}	–0.24 (0.08)	0.002	0.014 (0.083)	0.86
AL_{traj} × Time	0.0092 (0.015)	0.54	0.018 (0.018)	0.31
DS-B:	N = 706, K = 1.8		N = 706, K = 1.8	
AL_{traj}	–0.19 (0.082)	0.016	0.11 (0.086)	0.18
AL_{traj} × Time	–0.0067 (0.015)	0.66	–0.011 (0.018)	0.53
CDT:	N = 710, K = 1.9		N = 710, K = 1.9	
AL_{traj}	–0.089 (0.042)	0.033	–0.056 (0.048)	0.25
AL_{traj} × Time	–0.015 (0.010)	0.15	–0.016 (0.013)	0.19
Log_e (TRAILS A):	N = 695, K = 1.9		N = 695, K = 1.9	
AL_{traj}	0.038 (0.011)	0.001	0.026 (0.014)	0.051
AL_{traj} × Time	0.00086 (0.0024)	0.72	–0.0019 (0.0029)	0.52
Log_e (TRAILS B):	N = 685, K = 1.8		N = 685, K = 1.8	
AL_{traj}	0.065 (0.021)	0.002	0.015 (0.023)	0.50
AL_{traj} × Time	–0.0041 (0.0036)	0.26	–0.0047 (0.0044)	0.29
AFRICAN AMERICAN:				
MMSE, normalized:	N = 1,070, K = 1.8		N = 1,070, K = 1.8	
AL_{traj}	–0.64 (0.45)	0.16	–0.37 (0.43)	0.38
AL_{traj} × Time	0.046 (0.096)	0.63	0.039 (0.10)	0.70
CVLT-List A:	N = 1,051, K = 1.7		N = 1,051, K = 1.7	
AL_{traj}	–0.12 (0.18)	0.51	–0.062 (0.19)	0.74
AL_{traj} × Time	–0.038 (0.037)	0.29	–0.040 (0.040)	0.32
CVLT-DFR:	N = 1,032, K = 1.7		N = 1,032, K = 1.7	
AL_{traj}	0.06 (0.09)	0.49	0.0064 (0.089)	0.94
AL_{traj} × Time	–0.019 (0.018)	0.28	–0.016 (0.019)	0.41
BVRT:	N = 1,080, K = 1.8		N = 1,080, K = 1.8	
AL_{traj}	0.28 (0.14)	0.06	0.28 (0.16)	0.075
AL_{traj} × Time	–0.0042 (0.029)	0.89	0.0018 (0.032)	0.95
BTA:	N = 1,050, K = 1.7		N = 1,050, K = 1.7	
AL_{traj}	–0.10 (0.06)	0.13	–0.047 (0.069)	0.49
AL_{traj} × Time	–0.019 (.014)	0.16	–0.017 (0.015)	0.26
AF:	N = 1,081, K = 1.9		N = 1,081, K = 1.9	
AL_{traj}	0.043 (0.14)	0.76	0.056 (0.15)	0.71
AL_{traj} × Time	0.032 (0.025)	0.21	0.028 (0.027)	0.31
DS-F:	N = 1,078, K = 1.8		N = 1,078, K = 1.8	
AL_{traj}	–0.068 (0.059)	0.25	–0.037 (0.060)	0.54
AL_{traj} × Time	–0.0022 (0.011)	0.84	0.0034 (0.011)	0.77
DS-B:	N = 1,078, K = 1.8		N = 1,078, K = 1.8	
AL_{traj}	–0.082 (0.057)	0.15	–0.059 (0.056)	0.29
AL_{traj} × Time	0.0040 (0.011)	0.72	0.013 (0.012)	0.28
CDT:	N = 1,077, K = 1.9		N = 1,077, K = 1.9	
AL_{traj}	–0.041 (0.036)	0.26	–0.041 (0.038)	0.29
AL_{traj} × Time	–0.013 (0.0088)	0.15	–0.0088 (0.0095)	0.35
Log_e (TRAILS A):	N = 1,053, K = 1.8		N = 1,053, K = 1.8	
AL_{traj}	0.03 (0.01)	0.013	0.022 (0.013)	0.089
AL_{traj} × Time	–0.0012 (0.0026)	0.65	–0.000010 (0.0028)	0.99

