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Body mass index and allostatic load are directly associated with longitudinal increase in plasma neurofilament light among urban middle-aged adults

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Upon request, data can be made available to researchers with approved proposals, after they have agreed to confidentiality as required by our IRB. Policies are publicized on: https://handls.nih.gov. Data access request can be sent to principal investigators (PI) or the study manager, Jennifer Norbeck at norbeckje@mail.nih.gov. These data are owned by the National Institute on Aging at the NIH. The PIs have made those data restricted to the public for two main reasons: "(1) The study collects medical, psychological, cognitive, and psychosocial information on racial and poverty differences that could be misconstrued or willfully manipulated to promote racial discrimination; and (2) Although the sample is fairly large, there are sufficient identifiers that the PIs cannot guarantee absolute confidentiality for every participant as we have stated in acquiring our confidentiality certificate." Code book and statistical analysis script can be readily obtained from the corresponding author, upon request, by e-mail contact at baydounm@mail.nih.gov.

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ABSTRACT

Background: Plasma neurofilament light, a novel biomarker for age-related neurodegenerative disease, may be linked to cardiometabolic risk factors, including body mass index (BMI), the allostatic load total score (AL_{total}) and related continuous components (AL_{comp}). These relationships may differ by sex and race.

Methods: We used data from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study [*n*=608, Age at visit 1 (v_1:2004-2009): 30-66y, 42% male, 58% African American] to investigate associations of initial cardiometabolic risk factors and time-dependent plasma NfL levels over 3 visits (2004-2017; mean follow-up time±SD:7.72±1.28y), with outcomes being NfL_{v1} and annualized change in NfL (δNfL). We used mixed-effects linear regression and structural equations modeling (SM).

Results: BMI was associated with lower initial (γ_{01}=-0.014±0.002, *P*<0.001) but faster increase in plasma NfL over time (γ_{11}=+0.0012±0.0003, *P*<0.001), a pattern replicated for AL_{total}. High sensitivity C-reactive protein (hsCRP), serum total cholesterol, and resting heart rate at v_1 were linked with faster plasma NfL over-time increase overall, while being uncorrelated with NfL_{v1} (e.g. hsCRP×TIME, full model: γ_{11}=+0.004±0.002, *P*=0.015). In SM analyses, BMI's association with δNfL was significantly mediated through AL_{total} among women (Total effect =+0.0014±0.00038, *P*<0.001; Indirect effect=+0.00042±0.00019, *P*=0.025; mediation proportion=30%), with only a direct effect detected among African Americans (Total (effect=+0.0011±0.0004, p=0.015; Direct effect=+0.0010±0.00048, p=0.034). The positive associations between AL_{total}/BMI and δNfL were mediated through increased HbA1c levels, overall.

Conclusions: Cardiometabolic risk factors, particularly elevated HbA1c, should be screened and targeted for neurodegenerative disease, pending comparable longitudinal studies. Other

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studies examining the clinical utility of plasma NfL as a neurodegeneration marker should account for confounding effects of BMI and AL.

Key words: Neurofilament light, allostatic load, body mass index, urban adults, race, cognition

INTRODUCTION

When axons are damaged with age and in many neurodegenerative diseases, certain cytoskeletal proteins referred to as neurofilaments are often released into the extracellular space, then the cerebrospinal fluid (CSF), and finally may transmigrate into blood at a lower concentration (1). Neurofilament light chain (NfL) is a novel biomarker for neurodegenerative diseases detectable in blood, reflecting axonal degeneration. Accumulating data indicates that levels of plasma NfL are associated with Alzheimer's disease, and other neurodegenerative diseases (2-8). In fact, plasma NfL levels are associated with cognitive decline in non-demented adults (9, 10) and are able to predict the onset of AD(11, 12). Plasma NfL is attractive as a biomarker, as it uses less invasive procedures when contrasted to cerebrospinal fluid (CSF) assessments. NfL measured in CSF is positively correlated with plasma NfL (13, 14) and plasma NfL levels are associated with neuroimaging measures of cognition (1, 15, 16). Compared to neuroimaging measures or tests of cognitive performance, plasma NfL as a biomarker, reduces both time and expense in assessing risk for dementia with high-risk groups in randomized controlled trials. As for CSF NfL, plasma NfL concentration exhibits an upward trending trajectory with age. This positive correlation may be in part explained by increased body mass index (BMI) and other related metabolic disorders such as renal dysfunction as was shown in two recent studies (17, 18), which in turn are largely determined by poor dietary quality and other nutritional factors (19-24). Obesity,

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directly measured with BMI, along with its associated cardiometabolic disorders and markers of inflammation (e.g. abdominal obesity, hypertension, dyslipidemia, hyperglycemia, elevated blood C-reactive protein, reduced serum albumin), become more prevalent with age, particularly between early to mid-life(25, 26); they are also associated with later life cognitive decline and impairment(27-31) and adverse neuroimaging outcomes. (32-38) Moreover, neurocognitive outcomes were associated with CSF biomarkers of neurodegeneration (e.g. Aβ42:40 ratio, tau and NfL) (39-41), as well as plasma NfL in more recent studies (2-4, 15, 42-47). However, it is still unknown whether age-related cardiometabolic disorders are independent risk factors for the rate of increase in plasma NfL over time.

If these associations exist then they are likely to differ markedly across sociodemographic factors, particularly across sex and race groups, given the sex and race-specific associations between cardiometabolic risk and neurocognitive aging outcomes (48-51). Moreover, previous reports show a direct association between cardiometabolic risk and adverse neurocognitive outcomes, and increased plasma NfL with those same outcomes. Therefore, a positive association between cardiometabolic risk and plasma NfL would suggest that cardiometabolic risk needs to be accounted for as a potential confounder in studies of clinical utility for plasma NfL as an early marker of neurodegeneration. Plasma NfL may also be a pathway through which cardiometabolic risk is linked to neuro-cognitive outcomes.

The present study investigated the longitudinal associations of BMI (continuous and categorical) and the AL (total score and components) with plasma NfL (baseline BMI/AL vs. baseline plasma NfL; baseline BMI/AL vs. annual rate of change in plasma NfL), independently of key exogenous confounders, and across sex and race. The study also assessed whether the AL total score mediated the association between BMI and the annual

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rate of change in plasma NfL, across sex and race groups. Finally, the study tested which individual components of the AL mediated the total effects of AL and BMI on annual rate of change plasma NfL, overall and across sex and race groups.

MATERIALS AND METHODS

Database

The sample was selected from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study. Initiated in 2004, HANDLS is a longitudinal study involving socioeconomically diverse White and African American adult women and men who resided in Baltimore, MD. Baseline data (visit 1, v_1) were collected in two phases during 2004-2009. Phase I consisted of a home visit, whereby recruitment, consent and screening procedures as well as a household in-person interview were performed, including the first 24-hour dietary recall. During Phase II (v_1), an in-person complete physical health examination was performed within Medical Research Vehicles (MRV) including a second 24-hr dietary recall. Participants were invited to participate in follow-up in-person visits (v_2: 2009-2013 and v_3:2013-2017) whereby similar protocols as v_1 (Phase II) were applied. Fasting blood samples were drawn from participants who provided written informed consent during in-person examinations. The study protocol of HANDLS was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences, National Institutes of Health.

Study sample

In our present study, up to three repeats on plasma NfL concentrations were available from v_1, v_2 and/or v_3. AL components and therefore the total score, were measured also up to 3

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visits. However, in this study, we only examine v_1 exposures. As shown in the study design flowchart (**Figure 1**), among 3,720 initially recruited HANDLS participants, *n*=694 had complete v_1, v_2 and/or v_3 data on plasma NfL. Of those participants, *n*=608 had data on v_1 AL. Mean±SD follow-up time (between v_1 and v_3) for the final analytic sample with complete v_3 data (*n*=596 participants) was 7.72±1.28y. A detailed description for sample selection with respect to the plasma NfL outcome is shown in **Supplementary method 1**. Compared to the initial sample with incomplete data for our analysis, the final sample had a lower proportion of individuals living below poverty (27% vs. 44%, $p<0.001$, χ^2 test). Of *n*=608, 606 had complete data to compute δNfL_{obs}, and thus an additional *n*=2 were excluded for the structural equations modeling (SM) analysis.

Plasma Neurofilament Light

Fasting blood samples were collected between 9:30 am and 11:30 am into EDTA blood collection tubes. The tubes were centrifuged at 600*g* for 15 min followed by the removal of the buffy coat. These steps were repeated twice and samples were visually examined for hemolysis. Plasma samples were stored in aliquots at -80°C after their collection. Plasma NfL levels were quantified using the Simoa® NF-light Advantage Kit by Quanterix (Billerica, MA, USA) following kit instructions. Samples from the different visits were run on the same plate for each individual and plates were balanced for individuals within each demographic group (race/sex/poverty). Plasma samples were diluted fourfold, and concentrations were adjusted for this dilution correction. Pooled plasma samples from two individuals were run in duplicate on all plates intra-assay and inter-assay coefficient of variations were 4.5% and 7%, respectively. The limit of detection was 0.152 pg/ml and the lower limit of quantification was 0.696 pg/ml. The upper limit of detection was 1872 pg/ml. Plasma NfL was the main outcome of interest, measured for up to 3 repeats per participant, at v_1, v_2 and/or v_3.

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Allostatic load (AL)

We relied on a previously reported method to compute total AL score (52). This method sums cardiovascular (systolic and diastolic blood pressure, pulse rate), metabolic (total cholesterol, high density lipoprotein (HDL)-cholesterol, glycosylated Hb (HbA1C), sex-specific waist-to-hip ratio) and inflammatory (serum albumin and high sensitivity C-reactive protein (hsCRP)) risk indicators. As summarized in **Supplementary Table 1,** multiple clinical criteria were used to obtain risk indicators which were subsequently summed with equal weighting to compute a total AL score that ranges between 0 and 9, heretofore termed AL_{total}. The higher the AL_{total}, the more the overall cardiometabolic risk. Total cholesterol (mg/dL), HDL-cholesterol (mg/dL), hsCRP (mg/dL), albumin (g/dL) and glycosylated hemoglobin (%) were determined by contract laboratories (Quest Diagnostics, Chantilly, VA), using reference analytical methods. Using standard protocols, trained examiners measured waist-to-hip ratio, radial pulse (beats/min), and systolic and diastolic blood pressure (mmHg). In particular, blood pressure was measured using a mercury sphygmomanometer and the arithmetic mean of left and right systolic and diastolic pressures were used in this analysis.

Body mass index

Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). In part of the analysis, the total effect of BMI on plasma NfL change was tested as potentially being mediated through AL total score. In addition, both continuous BMI and weight status (categorical BMI) were included among potential exposures, alternative to AL_{total}, in mixed-effects linear regression models. Weight status was defined as: BMI_{v1}<18.5 $kg.m^{-2}$, or underweight; BMI_{v1}≥18.5, <25 $kg.m^{-2}$, or normal weight; $BMIv_1$≥25, <30 $kg.m^{-2}$, or overweight; BMI_{v1}≥30 $kg.m^{-2}$, or obese.