(*Continued*)

Table 3
(Continued)

	Allostatic Load Trajectory			
	Model 1[1]		Model 2[2]	
	β (SE)	*p*	β (SE)	*p*
Log$_e$ (TRAILS B):	N = 1,042, K = 1.8		N = 1,042, K = 1.8	
AL $_{traj}$	0.057 (0.020)	0.005	0.051 (0.020)	0.013
AL $_{traj}$ × Time	–0.0033 (0.0038)	0.38	–0.0017 (0.0041)	0.68

AL $_{traj}$, z-transformed probability of belonging to a group with increasing allostatic load over time according to group-based trajectory modeling; K, mean number of visits per subject; N, sample size; SE, standard error. [1]Model 1 is adjusted for age, sex, race, poverty status, inverse mills ratio as well as time on study in years between visits 1 and 2 and its interaction with allostatic load trajectory and covariates. [2]Model 2 is 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 2 and its interaction with allostatic load change and covariates. [3]Cognitive tests include the Mini-Mental State Examination (MMSE), the California Verbal Learning Test (CVLT) Immediate (List A) and Delayed Free Recall (DFR), the Benton Visual Retention Test (BVRT, # of errors), the Brief Test of Attention (BTA), the Animal Fluency test (AF), the Digit Span Forward and Backwards tests (DS-F and DS-B), the Clock Drawing Test (CDT), the Trail making test Part A and B (TRAILS A and B, in seconds); [4]Interpretation of uncorrected *p* values takes into account multiple testing, whereby familywise Bonferroni correction is made for 11 cognitive tests.

repeated measurements over a 5-year follow-up time period. A unique feature of the HANDLS study is that it provides the opportunity to control for a wide range of socio-demographic, lifestyle and health characteristics that may confound hypothesized relationships as well as to perform stratified analyses according to sex and race.

In conclusion, baseline AL was associated with worse attention or executive functioning and increasing AL was associated with worse non-verbal memory or visuo-constructional abilities at baseline, after controlling for key demographic, socioeconomic, lifestyle, and health confounders. These findings suggest reverse causality as a plausible explanation, although the relationship between AL and cognitive function could be bi-directional, necessitating further evaluation. Specifically, AL and worse attention or executive functioning may reinforce one another, and impaired non-verbal memory or visuo-constructional abilities at baseline may affect management of risk factors (e.g., taking medications), which in turn may affect change in AL over time. By contrast, baseline AL as well as AL change were not associated with change in cognitive function over a 5-year follow-up time. The relationships of AL and AL change with cognitive function did not vary according to sex and race. Further studies using longitudinal study designs with larger sample sizes and longer follow-up times are required to confirm and extend these findings.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-220888.

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Supplemental Material

Allostatic Load and Cognitive Function Among Urban Adults in the Healthy Aging in Neighborhoods of Diversity across the Life Span Study

Supplementary Table 1. Allostatic load criteria [1]

	High-risk clinical
Waist-to-Hip Ratio	>0.9 for men; >0.85 for women [2]
Albumin (g/dL)	< 3.8 [3]
C-reactive protein (mg/dL)	≥ 0.3 [4]
Total cholesterol (mg/dL)	≥240 [5]
HDL (mg/dL)	<40 [5]
Glycated hemoglobin (%)	≥6.4 [6, 7]
Resting heart rate (beat/min)	≥90 [8]
Systolic BP	≥140 [9]
Diastolic BP	≥90 [9]

HDL, high density lipoprotein; BP, blood pressure

Supplementary Table 2. Interaction effects by sex and race for the effects of baseline allostatic load on 11 cognitive test scores (baseline and between-visit change) [3,4]

	Model 1 [1]		Model 2 [2]	
	β (SE)	p	β (SE)	p
SEX				
MMSE, normalized [AL]	0.31 (0.510)	0.54	-0.12 (0.430)	0.79
MMSE, normalized [AL × Time]	0.15 (.12)	0.22	0.10 (0.12)	0.41
CVLT-List A [AL]	0.29 (0.220)	0.18	0.10 (0.200)	0.86
CVLT-List A [AL × Time]	0.058 (0.051)	0.25	0.058 (0.051)	0.26
CVLT-DFR [AL]	0.13 (0.100)	0.21	0.086 (0.097)	0.38
CVLT-DFR [AL × Time]	0.00094 (0.025)	0.97	-0.0054 (0.025)	0.83
BVRT [AL]	-0.37 (0.160)	0.02	-0.28 (0.15)	0.070
BVRT [AL × Time]	-0.030 (0.0373)	0.41	-0.023 (0.037)	0.53
BTA [AL]	0.17 (0.074)	0.02	0.14 (0.072)	0.057
BTA [AL × Time]	-0.0021 (0.018)	0.91	-0.0060 (0.018)	0.74
AF [AL]	0.27 (0.170)	0.11	0.19 (0.16)	0.23
AF [AL × Time]	-0.032 (0.035)	0.36	-0.039 (0.036)	0.28
DS-F [AL]	0.10 (0.070)	0.14	0.056 (0.064)	0.38
DS-F [AL × Time]	-0.0094 (0.015)	0.54	-0.013 (0.015)	0.37
DS-B [AL]	0.11 (0.069)	0.09	0.059 (0.062)	0.33
DS-B [AL × Time]	-0.0038 (0.015)	0.80	-0.0034 (0.015)	0.82
CDT [AL]	0.07 (0.040)	0.09	0.059 (0.039)	0.13
[AL × Time]	0.0022 (0.011)	0.84	0.00088 (0.011)	0.94
Log_e (TRAILS A) [AL]	0.027 (0.008)	0.001	0.0040 (0.012)	0.75
[AL × Time]	-0.00019 (0.0031)	0.95	-0.000084 (0.0031)	0.98
Log_e (TRAILS B) [AL]	-0.013 (0.022)	0.56	-0.0011 (0.020)	0.96
[AL × Time]	-0.00053 (0.0046)	0.91	-0.00013 (0.0046)	0.97
RACE				
MMSE, normalized [AL]	1.41 (0.52)	0.006	0.29 (0.43)	0.51
MMSE, normalized [AL × Time]	0.029 (0.13)	0.81	0.060 (0.12)	0.62
CVLT-List A [AL]	0.40 (0.23)	0.077	0.089 (0.21)	0.67
CVLT-List A [AL × Time]	0.10 (0.05)	0.048	0.092 (0.053)	0.082
CVLT-DFR [AL]	0.23 (0.10)	0.028	0.12 (0.09)	0.24
CVLT-DFR [AL × Time]	0.014 (0.025)	0.57	0.010 (0.026)	0.69
BVRT [AL]	-.35 (0.17)	0.034	-0.098 (0.16)	0.54
BVRT [AL × Time]	0.0089 (0.038)	0.81	0.022 (0.037)	0.57
BTA [AL]	0.10 (0.075)	0.18	0.016 (0.07)	0.82
BTA [AL × Time]	-0.011 (0.018)	0.56	-0.012 (0.018)	0.52
AF [AL]	0.38 (0.17)	0.029	0.12 (0.17)	0.48
AF [AL × Time]	0.031 (0.036)	0.39	0.035 (0.036)	0.33
DS-F [AL]	0.13 (0.071)	0.074	0.015 (0.065)	0.82
DS-F [AL × Time]	0.0040 (0.015)	0.79	-0.0018 (0.015)	0.91
DS-B [AL]	0.079 (0.070)	0.26	-0.062 (0.062)	0.32
DS-B [AL × Time]	0.0080 (0.015)	0.60	0.0069 (0.015)	0.65
CDT [AL]	.015 (0.040)	0.71	-0.019 (0.039)	0.62
CDT [AL × Time]	0.0097 (0.011)	0.38	0.0084 (0.011)	0.46
Log_e (TRAILS A) [AL]	-0.0089 (0.012)	0.48	0.0037 (0.012)	0.77
Log_e (TRAILS A) [AL × Time]	-0.00053 (0.0032)	0.87	0.00027 (0.0032)	0.93
Log_e (TRAILS B) [AL]	-0.017 (0.022)	0.45	0.021 (0.021)	0.31
Log_e (TRAILS B) [AL × Time]	-0.00015 (0.0047)	0.97	0.00026 (0.0047)	0.96