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Covariates

We assessed multiple covariates as potential confounders, given previous significant associations with plasma NfL and are considered antecedent risk factors to the AL. These included v_1 age (continuous, years), sex (male, female), race (White, African American), poverty status (below vs. above 125% the federal poverty line), educational attainment (less than high school, high school, more than high school). We operationalized poverty status using the 2004 US Census Bureau poverty thresholds (53) based on household income and total family size (including children <18 years). Some of the lifestyle and health-related factors were considered as potential confounders, given their potential impact on both AL and plasma NfL, while not necessarily on the causal pathway between AL and plasma NfL. Those factors were current smoking status (0=No vs. 1=Yes), illicit drug use (0=No vs. 1=Yes, using any of marijuana, opiates, and cocaine), the Healthy Eating Index 2010 (HEI-2010)(54), whereby overall diet quality was measured based on food and macronutrient-related US dietary guidelines for Americans, total energy intake (kcal/d), and the 20-item CES-D total score for depressive symptoms(55). Sex and race were the main effect modifiers in our analyses. Basic socio-demographic covariates were complete by design, while other measures assessed during the MRV phase of v_1 had some missing data. However, after accounting for missingness in all key variables (v_1 AL and δNfL), covariates had <5% missingness individually out of the final eligible sample (*n*=608). Thus, multiple imputation was conducted as described in the next section.

Statistical analysis

All analyses were conducted using Stata release 16 (56). First, study sample characteristics were described in terms of fixed, baseline and longitudinal changes in key variables across race and sex, using means and proportions, as well as bivariate linear, logistic, and

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multinomial logit models to examine racial and sex differences in continuous, binary and categorical multi-level covariates, respectively. We then further adjusted those models for the remaining socio-demographic factors among age, sex, race and poverty status to determine whether racial and sex differences remained statistically significant. Second, for testing our main hypotheses, a series of mixed-effects linear models were conducted (**Supplementary Method 2**). The outcome in these models was plasma NfL measured longitudinally with up to 3 repeats, while the main exposure was AL_{total} measured at v_1 (2004-2009). The modeling process consisted of 3 model sets, with increasing level of adjustment for potentially confounding covariates. These covariates were assumed to confound the relationship between v_1 AL_{total} and v_1 plasma NfL as well as v_1 AL_{total} and annualized change in plasma NfL, and thus were included among main effects and interacted with *TIME*: Model 1: only socio-demographic variables: age at v_1, sex, race, poverty status and educational attainment; Model 2: all other lifestyle and health-related covariates listed in the Covariates section, excluding BMI at v_1. We ensured sample size consistency across models by conducting multiple imputation for covariates (aside from socio-demographics). This was accomplished with chained equations (5 imputations, 10 iterations), with all covariates used simultaneously in the estimation process, similar to previous studies (57, 58). Nine continuous components of the allostatic load (AL_{comp}) measured at v_1 were considered as secondary predictors, substituting AL_{total} in these models, separately. Thus, in these multiple mixed-effects linear regression models, we applied **Models 1** and **2** to 1 key exposure (AL_{total}) and 9 secondary predictors (AL_{comp}), 1 key outcome (plasma NfL) with up to 3 repeats (effect of AL_{total} on v_1 plasma NfL (NfL_{v1}) and annualized change in NfL over time between v_1 and v_3 (δNfL)), and two main stratifying variables (race and sex). In all these models, plasma NfL was Log_e transformed, as done in other studies (e.g.(45)). Using a simplified model with *TIME* as the only predictor, annualized change in plasma NfL was also estimated for each participant in

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the final analytic sample, by predicting random effects from the model and estimating the empirical Bayes estimator for annualized change in plasma NfL, heretofore termed δNfL_{bayes}. This estimation process used the largest available sample with 1,2 or 3 repeats on plasma NfL and assumed missingness of outcome at random. Given that the variance of this estimator is significantly different from the observed annualized change, it was only used to validate the observed annualized change, heretofore termed δNfL_{obs}. The latter was estimated by taking the arithmetic mean for annualized changes between v_1 and v_2, v_2 and v_3 and between v_1 and v_3. Racial and sex differences in the association between v_1 AL_{total} and plasma NfL at v_1 were tested using AL_{total}×Race and AL_{total}×sex interaction terms in separate models, respectively. In each of these models, heterogeneity by race and sex in the association between AL_{total} and δNfL were tested by also adding AL_{total}×TIME×Race and AL_{total}×TIME×sex, respectively. This modeling process was repeated for BMI and weight status, substituting AL_{total}.

Two sets of structural equations models (SM) were constructed to test pathways explaining annual rate of change in plasma NfL, predicted from a simple mixed-effects regression model with random effects added to intercept and slope (observed annualized change, δNfL_{obs}), through mediating pathways involving several cardiometabolic risk factors. The first set of SM examined whether BMI at v_1 was associated with δNfL_{obss} through AL_{total} at v_1, overall and stratifying separately by sex and race. Thus, this set of SM attempted to test whether AL total score mediated the association between BMI and δNfL. In contrast, a second set of SMs examined individual continuous components of the AL (AL_{comp}, e.g. total cholesterol) as alternative mediators between AL_{total} at v_1 and δNfL_{obs}. In all these models, exogenous covariates included v1 age, sex, race, poverty status, education, current smoking, current illicit drug use, CES-D total score, HEI-2010 and mean energy intake (kcal/day) at v_1. These exogenous covariates were allowed to predict all 3 endogenous variables in the system,

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including [δNfL_{obs}], [v_1 BMI], [v_1 AL_{total}] and [v_1 AL_{comp}]. AL_{comp} included v_1 waist-to-hip ratio (WHR), v_1 serum albumin (ALB), v1 high-sensitivity C-reactive protein (hsCRP), v_1 Glycated hemoglobin (HBA1C), v_1 total cholesterol (CHOL), v_1 HDL-cholesterol (HDL-C), v_1 resting heart rate (RHR), v_1 systolic blood pressure (SBP) and v_1 diastolic blood pressure (DBP). Detailed description of the SM methods and the estimated parameters and statistics are provided in **Supplementary method 3**. In a sensitivity analysis with δNfL_{obs} as the final outcome, we examined the mediating effect of continuous AL_{comp} in the BMI- δNfL_{obs}, overall and by sex and race following a similar analytic strategy.

In all models (mixed-effects and SM), sample selectivity potentially caused by missingness on exposure and outcome data, relative to the initially recruited sample, was corrected by utilizing a two-stage Heckman selection process. As a first stage, using a probit model, we predicted an indicator of selection with socio-demographic factors. Those were in this case, v_1 age, race, sex and poverty status. This model yielded an inverse mills ratio (IMR), a function of the probability of being selected conditional on those socio-demographic factors. At the second stage, the main models testing the key hypotheses we estimated using multiple mixed-effects linear and SM models, adding among adjusted factors the IMR in addition to aforementioned covariates (59).

We set the type I error rate a priori for main effects and interactions to 0.05 and 0.10, respectively (60). We illustrated some of the main findings from specific mixed-effects linear regression models using predictive margins (with estimated 95% CI) of plasma NfL outcome across time, and by AL_{total} exposure, overall or stratified by race and/or sex. Pictural representations of SM models were also utilized, where appropriate, to illustrate the potential mediating effects of cardiometabolic risk factors, while stratifying by sex and race.

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RESULTS

Study sample characteristics by sex and race

Table 1 describes the characteristics of the study sample, while examining differences by sex and by race. The most notable differences were in BMI, which was higher among men compared to women, while the reverse was true for total caloric intake and current illicit drug use (P<0.05). AL_{total} on average reflected greater cardiometabolic risk among Whites (1.98 vs. 1.78, P=0.044). Sex and racial differences were also detected in continuous AL components. Specifically, men were at higher cardiometabolic risk than women on HDL-cholesterol and diastolic blood pressure, while the reverse was true for serum albumin, hsCRP and total cholesterol. Moreover, African Americans were at higher risk for lower albumin levels, and at lower risk for higher HDL-cholesterol compared with Whites. The Log_e transformed plasma NfL level at v_1 and v_3 were all on average higher among men compared with women, with no difference detected by sex for δNfL_{obs}. At each of v_1 and v_3, Log_e transformed plasma NfL level was also higher among Whites, even though δNfL_{obs} did not differ across racial groups.

Body mass index, weight status and their longitudinal association with plasma NfL

Our main hypotheses of associations of body mass index (and weight status) with time-dependent plasma NfL levels were examined by a series of mixed-effects linear regression models, with key findings presented in **Table 2**. Overall, baseline levels of plasma NfL were inversely associated with BMI (γ_{01}=-0.014±0.002, P<0.001) and higher weight status in both the reduced and full models. In contrast, BMI (γ_{11}=+0.0012±0.0003, P<0.001) and higher weight status at baseline were linked to faster increase in plasma NfL over time. Both associations were driven by the contrast between obesity vs. normal weight (γ_{01}=-

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0.234±0.045, $P<0.001$; γ_{11}= +0.017±0.006, $P<0.010$). The results were largely homogeneous across sex and race with few exceptions, particularly for the reduced model. When examining standardized regression coefficients (b), 1 SD increase in BMI was linked to a -0.19 SD lower baseline plasma NfL and with a 0.015-fold annual increase in SD of plasma NfL, yielding an increase of 0.15 SD over a period of 10 years. Both of these cross-sectional and longitudinal standardized effect sizes are considered weak to modest.

Allostatic Load (total score and components) and their longitudinal association with plasma NfL

Following a similar modeling approach (**Table 3**), we examined the associations of AL total score and AL continuous components in relation to time-dependent change in plasma NfL. Overall, there was a clear association between AL_{total} at v_1 and faster increase in plasma NfL, (P<0.001) while the same exposure was associated with lower baseline plasma NfL (P<0.05). Although largely homogeneous by sex and by race, this association differed markedly by these two socio-demographic groups when each component of AL was considered as the main exposure. One notable finding is that v_1 HbA1c was consistently associated with higher plasma NfL at baseline and faster increase in plasma NfL among Whites in both the reduced and full models (P<0.010 for HbA1c main effect and HbA1c×*TIME*), with P=0.007 for HbA1c×Race parameter. Other notable findings include the inverse relationship between v_1 WHR and v_1 plasma NfL among men with the reverse found in women and among African Americans and no association detected among Whites. In contrast, inverse associations of v_1 SBP and/or DBP with v1 plasma NfL were mostly detected among Whites. Moreover, v_1 serum albumin was inversely linked with plasma NfL at v_1 among men, an association not detected in women (P<0.01 for ALB×sex).

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hsCRP, Cholesterol, and RHR at v_1 were among continuous AL components associated with faster increase in plasma NfL over time in the total sample, while they were uncorrelated with baseline plasma NfL. In contrast, SBP and DBP had different associations with baseline vs. annualized rate of change in NfL, suggesting that both measures were inversely related to first-visit NfL while being associated with faster increase in NfL over time. Finally, higher HDL-cholesterol at v_1 was associated with higher v_1 plasma NfL, in the total sample.

Allostatic Load (total score and components) as a mediator between BMI and annualized change in NfL

Figure 2 shows the results from a structural equations model in which AL_{total} at v_1 was tested as a potential mediator between BMI at v_1 and annualized change in plasma NfL. Our results suggested that the total effect (TE) of BMI at v1 on δNfL_{obs} indicated a positive association between the two factors in the total sample (TE>0, P<0.05). This was also the case among women. However, only among women the indirect effect indicated a large portion of this TE was mediated through AL_{total}, with an estimated mediation proportion of 30% (TE=+0.0014±0.00038, p<0.001 ; IE=+0.00042±0.00019, p=0.025). In other groups and overall, where TE was statistically significant mostly as a direct effect and there was no significant indirect effect through AL_{total}. Specifically, among African Americans, most of the TE was a direct effect, DE (TE=+0.0011±0.0004, *P*=0.015; DE= +0.0010±0.00048, *P*=0.034).