AL, allostatic load; SE, standard error; [1] Model 1 is adjusted for age, sex, race, poverty status, inverse mills ratio as well as time on study in years between visits 1 and 2 and its interaction with allostatic load and covariates. [2] Model 2 is 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 2 and its interaction with allostatic load and covariates. [3] Cognitive tests include the Mini-Mental State Examination (MMSE), the California Verbal Learning Test (CVLT) Immediate (List A) and Delayed Free Recall (DFR), the Benton Visual Retention Test (BVRT, # of errors), the Brief Test of Attention (BTA), the Animal Fluency test (AF), the Digit Span Forward and Backwards tests (DS-F and DS-B), the Clock Drawing Test (CDT), the Trail making test Part A and B (TRAILS A and B, in seconds); [4] Interpretation of uncorrected P values takes into account multiple testing, whereby familywise Bonferroni correction is made for 11 cognitive tests.

Supplementary Table 3. Interaction effects by sex and race for the effects of allostatic load change on 11 cognitive test scores (baseline and between-visit change) [3, 4]

	Model 1 [1]		Model 2 [2]	
	β (SE)	p	β (SE)	p
SEX				
MMSE, normalized [AL_{traj}]	0.79 (0.70)	0.26	0.062 (0.59)	0.92
MMSE, normalized [$AL_{traj} \times$ Time]	0.10 (0.15)	0.49	0.083 (0.15)	0.58
CVLT-List A [AL_{traj}]	0.60 (0.30)	0.048	0.36 (0.28)	0.21
CVLT-List A [$AL_{traj} \times$ Time]	0.083 (0.062)	0.18	0.083 (0.062)	0.18
CVLT-DFR [AL_{traj}]	0.21 (0.14)	0.13	0.13 (0.13)	0.34
CVLT-DFR [$AL_{traj} \times$ Time]	0.018 (0.030)	0.55	0.015 (0.030)	0.63
BVRT [AL_{traj}]	-0.26 (0.22)	0.25	-0.095 (0.21)	0.65
BVRT [$AL_{traj} \times$ Time]	-0.026 (0.044)	0.55	-0.024 (0.044)	0.59
BTA [AL_{traj}]	0.16 (0.10)	0.12	0.085 (0.096)	0.37
BTA [$AL_{traj} \times$ Time]	-0.0093 (0.021)	0.67	-0.013 (0.022)	0.56
AF [AL_{traj}]	0.47 (0.24)	0.049	0.29 (0.22)	0.19
AF [$AL_{traj} \times$ Time]	-0.047 (0.042)	0.26	-0.049 (0.043)	0.26
DS-F [AL_{traj}]	0.16 (0.096)	0.104	0.019 (0.013)	0.13
DS-F [$AL_{traj} \times$ Time]	-0.016 (0.017)	0.37	-0.021 (0.018)	0.24
DS-B [AL_{traj}]	0.19 (0.095)	0.042	0.082 (0.085)	0.33
DS-B [$AL_{traj} \times$ Time]	-0.0087 (0.018)	0.63	-0.0093 (0.018)	0.61
CDT [AL_{traj}]	0.076 (0.054)	0.17	0.057 (0.054)	0.29
CDT [$AL_{traj} \times$ Time]	-0.0024 (0.014)	0.86	-0.0038 (0.014)	0.78
Log_e (TRAILS A) [AL_{traj}]	0.0066 (0.017)	0.70	0.016 (0.017)	0.36
Log_e (TRAILS A) [$AL_{traj} \times$ Time]	-0.0013 (0.0037)	0.72	-0.0011 (0.0038)	0.76
Log_e (TRAILS B) [AL_{traj}]	0.00090 (0.030)	0.98	0.025 (0.028)	0.37
Log_e (TRAILS B) [$AL_{traj} \times$ Time]	-0.0026 (0.0055)	0.64	-0.0027 (0.0055)	0.62