AL continuous components as mediators between AL_{total} and annualized change in plasma NfL

Table 4 presents results from the structural equation model testing direct and indirect effects of AL_{total} on δNfL_{obs} through alternative AL_{comp}, while stratifying by sex and by race groups. Focusing on models with significant total effects, the indirect effect (IE) was statistically

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significant only for HbA1c as the primary mediating factor in the total sample (IE=+0.0031±0.0012, $p<0.05$; TE=+0.0062±0.0023, $p<0.05$; mediation proportion: 50%). Most other models with significant total effects (e.g. WHR, hsCRP, CHOL, SBP, DBP) of AL_{total} on δNfL_{obs}, indicated that another pathway was at play not including each of those AL_{comp}.

Supplementary Table 2 tests similar mediating effects but replacing AL_{total} with continuous AL_{comp} while examining them overall and by race and sex. The results indicate that HbA1c, overall and among women, is also among the main mediators in the relationship between BMI and δNfL_{obs}, as was the case for the AL_{total}-δNfL_{obs} association. Specifically, a TE of +0.00140±0.0004 ($p<0.001$) was detected among women, of which +0.00023±0.00011 ($p=0.028$) was explained by the IE of HbA1c at baseline (or a mediation proportion of 16.4%). A similar pattern was observed overall with a mediation proportion ~19%. There were no significant indirect effects of HbA1c detected among men, Whites or African Americans, in the association between BMI and δNfL_{obs}.

DISCUSSION

This study is the first to examine associations comprehensively and longitudinally between cardiometabolic risk factors and plasma NfL, particularly in a racially diverse community-based sample of middle-aged urban adults. Among our key findings, BMI and AL_{total} were associated with lower initial but faster increase in plasma NfL over time. hsCRP, serum total cholesterol, and resting heart rate at v_1 were linked with faster increase in plasma NfL over time overall. In SM analyses, the association of BMI with δNfL was significantly mediated through AL_{total} among women and overall was mediated through HbA1c levels.

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Previous studies

Plasma NfL and its association with neurocognitive outcomes:

NfL has been posited as a biomarker of neuronal injury and recently the development of sensitive and accurate methods to measure plasma NfL have led to the examination of whether this non-invasive biomarker may be an indicator of neurodegeneration. Cross-sectional studies have reported that plasma NfL is elevated in patients with MCI and AD and that these levels correlate with other neurocognitive measures (15). Individuals with mild cognitive impairment or with AD dementia had higher baseline plasma NfL and longitudinal analyses showed faster rates of NfL were correlated with rates of cognitive and imaging measures as well as CSF biomarker levels(2). In fact, serum/plasma NfL predicts future development of sporadic and familial AD and is associated with faster cognitive decline and also with brain structure alterations (3, 4, 42, 47). However, plasma NfL was associated with changes in brain white matter and AD but not with preclinical phases of AD in another study(43). In non-demented adults, plasma NfL also was associated with cognitive decline (45, 61). These data are indicative that plasma NfL may have value in monitoring neurodegenerative disease progression. Furthermore, these studies point to plasma NfL as an easily accessible biomarker that shows promise for delineating early neurodegeneration in the pre-symptomatic stages of AD.

Cardiometabolic risk and its association with neuro-cognitive outcomes:

The association of obesity and other cardiometabolic factors with dementia is complex. These complexities lie in when during the lifespan these factors are considered and that they are often accompanied by a myriad of risk factors. For example, midlife obesity is associated with a significant risk for dementia and structural brain changes (27, 32). However, closer in

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time to the onset of disease (~5-10 yrs) low BMI is associated with increased dementia risk, possibly due to behavioral changes that accompany dementia including reduced physical activity and caloric intake (62, 63). Our data agree with the association of midlife obesity with dementia risk as BMI was associated with a faster increase of plasma NfL over time. AL_{total} was also associated with a faster increase in plasma NfL over time, indicating that other cardiometabolic risk factors may also influence dementia risk. Cardiovascular risk factors including hsCRP, serum total cholesterol, and resting heart rate at v1 were components of AL_{total} that were linked to higher NfL longitudinally. Vascular disorders, such as hypertension, also have complex risk associations with dementia. Evidence indicates that hypertension at midlife increases risk for dementia but is protective or not a significant risk factor for the elderly (>80 years)(64-66). Taken together, modifiable cardiometabolic risk factors at midlife may have long-term consequences that affect dementia risk and may be amenable to interventions for at risk populations.

Cardiometabolic risk, adiposity and their association with plasma NfL:

Plasma NfL and CSF NfL levels increase with age. Aging is associated with chronic health conditions, in particular cardiometabolic risk. Therefore, cardiometabolic risk and other age associated disease processes may be potential explanations for the observed increases in NfL over the lifetime. Despite this, few studies have examined cardiometabolic risk factors and plasma NfL. and findings are contrary to expectations, which demonstrates the need for further research. For instance, recent studies suggest that there is an inverse relationship between BMI and plasma NfL in healthy samples(17) and several clinical samples, including individuals with Type 2 Diabetes (18), Multiple Sclerosis (17) and women with anorexia(67, 68) However, a few studies found no relationship between BMI and plasma NfL in healthy controls (18, 68). Furthermore, one study examining renal function, another aspect of cardiometabolic risk, found a significant, positive correlation between serum creatinine levels

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and plasma NfL in non-demented samples aged 60 or olderin both healthy controls and patients with diabetes (18). Finally, another study examining glucose metabolism, yet another aspect of cardiometabolic risk, found that, in patients with Type 1 Diabetes, those with more frequent and severe hypoglycemic episodes had significantly higher plasma NfL compared to those with less frequent and less severe hypoglycemic episodes(69). Notably, the plasma NfL levels did not differ between healthy controls and patients with Type 1 Diabetes who had fewer and less severe hypoglycemic episodes. This, in tandem with the fact that both Type 1 Diabetes groups showed no differences in their cardiometabolic profiles, suggests that hypoglycemia, in particular, is associated with plasma NfL, which may indicate neuronal damage.

Given the paucity of research in cardiometabolic risk and NfL, several of our study findings are novel. Our findings indicate that AL mediates the association between BMI and the rate of change in plasma NfL only among women. Thus, plasma NfL increase over time is determined by BMI in women, a relationship largely explained by the multi-morbidity index of AL_{total}, reflecting cardiometabolic risk. In contrast, among African Americans, the putative effect of BMI on rate of change in plasma NfL is largely a direct effect perhaps explained by other factors associated with global adiposity that are not part of the multi-morbidity index of AL_{total}. Sex and race differences in mediating effects of AL_{total} in the BMI-δNfL_{obs} relationship may be explained by the possible inadequacy of the summary score of AL in some sub-groups as opposed to the continuous AL_{comp}. Our additional analyses indicated that overall, HbA1c is the most likely mediator in the relationship between BMI and change in plasma NfL over time, given the observed significant total and indirect effects, suggesting that the adverse potential effect of BMI on NfL over time is at least in part explained by a co-occurrence of an elevated HbA1c with elevated BMI.

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Moreover, HbA1c was the component of AL that explained its total effect on rate of change in NfL reflecting glucose metabolism disorders. This continuous component of AL consistently explained the association overall between BMI and rate of change in NfL, with the mediation mostly detected among women. Finally, measures of inflammation, lipid metabolism and hemodynamics were all related to increased plasma NfL over time in the total sample, without affecting baseline values of plasma NfL. This was not the case for SBP and DBP, which were associated with lower NfL at first-visit, while having a direct relationship with increase in NfL over time. This suggests that in this population of urban middle-aged adults, these 3 components of AL may have utility in predicting the pace of increase in plasma NfL over time, independently of its initial value.

Strengths and limitations

Our study has several notable strengths. First, this study has included adequate numbers of African Americans to power subset analysis which is critical for the field to move forward and examine the differential risk of dementia among African Americans. It is the first study to examine these important research questions between cardiometabolic risk and plasma NfL. This suggests cardiometabolic risk may be important to consider when examining the clinical utility of plasma NfL for predicting neuro-cognitive outcomes. In addition, plasma NfL may be on a pathway through which cardiometabolic risk can influence neurocognitive outcomes. Second, we ascertained temporality of association with a longitudinal study design examining baseline exposures against change in outcomes over time. Third, the sample size is large and adequately powered to test those associations across sex and race groups. Fourth, advanced statistical techniques were used, including multiple linear mixed-effects regression and structural equation models to test those associations and their heterogeneity across sex and race, while adjusting for key potential confounders and for sample selectivity using 2-stage Heckman selection.

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Nevertheless, our study has at least one notable limitation, which is the relative young age of our sample, leading to a low baseline plasma NfL compared to previous studies with older participants. Thus, the rate of increase in plasma NfL may have occurred at a slower pace compared with older adults. Many studies have indicated that increased risk of adverse cognitive outcomes later in life is a function of cardiometabolic and related lifestyle risk factors at midlife (27, 28). Therefore, our study shows that a midlife putative marker of neurodegeneration may in fact be longitudinally associated with cardiometabolic risk among middle-aged adults.

Conclusions

In conclusion, we report an association between cardiometabolic risk and an increase over time in plasma NfL. The association of BMI with δNfL was mediated through AL_{total} in women; and were mainly explained by elevations in HbA1c. Given that NfL may be a pathway through which cardiometabolic risk can lead to neurodegeneration, prevention efforts aimed at reducing plasma NfL should target cardiometabolic risk factors, particularly reduction of HbA1c levels.

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AUTHOR CONTRIBUTION

MAB: Study concept, plan of analysis, data management, statistical analysis, literature search and review, write-up of the manuscript, revision of the manuscript.

NNH: Data acquisition, plan of analysis, literature search and review, write-up of parts of the manuscript, revision of the manuscript.

AIM: Plan of analysis, assistance with statistical methods, literature search and review, write-up of parts of the manuscript, revision of the manuscript.

HAB: Plan of analysis, literature search and review, write-up of parts of the manuscript, revision of the manuscript.

JW: Assistance with statistical analysis, literature search and review, write-up of parts of the manuscript, revision of the manuscript.

MKE: Data acquisition, write-up of parts of the manuscript, revision of the manuscript.

ABZ: Data acquisition, plan of analysis, write-up of parts of the manuscript, revision of the manuscript.

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CONFLICT OF INTEREST: None declared.

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TABLE 1. Study sample characteristics by sex and by race: HANDLS, 2004-2017[1]

	Overall (n=608)	Women (n =352)	Men (n =256)	P_{sex}	Whites (n =257)	African Americans (n =351)	P_{race}
Socio-demographic, lifestyle and health-related factors at v_1							
% men	42.1	0.0	100.0	__	39.7	43.9	0.30
% African American	57.7	56.0	60.2	0.30	0.0	100.0	__
Age, years	47.7±0.4	47.7±0.5	47.6±0.5	0.90	48.4±0.5	47.2±0.5	0.11
% below Poverty	27.0	28.1	25.4	0.45	26.1	27.6	0.67
Education, %							
<High School	4.9	5.0	4.7	0.78	6.8	3.4	0.093
High School	58.2	57.1	59.8	Ref	59.5	57.3	Ref
>High School	36.9	37.9	35.5	0.53	33.7	39.3	0.28
Current illicit drug use, % yes	15.6	9.7	23.7	<0.001[4]	12.3	18.0	0.058
Current tobacco use, % yes	40.0	38.9	46.1	0.084	40.5	43.0	0.54
Healthy Eating index, HEI-2010 total score	42.3±0.5	42.9±0.7	41.3±0.7	0.12	41.4±0.8	42.9±0.7	0.18
Energy intake, kcal/d	1993±40	1697±47	2399±71	<0.001[4]	1996±73	1991±63	0.97
CES-D total score	14.3±0.4	14.6±0.6	13.9±0.7	0.41	15.2±0.7	13.6±0.6	0.070 [4]
Body mass index at v1, BMI_{v1} ,kg.m^{-2}	30.3±0.3	31.8±0.4	31.8±0.4	<0.001[4]	30.4±0.5	30.2±0.4	0.84
Weight status at v_1, %							
Underwt.: BMI_{v1}<18.5 kg.m^{-2}	3.0	2.8	3.1	0.23	3.1	2.8	0.84
Normal: BMI_{v1}≥18.5, <25	20.9	16.2	27.3	<0.001[4]	19.8	21.7	0.72
Overwt.: BMI_{v1}≥25, <30	30.4	26.1	36.3	<0.001[4]	31.5	29.6	0.72
Obese: BMI_{v1}≥30	45.7	54.8	33.2	Ref	45.5	45.9	Ref
Allostatic load total score at v_1, AL_{total}	1.87±0.05	1.91±0.06	1.80±0.08	0.28	1.98±0.07	1.78±0.06	0.044
Continuous components of the allostatic load at v_1, AL_{comp}							
Waist:hip ratio, WHR	0.95±0.02	0.94±0.04	0.96±0.00	0.75	0.99±0.05	0.92±0.00	0.081
Serum albumin, g/dL	4.33±0.01	4.28±0.01	4.40±0.02	<0.001[4]	4.36±0.02	4.30±0.01	0.006 [4]
hsCRP, mg/L [2]	0.74±0.05	0.99±0.07	0.40±0.08	<0.001[4]	0.81±0.07	0.69±0.08	0.26
Glycated hemoglobin, HbA1C, %	5.85±0.04	5.85±0.05	5.86±0.06	0.93	5.83±0.06	5.87±0.04	0.55
Total cholesterol, mg/dL	186.1±1.7	190.2±2.2	180.5±2.6	0.004 [4]	189.6±2.7	183.6±2.1	0.075
HDL-cholesterol, mg/dL	53.5±0.7	55.9±0.9	50.3±1.1	<0.001[4]	50.2±0.9	56.0±1.0	<0.001[4]
Resting heart rate, beat/min	66.9±0.5	67.3±0.6	66.4±0.7	0.32	67.7±0.7	66.4±0.6	0.14
Systolic blood pressure, mm Hg	119.5±0.7	119.1±0.9	120.0±1.0	0.48	119.3±1.1	119.7±0.8	0.76
Diastolic blood pressure, mm Hg	72.9±0.4	71.7±0.5	74.5±0.7	0.001[4]	72.4±0.6	73.2±0.6	0.32
Plasma NfL, Log_e transformed							
NfL_{v1}	1.98±0.02	1.95±0.03	2.03±0.03	0.039 [4]	2.11±0.03	1.89±0.03	<0.001[4]
NfL_{v3}	2.35±0.02	2.28±0.03	2.44±0.04	0.002 [4]	2.41±0.04	2.30±0.03	0.038
δNfL_{obs} [3]	0.0492±0.0027	0.0462±0.0043	0.0532±0.0047	0.20	0.0468±0.0044	0.0508±0.0033	0.47

Abbreviations: AL_{comp}=Allostatic load continuous components; AL_{total}=Allostatic load total score; BMI=Body mass index; bayes=Empirical bayes estimator; CES-D=Center for Epidemiologic Studies-Depression; δ=Annualized rate of change; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; HDL=High Density Lipoprotein; HEI=Healthy Eating Index; Hg=mercury; hsCRP=High sensitivity C-reactive protein; NfL=plasma Neurofilament Light; Overwt.=Overweight; Underwt.=underweight; v_1=Visit 1; v_2=Visit 2; v_3=Visit 3; WHR=Waist:hip ratio.

[1] Values are means±SE for continuous variables or % for categorical variables.

[2] high sensitivity C-reactive protein (hsCRP) was Log_e transformed.

[3] Observed annual rate of change in NfL between v_1 and v_3, validated against the empirical bayes estimator predicted from mixed-effects linear regression model with NfL as outcome and *TIME* as the only predictor (Pearson's r>0.80). N=606. See **Table 4** for sample sizes within sex and race strata. 1 SD of δNfL_{obs} is 0.0665. All other SD can be obtained from this Table as sqrt(N)×SE to assess clinically meaningful effects.

[4] P<0.05 upon further adjustment for age, sex, race and poverty status in multiple linear and multinomial logit models.

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TABLE 2. Body mass index and weight status (at v_1) and their association with baseline and annualized change in plasma NfL between v_1 and v_3, overall and by sex and race: mixed-effects linear regression models; HANDLS, 2004-2017[1]

	Overall (n =608)	Women (n =352)	Men (n =256)	P_{sex} [2]	Whites (n =257)	African Americans (n =351)	P_{race} [3]
Model 1.A.							
BMI_{v1}, γ_{0a}	-0.015±0.002***	-0.014±0.003***	-0.016±0.005***	0.56	-0.014±0.004***	-0.014±0.003***	0.72
BMI_{v1}×*TIME*, γ_{1a}	+0.0012±0.0003***	+0.0011±0.0003***	+0.0014±0.0006**	0.65	+0.0007±0.0005	+0.0014±0.0004***	0.21
Model 2.A.							
BMI_{v1}, γ_{0a}	-0.014±0.002***	-0.013±0.003***	-0.016±0.005**	0.58	-0.014±0.004***	-0.013±0.003***	0.81
BMI_{v1}×*TIME*, γ_{1a}	+0.0012±0.0003***	+0.0012±0.0003***	+0.0014±0.0006*	0.60	+0.0008±0.005	+0.0013±0.0003***	0.15
Model 1.B.							
[Underwt. vs. Normal] , γ_{0a}	+0.170±0.103	+0.176±0.129	+0.160±0.165	1.00	+0.343±0.155*	+0.028±0.137	0.10
[Overwt. vs. Normal] , γ_{0a}	-0.085±0.047	-0.025±0.064	-0.122±0.071	0.27	+0.034±0.073	-0.163±0.052**	0.054
[Obese vs. Normal] , γ_{0a}	-0.245±0.045***	-0.223±0.057***	-0.245±0.072**	0.75	-0.177±0.069*	-0.281±0.059***	0.16
[Underwt. vs. Normal] ×*TIME*, γ_{1a}	-0.016±0.013	-0.003±0.016	-0.034±0.022	0.23	-0.015±0.019	-0.014±0.018	0.91
[Overwt. vs. Normal] ×*TIME*, γ_{1a}	+0.001±0.006	+0.009±0.008	+0.007±0.010	0.89	-0.002±0.009	+0.016±0.008*	0.15
[Obese vs. Normal] ×*TIME*, γ_{1a}	+0.017±0.006**	+0.023±0.007**	+0.010±0.010	0.22	+0.011±0.009	+0.022±0.008**	0.39
Model 2.B.							
[Underwt. vs. Normal] , γ_{0a}	+0.138±0.104	+0.109±0.127	+0.163±0.167	0.95	+0.344±0.155*	-0.020±0.137	0.093
[Overwt. vs. Normal] , γ_{0a}	-0.077±0.047	-0.015±0.062	-0.115±0.072	0.27	+0.041±0.073	-0.156±0.062*	0.061
[Obese vs. Normal] , γ_{0a}	-0.234±0.045***	-0.206±0.056***	-0.239±0.074**	0.70	-0.171±0.070*	-0.274±0.060***	0.17
[Underwt. vs. Normal] ×*TIME*, γ_{1a}	-0.018±0.013	-0.005±0.016	-0.036±0.022	0.20	-0.023±0.019	-0.011±0.018	0.91
[Overwt. vs. Normal] ×*TIME*, γ_{1a}	+0.009±0.006	+0.009±0.008	+0.006±0.010	0.94	-0.002±0.009	+0.015±0.008	0.14
[Obese vs. Normal] ×*TIME*, γ_{1a}	+0.017±0.006**	+0.0237±0.007**	+0.008±0.010	0.23	+0.014±0.009	+0.020±0.008*	0.34

Abbreviations: BMI=Body mass index; CES-D=Center for Epidemiologic Studies-Depression; δ=Annualized rate of change; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; HEI=Healthy Eating Index; NfL=plasma Neurofilament Light; Overwt.=Overweight; Underwt.=underweight; v_1=Visit 1; v_2=Visit 2; v_3=Visit 3.

[1] Values are fixed effects γ±SE. Models 1A.-1B included each of v_1 BMI and weight status, z-scored), separately as the main predictor for v1 NfL and NfL annualized change over time (δNfL), using a series of mixed-effects linear regression models, carried out in the overall population, and stratified by sex and by race, separately. These models adjusted only for age, sex, race, poverty status, educational attainment and the inverse mills ratio. Models 2A-2B followed a similar approach but adjusted further for selected lifestyle and health-related factors, namely current drug use, current tobacco use, HEI-2010, total energy intake, and the CES-D total score.

[2] P_{sex} are based on separate models testing the statistical significance for Sex×BMI/[weight status] and Sex×BMI/[weight status] ×TIME in models that are unstratified by sex or race to which these 2-way and 3-way interaction terms were included for each socio-demographic factor, separately.

[3] P_{race} are based on separate models testing the statistical significance for Race×BMI/[weight status] and Race×BMI/[weight status] ×TIME in models that are unstratified by sex or race to which these 2-way and 3-way interaction terms were included for each socio-demographic factor, separately.

*P<0.05; **P<0.010; ***P<0.001 for null hypothesis that fixed effect γ=0.