RACE				
MMSE, normalized [AL_{traj}]	1.31 (0.70)	0.062	-0.019 (0.12)	0.88
MMSE, normalized [$AL_{traj} \times$ Time]	-0.0057 (0.15)	0.97	.064 (0.15)	0.67
CVLT-List A [AL_{traj}]	0.49 (0.31)	0.12	-0.060 (0.29)	0.84
CVLT-List A [$AL_{traj} \times$ Time]	0.093 (0.065)	0.15	0.099 (0.065)	0.13
CVLT-DFR [AL_{traj}]	0.19 (0.14)	0.19	-0.00087 (0.14)	0.99
CVLT-DFR [$AL_{traj} \times$ Time]	0.044 (0.032)	0.16	0.044 (0.032)	0.16
BVRT [AL_{traj}]	-0.30 (0.22)	0.18	.062 (0.22)	0.77
BVRT [$AL_{traj} \times$ Time]	0.025 (0.045)	0.58	0.030 (0.046)	0.50
BTA [AL_{traj}]	0.25 (0.10)	0.013	0.14 (0.098)	0.16
BTA [$AL_{traj} \times$ Time]	-0.026 (0.022)	0.25	-0.029 (0.023)	0.19
AF [AL_{traj}]	0.63 (0.24)	0.008	0.23 (0.23)	0.32
AF [$AL_{traj} \times$ Time]	0.063 (0.043)	0.15	0.074 (0.044)	0.093
DS-F [AL_{traj}]	0.17 (0.09)	0.085	-0.0027 (0.089)	0.98
DS-F [$AL_{traj} \times$ Time]	-0.0090 (0.018)	0.62	-0.014 (0.018)	0.46
DS-B [AL_{traj}]	0.12 (0.096)	0.19	-0.084 (0.086)	0.33
DS-B [$AL_{traj} \times$ Time]	0.011 (0.018)	0.52	0.013 (0.018)	0.48
CDT [AL_{traj}]	0.043 (0.055)	0.43	-0.0082 (0.054)	0.88
CDT [$AL_{traj} \times$ Time]	0.0037 (0.014)	0.79	0.0037 (0.014)	0.79
Log_e (TRAILS A) [AL_{traj}]	-0.016 (0.017)	0.33	0.00026 (0.0032)	0.94
Log_e (TRAILS A) [$AL_{traj} \times$ Time]	-0.0012 (0.0038)	0.76	-0.0010 (0.0038)	0.79
Log_e (TRAILS B) [AL_{traj}]	-.013 (.030)	0.66	0.037 (0.028)	0.19
Log_e (TRAILS B) [$AL_{traj} \times$ Time]	0.00033 (0.0055)	0.95	-0.00027 (0.0056)	0.96

AL_{traj}, z-transformed probability of belonging to a group with increasing allostatic load over time according to group-based trajectory modeling; SE, standard error; [1] Model 1 is adjusted for age, sex, race, poverty status, inverse mills ratio as well as time on study in years between visits 1 and 2 and its interaction with trajectory in allostatic load and covariates. [2] Model 2 is 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 2 and its interaction with trajectory in allostatic load and covariates. [3] Cognitive tests include the Mini-Mental State Examination (MMSE), the California Verbal Learning Test (CVLT) Immediate (List A) and Delayed Free Recall (DFR), the Benton Visual Retention Test (BVRT, # of errors), the Brief Test of Attention (BTA), the Animal Fluency test (AF), the Digit Span Forward and Backwards tests (DS-F and DS-B), the Clock Drawing Test (CDT), the Trail making test Part A and B (TRAILS A and B, in seconds); [4] Interpretation of uncorrected P values takes into account multiple testing, whereby familywise Bonferroni correction is made for 11 cognitive tests.