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TABLE 3. Allostatic load total score and components (at v_1) and its association with baseline and annualized change in plasma NfL between v_1 and v_3, overall and by sex and race: mixed-effects linear regression models; HANDLS, 2004-2017[1]

	Overall (n =608)	Women (n =352)	Men (n =256)	P_{sex} [3]	Whites (n =257)	African Americans (n =351)	P_{race} [4]
Model 1.A.							
AL_{total}, γ_{0a}	-0.038±0.015*	-0.029±0.019	-0.039±0.023	0.52	-0.005±0.023	-0.057±0.020**	0.15
AL_{total}×*TIME*, γ_{1a}	+0.0066±0.0018***	+0.006±0.002**	+0.008±0.003*	0.75	+0.004±0.003	+0.008±0.002**	0.25
Model 2.A.							
AL_{total}, γ_{0a}	-0.033±0.015*	-0.027±0.018	-0.037±0.024	0.68	-0.003±0.023	-0.050±0.019*	0.65
AL_{total} ×*TIME*, γ_{1a}	+0.0067±0.0018***	+0.006±0.002**	+0.008±0.003*	0.75	+0.004±0.003	+0.008±0.002**	0.19
Model 1.B.							
WHR, γ_{0a}	+0.053±0.033	+0.063±0.030*	-1.247±0.465**	<0.001	+0.065±0.032	-1.047±0.349**	0.008
WHR×*TIME*, γ_{1a}	+0.004±0.004	+0.003±0.004	+0.119±0.062	0.066	+0.0035±0.0040	+0.074±0.045	0.084
Model 2.B.							
WHR, γ_{0a}	+0.053±0.032	+0.064±0.029*	-1.179±0.474*	0.001	+0.064±0.032	-0.991±0.345**	0.008
WHR ×*TIME*, γ_{1a}	+0.005±0.004	+0.003±0.004	+0.112±0.063	0.077	+0.0034±0.0039	+0.0711±0.044	0.064
Model 1.C.							
ALB, γ_{0a}	-0.092±0.064	+0.045±0.078	-0.301±0.106**	0.004	-0.064±0.101	-0.127±0.083	0.90
ALB×*TIME*, γ_{1a}	+0.014±0.008	+0.003±0.010	+0.029±0.014*	0.14	+0.010±0.012	+0.017±0.011	0.56
Model 2.C.							
ALB, γ_{0a}	-0.107±0.064	+0.007±0.077	-0.303±0.107**	0.006	-0.062±0.102	-0.146±0.082	0.81
ALB ×*TIME*, γ_{1a}	+0.013±0.008	+0.003±0.010	+0.027±0.014	0.17	+0.007±0.012	+0.017±0.011	0.46
Model 1.D. [2]							
hsCRP, γ_{0a}	-0.008±0.008	-0.015±0.010	+0.004±0.014	0.19	-0.010±0.012	-0.008±0.011	0.90
hsCRP×*TIME*, γ_{1a}	+0.004±0.002*	+0.006±0.002**	+0.001±0.003	0.059	+0.005±0.003*	+0.003±0.002	0.53
Model 2.D. [2]							
hsCRP, γ_{0a}	-0.008±0.008	-0.015±0.010	+0.003±0.015	0.24	-0.010±0.013	-0.018±0.011	0.88
hsCRP×*TIME*, γ_{1a}	+0.004±0.002*	+0.006±0.002**	+0.001±0.003	0.074	+0.005±0.002*	+0.004±0.002	0.54
Model 1.E. [b]							
HbA1C, γ_{0a}	+0.026±0.019	+0.032±0.025	+0.015±0.028	0.78	+0.080±0.025**	-0.035±0.027	0.007
HbA1C×*TIME*, γ_{1a}	+0.0078±0.0023**	+0.0098±0.0052**	+0.0061±0.0036	0.35	+0.0084±0.0030**	+0.0068±0.0034*	0.70
Model 2.E. [b]							
HbA1C, γ_{0a}	+0.030±0.019	+0.030±0.024	+0.021±0.029	0.98	+0.076±0.025**	-0.024±0.028	0.021
HbA1C×*TIME*, γ_{1a}	+0.0076±0.0023**	+0.0099±0.0030**	+0.0055±0.0037	0.30	+0.0088±0.0029**	+0.0051±0.0035	0.60
Model 1.F.							
CHOL, γ_{0a}	-0.0004±0.0004	+0.0001±0.0005	-0.0011±0.0007	0.13	-0.0004±0.0006	-0.0004±0.0006	0.89
CHOL×*TIME*, γ_{1a}	+0.00014±0.00005**	+0.00006±0.00006	+0.00025±0.00009**	0.069	+0.00016±0.00007*	+0.00012±0.00007	0.66
Model 2.F.							
CHOL, γ_{0a}	-0.0004±0.0004	+0.0001±0.0005	-0.0011±0.0007	0.17	-0.0004±0.0006	-0.0004±0.0006	0.87
CHOL×*TIME*, γ_{1a}	+0.00014±0.00005**	+0.00006±0.00006	+0.00026±0.00009**	0.060	+0.00017±0.00007*	+0.00014±0.00007	0.69
Model 1.G.							
HDL-C, γ_{0a}	+0.0034±0.0010**	+0.0029±0.0013*	+0.0037±0.0017*	0.35	+0.0031±0.0019	+0.0034±0.0012**	0.88
HDL-C×*TIME*, γ_{1a}	-0.00017±0.00014	-0.00030±0.00016	-0.00002±0.00023	0.33	-0.00010±0.00024	-0.00018±0.00017	0.80
Model 2.G.							
HDL-C, γ_{0a}	+0.0030±0.0010**	+0.0025±0.0013	+0.0036±0.0017*	0.54	+0.0030±0.0019	+0.0028±0.0013*	0.89
HDL-C×*TIME*, γ_{1a}	-0.0002±0.0001	-0.00032±0.00017	-0.00001±0.00024	0.31	-0.00019±0.00024	-0.00013±0.00017	0.81
Model 1.H.							
RHR, γ_{0a}	-0.0017±0.0015	-0.0031±0.0020	-0.00043±0.0024	0.43	-0.00205±0.00231	-0.0018±0.0020	0.99
RHR×*TIME*, γ_{1a}	+0.00087±0.00019***	+0.00077±0.00024**	+0.00096±0.00031**	0.60	+0.00069±0.00028*	+0.00100±0.00026***	0.47
Model 2.H.							
RHR, γ_{0a}	-0.0019±0.0015	-0.0029±0.0019	-0.0005±0.0024	0.51	-0.00213±0.00230	-0.0017±0.0020	0.89
RHR×*TIME*, γ_{1a}	+0.00087±0.00019***	+0.00081±0.00024**	+0.00096±0.00031**	0.68	+0.00062±0.00028*	+0.0010±0.0002***	0.46
Model 1.I.							
SBP, γ_{0a}	-0.0033±0.0011**	-0.0037±0.0013**	-0.0023±0.0019	0.67	-0.0052±0.0016**	-0.0013±0.0016	0.023
SBP×*TIME*, γ_{1a}	+0.00040±0.00014**	+0.00019±0.00016	+0.00074±0.00025**	0.062	+0.00024±0.00019	+0.00056±0.00020**	0.36
Model 2.I.							
SBP, γ_{0a}	-0.0030±0.0011**	-0.0035±0.0013**	-0.0020±0.0010	0.64	-0.0049±0.0016**	-0.0007±0.0016	0.019
SBP×*TIME*, γ_{1a}	+0.00039±0.00014**	+0.0002±0.0002	+0.00070±0.00026**	0.063	+0.00021±0.00019	+0.00053±0.00020**	0.27
Model 1.J.							
DBP, γ_{0a}	-0.0052±0.0017**	-0.0082±0.0021***	-0.0012±0.0027	0.047	-0.0104±0.0026***	-0.0015±0.002	0.002
DBP×*TIME*, γ_{1a}	+0.0005±0.0002*	+0.0003±0.0003	+0.0007±0.0003*	0.32	+0.0003±0.0003	+0.00063±0.00027*	0.50
Model 2.J.							
DBP, γ_{0a}	-0.0045±0.0017**	-0.0071±0.0021**	-0.0010±0.0027	0.069	-0.0098±0.0027***	-0.0005±0.0021	0.002
DBP×*TIME*, γ_{1a}	+0.00048±0.00021*	+0.00034±0.00027	+0.00068±0.00034	0.32	+0.0002±0.0003	+0.00056±0.00028*	0.38

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Abbreviations: ALB=Albumin; AL_{comp}=Continuous components of the allostatic load; AL_{total}=Allostatic Load total score; CES-D=Center for Epidemiologic Studies-Depression; CHOL=Total cholesterol; δ=Annualized rate of change; DBP=Diastolic Blood Pressure; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; HbA1C=Glycated Hemoglobin; HDL-C=High Density Lipoprotein-cholesterol; HEI=Healthy Eating Index; RHR=Resting Heart Rate; hsCRP=High sensitivity C-reactive protein; NfL=plasma Neurofilament Light; Overwt.=Overweight; SBP=Systolic Blood Pressure; Underwt.=underweight; v_1=Visit 1; v_2=Visit 2; v_3=Visit 3.

[1] Values are fixed effects γ±SE. Models 1A-1J included each of v_1 AL_{total} and AL_{comp}, separately as the main predictor for v_1 NfL and NfL annualized change over time (δNfL), using a series of mixed-effects linear regression models, carried out in the overall population, and stratified by sex and by race, separately. These models adjusted only for age, sex, race, poverty status, educational attainment, and the inverse mills ratio. Models 2A-2I followed a similar approach but adjusted further for selected lifestyle and health-related factors, namely current drug use, current tobacco use, HEI-2010, total energy intake, and the CES-D total score.

[2] hsCRP was Log_e transformed. All the continuous predictors, including main exposure variables, were centered at their respective means.

[3] P_{sex} are based on separate models testing the statistical significance for Sex×AL and Sex×AL×TIME in models that are unstratified by sex or race to which these 2-way and 3-way interaction terms were included for each socio-demographic factor, separately.

[4] P_{race} are based on separate models testing the statistical significance for Race×AL and Race×AL×TIME in models that are unstratified by sex or race to which these 2-way and 3-way interaction terms were included for each socio-demographic factor, separately.

*P<0.05; **P<0.010; ***P<0.001 for null hypothesis that fixed effect γ=0.

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TABLE 4. AL_{total} (at v_1) → AL_{comp} (at v_1) → annualized change in NfL between v_1 and v_3 (δNfL_{obs}), overall and by sex and race: Structural equations model; HANDLS, 2004-2017[4]

	Overall (n =606)	Women (n =351)	Men (n =255)	P_{sex} [1]	Whites (n =255)	African Americans (n =351)	P_{race} [2]
WHR							
AL_{total}→WHR	**+0.0411±0.0185***	+0.0560±0.0333	**+0.0273±0.0027*****	0.39	+0.0600±0.0439	**+0.0277±0.0026*****	0.46
WHR→δNfL_{obs}	+0.0054±0.0051	+0.0038±0.0045	**+0.1989±0.0908***	0.032	+0.0045±0.0054	+0.0848±0.0592	0.18
AL_{total}→ δNfL_{obs}	**+0.0059±0.0023***	**+0.0098±0.0028*****	-0.0037±0.0046	0.012	**+0.0089±0.0038***	+0.0013±0.0033	0.13
Total effect (AL_{total})	**+0.0062±0.0023****	**+0.0101±0.0028*****	+0.0018±0.0040	---	**+0.0092±0.0038***	+0.0036±0.0029	---
Indirect effect (AL_{tota})	+0.0002±0.0002	+0.0002±0.0003	**+0.0054±0.0025***	---	+0.0003±0.0004	+0.0023±0.0017	---
ALB							
AL_{total}→ALB	**-0.0368±0.0093*****	**-0.0488±0.0126*****	-0.0179±0.0138	0.099	**-0.0391±0.0140****	**-0.0394±0.0126****	0.99
ALB→δNfL_{obs}	-0.0034±0.0101	-0.0057±0.0118	+0.0098±0.0178	0.47	-0.0311±0.0169	+0.0140±0.0124	0.031
AL_{total}→ δNfL_{obs}	**+0.0060±0.0023***	**+0.0098±0.0029****	+0.0019±0.0040	0.11	**+0.0079±0.0038***	+0.0041±0.0030	0.43
Total effect (AL_{total})	+0.0062±0.0023	**+0.0101±0.0028*****	+0.0018±0.0040	---	**+0.0092±0.0038***	+0.0036±0.0029	---
Indirect effect (AL_{total})	+0.0001±0.0004	+0.0003±0.0006	-0.0002±0.0003	---	+0.0012±0.0008	-0.0006±0.0005	---
hsCRP [3]							
AL_{total}→hsCRP	**+0.5602±0.0400*****	**+0.6194±0.0534*****	**+0.4928±0.0611*****	0.12	**+0.5687±0.0524*****	**+0.5377±0.0580*****	0.69
hsCRP→δNfL_{obs}	-0.0009±0.0024	+0.0018±0.0028	-0.0055±0.0040	0.13	-0.0011±0.0045	-0.001±0.0027	0.98
AL_{total}→ δNfL_{obs}	**+0.0067±0.0027***	**+0.0090±0.0033****	+0.0045±0.0044	0.41	**+0.0098±0.0046***	+0.0041±0.0033	0.31
Total effect (AL_{total})	**+0.0062±0.0023****	**+0.0101±0.0028*****	+0.0017±0.0040	---	+0.0092±0.0038	+0.0036±0.0029	---
Indirect effect (AL_{total})	-0.0005±0.0013	+0.0011±0.0017	-0.0027±0.0020	---	-0.0006±0.0026	-0.0005±0.0014	---
HbA1C							
AL_{total}→HbA1C	**+0.3657±0.0285*****	**+0.3922±0.0347*****	**+0.3544±0.0479*****	0.52	**+0.4169±0.0490*****	**+0.3200±0.0338*****	0.10
HbA1C→δNfL_{obs}	**+0.0085±0.0033****	+0.0072±0.0043	+0.0098±0.0051	0.71	+0.0074±0.0048	**+0.0095±0.0046***	0.76
AL_{total}→ δNfL_{obs}	+0.0030±0.0026	**+0.0073±0.0032***	-0.0017±0.0043	0.10	+0.0061±0.0043	+0.0006±0.0033	0.31
Total effect (AL_{total})	**+0.0062±0.0023***	**+0.0101±0.0028*****	+0.0018±0.0040	---	+0.0092±0.0038	+0.0036±0.0029	---
Indirect effect (AL_{total})	**+0.0031±0.0012***	+0.0028±0.0017	+0.0035±0.0019	---	+0.0031±0.0020	**+0.0030±0.0015***	---
CHOL							
AL_{total}→CHOL	**+4.555±1.4354****	+2.4277±1.9497	**+7.4950±2.1194*****	0.079	**+5.8848±2.3200***	**+3.8843±1.8562***	0.50
CHOL→δNfL_{obs}	+0.0000±0.0001	+0.0000±0.0001	+0.0000±0.0001	0.86	-0.0001±0.0001	+0.0001±0.0001	0.23
AL_{total}→ δNfL_{obs}	**+0.0061±0.0023****	**+0.0100±0.0028*****	+0.0016±0.0040	0.088	**+0.0095±0.0038***	+0.0032±0.0029	0.19
Total effect (AL_{total})	**+0.0062±0.0023****	+0.0101±0.0028	+0.0017±0.0040	---	+0.0092±0.0038	+0.0036±0.0029	---
Indirect effect (AL_{total})	+0.0001±0.0003	+0.0001±0.0002	+0.0002±0.0009	---	-0.0003±0.0006	+0.0004±0.0004	---
HDL-C							
AL_{total}→HDL-C	**-5.7701±0.5346*****	**-5.3073±0.7133*****	**-6.0073±0.8018*****	0.51	-4.9331±0.6840	-6.2943±0.7649	0.18
HDL-C→δNfL_{obs}	-0.0001±0.0002	-0.0001±0.0002	-0.0001±0.0003	0.96	-0.0002±0.0003	+0.0000±0.0002	0.35
AL_{total}→ δNfL_{obs}	**+0.0058±0.0025***	**+0.0097±0.0030****	+0.0014±0.0044	0.12	**+0.0084±0.0042***	+0.0035±0.0032	0.72
Total effect (AL_{total})	+0.0062±0.0023	**+0.0101±0.0028*****	+0.0017±0.0040	---	+0.0092±0.0038	+0.0036±0.0029	---
Indirect effect (AL_{total})	+0.0004±0.0010	+0.0004±0.0011	+0.0004±0.0019	---	+0.0008±0.0017	+0.0001±0.0013	---
RHR							
AL_{total}→RHR	**+2.7833±0.3786*****	**+2.7503±0.4903*****	**+3.1124±0.5822*****	0.63	**+3.0838±0.5950*****	**+2.7980±0.4917*****	0.71
RHR→δNfL_{obs}	+0.0003±0.0002	+0.0003±0.0003	+0.0004±0.0004	0.85	+0.0001±0.0004	+0.0005±0.0003	0.48
AL_{total}→ δNfL_{obs}	**+0.0052±0.0024***	**+0.0093±0.0029****	+0.0005±0.0042	0.085	**+0.0088±0.0040***	+0.0022±0.0030	0.19
Total effect (AL_{total})	**+0.0062±0.0023****	**+0.0101±0.0028*****	+0.0018±0.0040	---	**+0.0092±0.0038***	+0.0036±0.0029	…
Indirect effect (AL_{total})	+0.0010±0.0007	+0.0008±0.0008	+0.0012±0.0013	---	+0.0004±0.0012	+0.0014±0.0009	---
SBP							
AL_{total}→SBP	**+5.5879±0.4957*****	**+6.0208±0.6872*****	**+4.8958±0.7195*****	0.26	**+6.0278±0.8259*****	**+5.2905±0.6207*****	0.48
SBP→δNfL_{obs}	+0.0045±0.0025	+0.0002±0.0002	+0.0004±0.0003	0.54	+0.0003±0.0003	+0.0003±0.0003	0.91
AL_{total}→ δNfL_{obss}	+0.0003±0.0002	**+0.0091±0.0031****	-0.0003±0.0043	0.076	+0.0076±0.0042	+0.0020±0.0032	0.28
Total effect (AL_{total})	**+0.0062±0.0023***	**+0.0101±0.0028*****	+0.0017±0.0040	---	**+0.0092±0.0038***	+0.0036±0.0029	---
Indirect effect (AL_{total})	+0.0016±0.0011	+0.0010±0.0013	+0.0020±0.0017	---	+0.0016±0.0017	+0.0016±0.0013	---
DBP							
AL_{total}→DBP	**+3.1337±0.3384*****	**+3.2288±0.4412*****	**+2.9112±0.5342*****	0.65	**+2.7516±0.5047*****	**+3.4213±0.4603*****	0.33
DBP→δNfL_{obs}	+0.0001±0.0003	-0.0001±0.0003	+0.0003±0.0005	0.41	+0.0000±0.0005	+0.0001±0.0003	0.90
AL_{total}→ δNfL_{obs}	**+0.0059±0.0025***	**+0.0105±0.0030*****	+0.0008±0.0042	0.057	**+0.0091±0.0040***	+0.0032±0.0031	0.25
Total effect (AL_{total})	**+0.0062±0.0023****	**+0.0101±0.0028*****	+0.0017±0.0040	---	**+0.0092±0.0038***	+0.0036±0.0029	---
Indirect effect (AL_{total})	+0.0003±0.0009	-0.0004±0.0011	+0.0010±0.0014	---	+0.0001±0.0013	+0.0004±0.0012	---

Abbreviations: ALB=Albumin; AL_{comp}=Continuous components of the allostatic load; AL_{total}=Allostatic Load total score; CES-D=Center for Epidemiologic Studies-Depression; CHOL=Total cholesterol; δ=Annualized rate of change; DBP=Diastolic Blood Pressure; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; HbA1C=Glycated Hemoglobin; HDL-C=High Density Lipoprotein-cholesterol; HEI=Healthy Eating Index; RHR=Resting Heart Rate; hsCRP=High sensitivity C-reactive Protein; NfL=plasma Neurofilament Light; SBP=Systolic Blood Pressure; v_1=Visit 1; v_2=Visit 2; v_3=Visit 3.

[1] *P*-value associated with null hypothesis of no difference in path coefficient α, by sex, using Wald test (χ^2 test, 1 d.f.) for group invariance.

[2] *P*-value associated with null hypothesis of no difference in path coefficient α, by race, using Wald test (χ^2 test, 1 d.f.) for group invariance.

[3] hsCRP was Log_e transformed.

[4] Exogenous variables in the models were: age, sex, race, poverty status, educational attainment, current drug use, current tobacco use, HEI-2010, total energy intake, the CES-D total score and the inverse mills ratio.

*P<0.05; **P<0.010; ***P<0.001 for null hypothesis that path coefficient α=0.

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REFERENCES

1. Zhao Y, Xin Y, Meng S, He Z, Hu W. Neurofilament light chain protein in neurodegenerative dementia: A systematic review and network meta-analysis. Neurosci Biobehav Rev. 2019 Jul;102:123-38.
2. Mattsson N, Cullen NC, Andreasson U, Zetterberg H, Blennow K. Association Between Longitudinal Plasma Neurofilament Light and Neurodegeneration in Patients With Alzheimer Disease. JAMA Neurol. 2019 Jul 1;76:791-9.
3. Preische O, Schultz SA, Apel A, Kuhle J, Kaeser SA, Barro C, Graber S, Kuder-Buletta E, LaFougere C, Laske C, et al. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. Nat Med. 2019 Feb;25:277-83.
4. Weston PSJ, Poole T, O'Connor A, Heslegrave A, Ryan NS, Liang Y, Druyeh R, Mead S, Blennow K, Schott JM, et al. Longitudinal measurement of serum neurofilament light in presymptomatic familial Alzheimer's disease. Alzheimers Res Ther. 2019 Feb 20;11:19.
5. Scherling CS, Hall T, Berisha F, Klepac K, Karydas A, Coppola G, Kramer JH, Rabinovici G, Ahlijanian M, Miller BC, et al. Cerebrospinal fluid neurofilament concentration reflects disease severity in frontotemporal degeneration. Ann Neurol. 2014 Jan;75:116-26.
6. Teunissen CE, Dijkstra C, Polman C. Biological markers in CSF and blood for axonal degeneration in multiple sclerosis. Lancet Neurol. 2005 Jan;4:32-41.
7. Shahim P, Gren M, Liman V, Andreasson U, Norgren N, Tegner Y, Mattsson N, Andreasen N, Ost M, Zetterberg H, et al. Serum neurofilament light protein predicts clinical outcome in traumatic brain injury. Sci Rep. 2016 Nov 7;6:36791.
8. Khalil M, Teunissen CE, Otto M, Piehl F, Sormani MP, Gattringer T, Barro C, Kappos L, Comabella M, Fazekas F, et al. Neurofilaments as biomarkers in neurological disorders. Nat Rev Neurol. 2018 Oct;14:577-89.
9. Beydoun MA, Noren Hooten N, Beydoun HA, Maldonado AI, Weiss J, Evans MK, Zonderman AB. Plasma neurofilament light as a potential biomarker for cognitive decline in a longitudinal study of middle-aged urban adults. Transl Psychiatry. 2021 Aug 21;11:436.
10. He L, Morley JE, Aggarwal G, Nguyen AD, Vellas B, de Souto Barreto P, Group MD. Plasma neurofilament light chain is associated with cognitive decline in non-dementia older adults. Sci Rep. 2021 Jun 28;11:13394.
11. Weston PSJ, Poole T, Ryan NS, Nair A, Liang Y, Macpherson K, Druyeh R, Malone IB, Ahsan RL, Pemberton H, et al. Serum neurofilament light in familial Alzheimer disease: A marker of early neurodegeneration. Neurology. 2017 Nov 21;89:2167-75.
12. Sanchez-Valle R, Heslegrave A, Foiani MS, Bosch B, Antonell A, Balasa M, Llado A, Zetterberg H, Fox NC. Serum neurofilament light levels correlate with severity measures and neurodegeneration markers in autosomal dominant Alzheimer's disease. Alzheimers Res Ther. 2018 Nov 3;10:113.
13. Raket LL, Kuhnel L, Schmidt E, Blennow K, Zetterberg H, Mattsson-Carlgren N. Utility of plasma neurofilament light and total tau for clinical trials in Alzheimer's disease. Alzheimers Dement (Amst). 2020;12:e12099.
14. Hansson O, Janelidze S, Hall S, Magdalinou N, Lees AJ, Andreasson U, Norgren N, Linder J, Forsgren L, Constantinescu R, et al. Blood-based NfL: A biomarker for differential diagnosis of parkinsonian disorder. Neurology. 2017 Mar 7;88:930-7.
15. Mattsson N, Andreasson U, Zetterberg H, Blennow K, Alzheimer's Disease Neuroimaging I. Association of Plasma Neurofilament Light With Neurodegeneration in Patients With Alzheimer Disease. JAMA Neurol. 2017 May 1;74:557-66.
16. Jin M, Cao L, Dai YP. Role of Neurofilament Light Chain as a Potential Biomarker for Alzheimer's Disease: A Correlative Meta-Analysis. Front Aging Neurosci. 2019;11:254.
17. Manouchehrinia A, Piehl F, Hillert J, Kuhle J, Alfredsson L, Olsson T, Kockum I. Confounding effect of blood volume and body mass index on blood neurofilament light chain levels. Ann Clin Transl Neurol. 2020 Jan;7:139-43.
18. Akamine S, Marutani N, Kanayama D, Gotoh S, Maruyama R, Yanagida K, Sakagami Y, Mori K, Adachi H, Kozawa J, et al. Renal function is associated with blood neurofilament light chain level in older adults. Sci Rep. 2020 Nov 23;10:20350.