Supplementary Table 4. Relationship of allostatic load and allostatic load trajectory with 11 cognitive test scores (baseline and between-visit change) in fully-adjusted models [1, 3]

	AL		**AL $_{traj}$**	
COGNITIVE TESTS [2]	β (SE)	p	β (SE)	p
MMSE, normalized:	N= 2,223, K=1.6		N= 1,768, K=1.8	
[AL | AL $_{traj}$]	-0.26 (0.27)	0.33	-0.22 (0.34)	0.52
[AL × Time | AL $_{traj}$ × Time]	0.051 (0.074)	0.49	0.061 (0.085)	0.47
CVLT-List A:	N= 2,119, K=1.6		N= 1,744, K=1.7	
[AL | AL $_{traj}$]	-0.054 (0.13)	0.67	-0.074 (0.16)	0.65
[AL × Time | AL $_{traj}$ × Time]	0.0033 (0.032)	0.92	-0.036 (0.035)	0.30
CVLT-DFR:	N=2,066, K=1.5		N=1,702, K=1.6	
[AL | AL $_{traj}$]	-0.020 (0.060)	0.74	0.037 (0.076)	0.63
[AL × Time | AL $_{traj}$ × Time]	-0.0012 (0.015)	0.94	-0.021 (0.017)	0.22
BVRT:	N=2,235, K=1.7		N=1,784, K=1.8	
[AL | AL $_{traj}$]	0.12 (0.096)	0.19	0.29 (0.12)	0.015
[AL × Time | AL $_{traj}$ × Time]	-0.016 (0.023)	0.48	-0.024 (0.026)	0.34
BTA:	N=2,129, K=1.6		N=1,738, K=1.7	
[AL | AL $_{traj}$]	-0.0092 (0.044)	0.83	-0.088 (0.056)	0.11
[AL × Time | AL $_{traj}$ × Time]	-0.013 (0.011)	0.23	-0.0049 (0.013)	0.69
AF:	N= 2,253, K=1.7		N= 1,794, K=1.9	
[AL | AL $_{traj}$]	-0.038 (0.10)	0.71	-0.097 (0.13)	0.46
[AL × Time | AL $_{traj}$ × Time]	0.010 (0.022)	0.62	0.00025 (0.024)	0.99
DS-F:	N=2,229, K=1.6		N=1,783, K=1.8	
[AL | AL $_{traj}$]	-0.026 (0.039)	0.51	-0.019 (0.051)	0.71
[AL × Time | AL $_{traj}$ × Time]	0.013 (0.0093)	0.14	0.010 (0.010)	0.33
DS-B:	N= 2,226, K=1.6		N= 1,784, K=1.8	
[AL | AL $_{traj}$]	-0.0091 (0.038)	0.81	0.015 (0.049)	0.76
[AL × Time | AL $_{traj}$ × Time]	0.0058 (0.0094)	0.54	0.0017 (0.010)	0.87
CDT:	N=2,244, K=1.7		N=1,787, K=1.9	
[AL | AL $_{traj}$]	-0.036 (0.024)	0.14	-0.063 (0.030)	0.040
[AL × Time | AL $_{traj}$ × Time]	-0.0021 (0.0067)	0.75	-0.0050 (0.0078)	0.52
Log_e (TRAILS A):	N=2,187, K=1.7		N= 1,748, K=1.8	
[AL | AL $_{traj}$]	0.014 (0.0077)	0.053	0.02 (0.009)	0.042
[AL × Time | AL $_{traj}$ × Time]	-0.00096 (0.0019)	0.61	-0.0011 (0.0021)	0.59
Log_e (TRAILS B):	N=2,166, K=1.6		N=1,727, K= 1.8	
[AL | AL $_{traj}$]	0.020 (0.013)	0.11	0.033 (0.02)	0.039
[AL × Time | AL $_{traj}$ × Time]	-0.0029 (0.0028)	0.29	-.0039 (0.0032)	0.22