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19. Artegoitia VM, Krishnan S, Bonnel EL, Stephensen CB, Keim NL, Newman JW. Healthy eating index patterns in adults by sex and age predict cardiometabolic risk factors in a cross-sectional study. BMC Nutr. 2021 Jun 22;7:30.
20. Mousavi SM, Milajerdi A, Pouraram H, Saadatnia M, Shakeri F, Keshteli AH, Tan SC, Esmaillzadeh A. Adherence to Alternative Healthy Eating Index (AHEI-2010) is not associated with risk of stroke in Iranian adults: A case-control study. Int J Vitam Nutr Res. 2021 Jan;91:48-55.
21. Sullivan VK, Petersen KS, Fulgoni VL, 3rd, Eren F, Cassens ME, Bunczek MT, Kris-Etherton PM. Greater Scores for Dietary Fat and Grain Quality Components Underlie Higher Total Healthy Eating Index-2015 Scores, While Whole Fruits, Seafood, and Plant Proteins Are Most Favorably Associated with Cardiometabolic Health in US Adults. Curr Dev Nutr. 2021 Mar;5:nzab015.
22. Millar SR, Navarro P, Harrington JM, Perry IJ, Phillips CM. Dietary Quality Determined by the Healthy Eating Index-2015 and Biomarkers of Chronic Low-Grade Inflammation: A Cross-Sectional Analysis in Middle-to-Older Aged Adults. Nutrients. 2021 Jan 14;13.
23. Lim CGY, Whitton C, Rebello SA, van Dam RM. Diet Quality and Lower Refined Grain Consumption are Associated With Less Weight Gain in a Multi-Ethnic Asian Adult Population. J Nutr. 2021 Aug 7;151:2372-82.
24. Fanelli Kuczmarski M, Hossain S, Beydoun MA, Maldonando A, Evans MK, Zonderman AB. Association of DASH and Depressive Symptoms with BMI over Adulthood in Racially and Socioeconomically Diverse Adults Examined in the HANDLS Study. Nutrients. 2019 Dec 3;11.
25. Wang Y, Beydoun MA. The obesity epidemic in the United States--gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. Epidemiol Rev. 2007;29:6-28.
26. Wang Y, Beydoun MA, Min J, Xue H, Kaminsky LA, Cheskin LJ. Has the prevalence of overweight, obesity and central obesity levelled off in the United States? Trends, patterns, disparities, and future projections for the obesity epidemic. Int J Epidemiol. 2020 Jun 1;49:810-23.
27. Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. Obes Rev. 2008 May;9:204-18.
28. Beydoun MA, Kivimaki M. Midlife obesity, related behavioral factors, and the risk of dementia in later life. Neurology. 2020 Jan 14;94:53-4.
29. Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, Deal JA, McKhann GM, Mosley TH, Sharrett AR. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. JAMA neurology. 2017;74:1246-54.
30. Atti AR, Valente S, Iodice A, Caramella I, Ferrari B, Albert U, Mandelli L, De Ronchi D. Metabolic syndrome, mild cognitive impairment, and dementia: a meta-analysis of longitudinal studies. The American Journal of Geriatric Psychiatry. 2019;27:625-37.
31. Legdeur N, Van Der Lee SJ, De Wilde M, Van Der Lei J, Muller M, Maier AB, Visser PJ. The association of vascular disorders with incident dementia in different age groups. Alzheimer's research & therapy. 2019;11:1-8.
32. Driscoll I, Beydoun MA, An Y, Davatzikos C, Ferrucci L, Zonderman AB, Resnick SM. Midlife obesity and trajectories of brain volume changes in older adults. Hum Brain Mapp. 2012 Sep;33:2204-10.
33. de la Torre J. The vascular hypothesis of Alzheimer’s disease: a key to preclinical prediction of dementia using neuroimaging. Journal of Alzheimer's Disease. 2018;63:35-52.
34. Gomez G, Beason-Held LL, Bilgel M, An Y, Wong DF, Studenski S, Ferrucci L, Resnick SM. Metabolic syndrome and amyloid accumulation in the aging brain. Journal of Alzheimer's Disease. 2018;65:629-39.
35. Li D, Hagen C, Fett AR, Bui HH, Knopman D, Vemuri P, Machulda MM, Jack Jr CR, Petersen RC, Mielke MM. Longitudinal association between phosphatidylcholines, neuroimaging measures of Alzheimer's disease pathophysiology, and cognition in the Mayo Clinic Study of Aging. Neurobiology of aging. 2019;79:43-9.
36. Spinelli M, Fusco S, Grassi C. Brain insulin resistance and hippocampal plasticity: mechanisms and biomarkers of cognitive decline. Frontiers in neuroscience. 2019;13:788.

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37. Suzuki H, Venkataraman AV, Bai W, Guitton F, Guo Y, Dehghan A, Matthews PM. Associations of regional brain structural differences with aging, modifiable risk factors for dementia, and cognitive performance. JAMA network open. 2019;2:e1917257-e.
38. Van Etten EJ, Bharadwaj PK, Nguyen LA, Hishaw GA, Trouard TP, Alexander GE. Right hippocampal volume mediation of subjective memory complaints differs by hypertension status in healthy aging. Neurobiology of Aging. 2020;94:271-80.
39. Sánchez-Benavides G, Suárez-Calvet M, Milà-Alomà M, Arenaza-Urquijo EM, Grau-Rivera O, Operto G, Gispert JD, Vilor-Tejedor N, Sala-Vila A, Crous-Bou M. Amyloid-β positive individuals with subjective cognitive decline present increased CSF Neurofilament Light levels that relates to lower hippocampal volume. Neurobiology of Aging. 2021.
40. de Wolf F, Ghanbari M, Licher S, McRae-McKee K, Gras L, Weverling GJ, Wermeling P, Sedaghat S, Ikram MK, Waziry R. Plasma tau, neurofilament light chain and amyloid-β levels and risk of dementia; a population-based cohort study. Brain. 2020;143:1220-32.
41. Olsson B, Portelius E, Cullen NC, Sandelius Å, Zetterberg H, Andreasson U, Höglund K, Irwin DJ, Grossman M, Weintraub D. Association of cerebrospinal fluid neurofilament light protein levels with cognition in patients with dementia, motor neuron disease, and movement disorders. JAMA neurology. 2019;76:318-25.
42. Rajan KB, Aggarwal NT, McAninch EA, Weuve J, Barnes LL, Wilson RS, DeCarli C, Evans DA. Remote Blood Biomarkers of Longitudinal Cognitive Outcomes in a Population Study. Ann Neurol. 2020 Dec;88:1065-76.
43. Nyberg L, Lundquist A, Nordin Adolfsson A, Andersson M, Zetterberg H, Blennow K, Adolfsson R. Elevated plasma neurofilament light in aging reflects brain white-matter alterations but does not predict cognitive decline or Alzheimer's disease. Alzheimers Dement (Amst). 2020;12:e12050.
44. He L, de Souto Barreto P, Aggarwal G, Nguyen AD, Morley JE, Li Y, Bateman RJ, Vellas B, Group MD. Plasma Abeta and neurofilament light chain are associated with cognitive and physical function decline in non-dementia older adults. Alzheimers Res Ther. 2020 Oct 8;12:128.
45. Mielke MM, Syrjanen JA, Blennow K, Zetterberg H, Vemuri P, Skoog I, Machulda MM, Kremers WK, Knopman DS, Jack C et al. Plasma and CSF neurofilament light: Relation to longitudinal neuroimaging and cognitive measures. Neurology. 2019 Jul 16;93:e252-e60.
46. Merluzzi AP, Vogt NM, Norton D, Jonaitis E, Clark LR, Carlsson CM, Johnson SC, Asthana S, Blennow K, Zetterberg H, et al. Differential effects of neurodegeneration biomarkers on subclinical cognitive decline. Alzheimers Dement (N Y). 2019;5:129-38.
47. de Wolf F, Ghanbari M, Licher S, McRae-McKee K, Gras L, Weverling GJ, Wermeling P, Sedaghat S, Ikram MK, Waziri R, et al. Plasma tau, neurofilament light chain and amyloid-beta levels and risk of dementia; a population-based cohort study. Brain. 2020 Apr 1;143:1220-32.
48. Peterson RL, Fain MJ, A. Butler E, Ehiri JE, Carvajal SC. The role of social and behavioral risk factors in explaining racial disparities in age-related cognitive impairment: A structured narrative review. Aging, Neuropsychology, and Cognition. 2020;27:173-96.
49. Morris JC, Schindler SE, McCue LM, Moulder KL, Benzinger TL, Cruchaga C, Fagan AM, Grant E, Gordon BA, Holtzman DM. Assessment of racial disparities in biomarkers for Alzheimer disease. JAMA neurology. 2019;76:264-73.
50. Levine DA, Gross AL, Briceño EM, Tilton N, Giordani BJ, Sussman JB, Hayward RA, Burke JF, Hingtgen S, Elkind MS. Sex Differences in Cognitive Decline Among US Adults. JAMA network open. 2021;4:e210169-e.
51. Zahodne LB, Manly JJ, Smith J, Seeman T, Lachman ME. Socioeconomic, health, and psychosocial mediators of racial disparities in cognition in early, middle, and late adulthood. Psychology and aging. 2017;32:118.
52. Seeman T, Merkin SS, Crimmins E, Koretz B, Charette S, Karlamangla A. Education, income and ethnic differences in cumulative biological risk profiles in a national sample of US adults: NHANES III (1988-1994). Social science & medicine. 2008 Jan;66:72-87.
53. Bureau UC. US Census Bureau, Social, Economic, and Housing Statistics Division. [accessed January 2016] Poverty Thresholds, 2004. 2014. 2004.