AL, allostatic load; AL $_{traj}$, z-transformed probability of belonging to a group with increasing allostatic load over time according to group-based trajectory modeling; K, mean number of visits per subject; N, sample size; SE, standard error; [1] Models are adjusted for age, sex, race, poverty status, education, literacy, smoking, drug use, 2010 healthy eating index, body mass index, hypertension, diabetes, dyslipidemia, cardiovascular disease, depressive symptoms score, self-rated health, inverse mills ratio as well as time on study in years between visits 1 and 2 and its interaction with allostatic load or allostatic load trajectory and covariates. [2] Cognitive tests include the Mini-Mental State Examination (MMSE), the California Verbal Learning Test (CVLT) Immediate (List A) and Delayed Free Recall (DFR), the Benton Visual Retention Test (BVRT, # of errors), the Brief Test of Attention (BTA), the Animal Fluency test (AF), the Digit Span Forward and Backwards tests (DS-F and DS-B), the Clock Drawing Test (CDT), the Trail making test Part A and B (TRAILS A and B, in seconds); [3]Interpretation of uncorrected P values takes into account multiple testing, whereby familywise Bonferroni correction is made for 11 cognitive tests.

Supplementary Material 1. Cognitive Tests

Mini-Mental State Examination (MMSE)

The MMSE [10] is a cognitive screener that captures global cognitive functioning by briefly measuring orientation, concentration, immediate and short-term memory, language and constructional praxis. Scores range from 0 to 30. Higher scores suggest better cognitive function.

California Verbal Learning Test (CVLT)

The CVLT [11] is a verbal learning and memory test that includes a 16-item word list. A modified version of the CVLT was used with three, as opposed to five, learning trials. Cued recall was not administered. To capture verbal learning and memory, CVLT outcomes variables were total correct score for List A (learning) and List A long-delay free recall (memory). The learning score ranged from 0 to 48 and the memory score ranged from 0 to 16. Higher scores indicate better verbal learning and memory. A more comprehensive description of CVLT can be found elsewhere [11].

Benton Visual Retention Test (BVRT)

The BVRT [12] is a measure of non-verbal memory and visuo-constructional abilities. Administration A, Form D was used. A modified error scoring system based on the BVRT manual was used to guide two trained examiners in scoring the BVRT. Resolution of discrepancies in scoring were attempted by the two examiners, however, if a consensus could not be achieved, a research psychologist provided the score. The outcome variable was total errors, with higher values indicating lower visual memory scores.

Digit Span Forward and Backward (DS-F and DS-B)

The Wechsler Adult Intelligence Scale, Revised [13] Digit Span Forward and Backward primarily capture attention and working memory, a component of executive function. The tests were administered according to the manual's instructions. The outcome variable was the total score, which was the total number of correct answers for each test.

Category Fluency

Category fluency [14, 15] is a measure of semantic verbal fluency, where participants are asked to generate as many animals as possible within a 60 second duration. Higher scores indicate better category fluency. The outcome variable was the total number of correctly generated words (i.e., words that were *not* intrusions and perseverations).

Brief Test of Attention (BTA)

For the BTA [16], a test of divided auditory attention, the examiner administered up to 10 trials of letters and numbers (4-18 items) that increased in length with each trial. Only the numbers portion of the test was administered. For each trial, participants were asked to disregard the number of letters read, while tracking how many numbers were recited. They were also told to keep their hands in fists to avoid finger counting. The outcome variable was the total number of correct trials.

Trail Making Tests A and B (TRAILS A and B)

The Trail Making Tests A and B [17] primarily capture attention and executive functioning, respectively. The main executive function subdomain that TRAILS B captures is set-shifting and cognitive control. Both trials also measure visuo-motor scanning and processing speed. Participants were asked to draw a line between consecutive numbers (TRAILS A) and alternate between numbers and letters (TRAILS B) as quickly as they could. They were informed that they were being timed. The examiner pointed out errors that were then corrected by the participant. Errors were captured via increased time. Scores for TRAILS A and B reflected seconds to completion, where higher scores indicate poorer performance.

Clock Drawing Test – Clock to Command (CDT)

The Clock Drawing Test [18] is a measure of visuo-spatial abilities, that also captures elements of memory and executive function. Participants are instructed to draw a clock, put in all of the numbers, and set the hands to 10 minutes past 11. Performance is based on correct drawings of the clock face (0-2), numbers (0-4) and hands (0-4). Scores ranged from 0 to 10, with higher scores indicating better performance. Participants who did not score a perfect score on the command portion of the test were also asked to copy a clock with the hands set to 10 minutes after 11.

Wide Range Achievement Test – 3rd Edition: Word and Letter Reading Subtest (WRAT)

The WRAT Word and Letter Reading Subtest [19] is a test of reading ability that is often used as a proxy for literacy and quality of education. Participants were instructed to correctly read a list of 50 words that increased in difficulty. If the first five words were not correctly pronounced, letter reading was also administered. Standard instructions were used with the tan form. The outcome variable used was the total number of correctly pronounced words.

Supplementary Material 2. Depressive Symptoms Questionnaire

Center for Epidemiological Studies Depression Scale (CES-D)

The CES-D [20] is a 20-item measure of depressive symptomatology. Participants are asked to consider the frequency and severity of their symptoms over the last week. Scores ranged from 0 to 60. Scores of $\geq$16 indicated significant depressive symptoms and scores of $\geq$20 indicated a clinically significant amount of depressive symptoms.

Supplementary Material 3. Mixed-effects linear regression models

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

Multi-level models versus **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 (11 cognitive test scores measured at v_1 and/or v_2) for each individual "i" and visit "j"; π_{0i} is the level-1 intercept for individual i; π_{1i} is the level-1 slope for individual i; γ_{00} is the level-2 intercept of the random intercept π_{0i} ; γ_{10} is the level-2 intercept of the slope π_{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}). ζ_{0i} and ζ_{1i} are level-2 disturbances; ε_{ij} is the within-person level-1 disturbance [21].

It is worth noting that the models were fit using the entire HANDLS study cohort with complete data on either v_1 or v_2 for each cognitive test score, those models were used to improve reliability of predicted estimates. Empirical bayes estimators for annual rate of change in each cognitive test scores (δ) were also predicted from time-interval mixed-effects models, with up to 2 repeats on each outcome, without adding any covariates in the model aside from *TIME*. The annualized change in each cognitive test score is presented in Table 1 for descriptive purposes.

Supplementary Material 4. Group-based trajectory modeling details

Group	Parameter	Standard Estimate	T for H0: Error	Parameter=0	Prob > T
1	Intercept	-3.31815	1.76876	-1.876	0.0607
	Linear	0.09222	0.06508	1.417	0.1565
	Quadratic	-0.00048	0.00061	-0.79	0.4296
2	Intercept	-0.61891	0.40168	-1.541	0.1234
	Linear	0.04652	0.01571	2.961	0.0031
	Quadratic	-0.00036	0.00015	-2.338	0.0194

Group membership

1	**(%)**	**22.62374**	**8.88000**	**2.548**	**0.0109**
2	**(%)**	**77.37626**	**8.88000**	**8.714**	**0.0000**

BIC= -6393.51 (N=3940) BIC= -6391.67 (N=2328) AIC= -6371.53 ll= -6364.53

Parameter estimates for adding risk factors

-3.31815, 0.09222, -0.00048, -0.61891, 0.04652, -0.00036, 1.22968

Parameter estimates

-3.31815, 0.09222, -0.00048, -0.61891, 0.04652, -0.00036, 22.62374, 77.37626

Entropy = 0.365

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