ORIGINAL UNEDITED MANUSCRIPT

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54. Beydoun MA, Hossain S, Beydoun HA, Shaked D, Weiss J, Evans MK, Zonderman AB. Red Cell Distribution Width Is Directly Associated with Poor Cognitive Performance among Nonanemic, Middle-Aged, Urban Adults. J Nutr. 2020 Jan 1;150:128-39.
55. Nguyen HT, Kitner-Triolo M, Evans MK, Zonderman AB. Factorial invariance of the CES-D in low socioeconomic status African Americans compared with a nationally representative sample. Psychiatry Res. 2004 Apr 30;126:177-87.
56. STATA. Statistics/Data Analysis: Release 16.0. Texas: Stata Corporation; 2019.
57. Beydoun HA, Huang S, Beydoun MA, Hossain S, Zonderman AB. 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. 2019 Sep 29;11.
58. Beydoun MA, Beydoun HA, Mode N, Dore GA, Canas JA, Eid SM, Zonderman AB. Racial disparities in adult all-cause and cause-specific mortality among us adults: mediating and moderating factors. BMC Public Health. 2016 Oct 22;16:1113.
59. Beydoun MA, Beydoun HA, Kitner-Triolo MH, Kaufman JS, Evans MK, Zonderman AB. Thyroid hormones are associated with cognitive function: moderation by sex, race, and depressive symptoms. J Clin Endocrinol Metab. 2013 Aug;98:3470-81.
60. Selvin S. Statistical Analysis of Epidemiologic Data. 3rd ed: Oxford University Press; 2004.
61. Dorst J, Schuster J, Dreyhaupt J, Witzel S, Weishaupt JH, Kassubek J, Weiland U, Petri S, Meyer T, Grehl T, et al. Effect of high-caloric nutrition on serum neurofilament light chain levels in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2020 Sep;91:1007-9.
62. Albanese E, Launer LJ, Egger M, Prince MJ, Giannakopoulos P, Wolters FJ, Egan K. Body mass index in midlife and dementia: Systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies. Alzheimers Dement (Amst). 2017;8:165-78.
63. Kivimaki M, Luukkonen R, Batty GD, Ferrie JE, Pentti J, Nyberg ST, Shipley MJ, Alfredsson L, Fransson EI, Goldberg M, et al. Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. Alzheimers Dement. 2018 May;14:601-9.
64. Legdeur N, van der Lee SJ, de Wilde M, van der Lei J, Muller M, Maier AB, Visser PJ. The association of vascular disorders with incident dementia in different age groups. Alzheimers Res Ther. 2019 May 17;11:47.
65. Corrada MM, Hayden KM, Paganini-Hill A, Bullain SS, DeMoss J, Aguirre C, Brookmeyer R, Kawas CH. Age of onset of hypertension and risk of dementia in the oldest-old: The 90+ Study. Alzheimers Dement. 2017 Feb;13:103-10.
66. de la Torre J. The Vascular Hypothesis of Alzheimer's Disease: A Key to Preclinical Prediction of Dementia Using Neuroimaging. J Alzheimers Dis. 2018;63:35-52.
67. Nielsen HH, Soares CB, Hogedal SS, Madsen JS, Hansen RB, Christensen AA, Madsen C, Clausen BH, Frich LH, Degn M, et al. Acute Neurofilament Light Chain Plasma Levels Correlate With Stroke Severity and Clinical Outcome in Ischemic Stroke Patients. Front Neurol. 2020;11:448.
68. Wentz E, Dobrescu SR, Dinkler L, Gillberg C, Gillberg C, Blennow K, Rastam M, Zetterberg H. Thirty years after anorexia nervosa onset, serum neurofilament light chain protein concentration indicates neuronal injury. Eur Child Adolesc Psychiatry. 2020 Oct 11.
69. Sampedro F, Stantonyonge N, Martinez-Horta S, Alcolea D, Lleo A, Munoz L, Perez-Gonzalez R, Marin-Lahoz J, Gomez-Anson B, Chico A. Increased plasma neurofilament light chain levels in patients with type-1 diabetes with impaired awareness of hypoglycemia. BMJ Open Diabetes Res Care. 2020 Jul;8.

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FIGURE 1

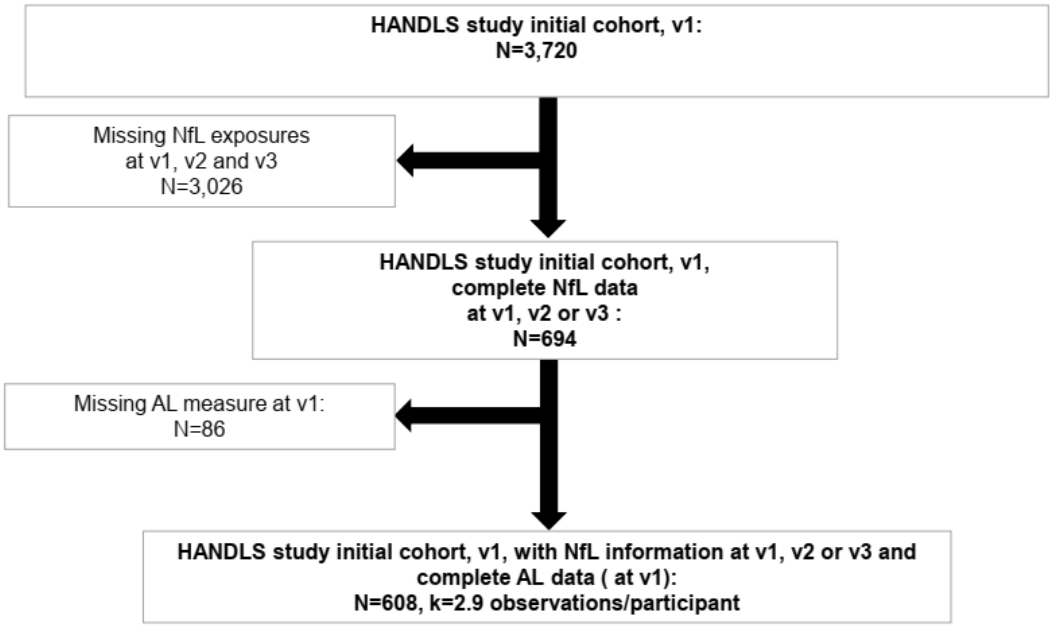

FIGURE 1. PARTICIPANT FLOWCHART

Abbreviations: AL=Allostatic Load; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; NfL=plasma Neurofilament Light; v_1=Visit 1; v_2=Visit 2; v_3=Visit 3.

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Figure 2
FIGURE 2.

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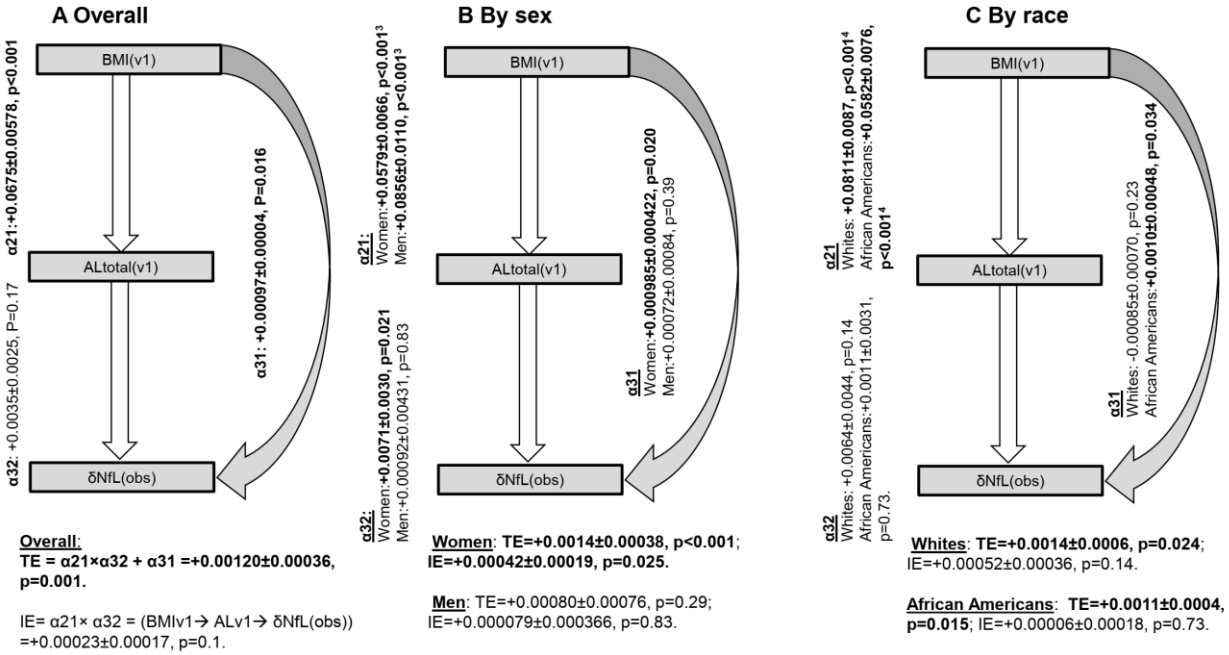

FIGURE 2. BMI at v_1 → allostatic load at v_1 → annualized change in NfL between v_1 and v_3 (δNfL_{obs}), overall and by sex and race: Structural equations model; HANDLS, 2004-2017[1-4]

Abbreviations: AL=Allostatic Load; BMI=Body Mass index; CES-D=Center for Epidemiologic Studies-Depression; δ=Annualized rate of change; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; HEI=Healthy Eating Index; IE=Indirect effect; NfL=plasma Neurofilament Light; TE=total effect; v_1=Visit 1; v_2=Visit 2; v_3=Visit 3.

[1] Values are unstandardized path coefficients α ±SE, total effects (TE), direct effects (DE) and indirect effects (IE) with associated P-values. See

Table 4 for sample sizes, overall and by strata.

[2] Exogenous variables in the models were: age, sex, race, poverty status, educational attainment, current drug use, current tobacco use, HEI-2010, total energy intake, the CES-D total score and the inverse mills ratio.

[3] P-value associated with null hypothesis of no difference in path coefficient α, by sex, using Wald test (χ^2 test, 1 d.f.) for group invariance.

[4] P-value associated with null hypothesis of no difference in path coefficient α, by race, using Wald test (χ^2 test, 1 d.f.) for group invariance.

*P<0.05; **P<0.010; ***P<0.001 for null hypothesis that path coefficient α=0.

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