

BMJ Open Role of cumulative biological risk in mediating socioeconomic disparities in cognitive function in the elderly: a mediation analysis

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ABSTRACT

Objectives To evaluate whether allostatic load (AL), a measure of cumulative biological risk, fully or partially mediates observed socioeconomic status (SES) differences in cognitive function in the elderly.

Design Cross-sectional mediation analysis.

Setting Community-dwelling US elderly who participated in the National Health and Nutrition Examination Survey (NHANES).

Participants The NHANES uses a complex, multistage, probability sampling design to select a nationally representative sample. Of the 4976 elderly (60 years or older) who were selected, 3234 agreed to participate in the household and medical exam interviews (65% response rate).

Primary and secondary outcome

measures Performance on the Digit Symbol Substitution Test (DSST)—a measure of cognitive function.

Results Relative to participants with the lowest level of education or family income, participants who were college graduates ($\beta=24.4$, 95% CI 22 to 26.8, $p<0.0001$) or in the highest income quartile ($\beta=17.3$, 95% CI 15.2 to 19.4, $p<0.0001$) had the highest DSST scores and the least AL burden ($\beta=-0.72$, 95% CI -0.98 to -0.47 and $\beta=-0.82$, 95% CI -1 to -0.57 ; $p<0.0001$, respectively). Although, AL was significantly negatively associated with cognitive performance ($\beta = -1$, 95% CI -1.4 to -0.5 , $p<0.0001$), it mediated at most 4.5% of the SES effect on DSST performance.

Conclusions The findings suggest that AL, as measured by a summary index of parameters for cardiovascular function, metabolism and chronic inflammation, is not a significant mediator of SES-related differences in cognitive function in the elderly. Further efforts are required to elucidate the exact physiological pathways and mechanisms through which SES impacts cognitive function in late life.

INTRODUCTION

The number of people afflicted with dementia is projected to almost triple by 2050 primarily due to large increases in the elderly population and particularly the oldest old.^{1 2} As a result, the public health, social and economic burden of caring for those with late-life cognitive disorders will continue to grow.³⁻⁵ After

Strengths and limitations of this study

- Methodological advantages over previous studies consist of the use of a large, nationally representative sample of US elderly and multiple imputations to account for missing data.
- The analyses used a comprehensive Allostatic Load (AL) Index, simultaneous measurements of socioeconomic status and cognitive function, and controlled for important demographic confounders.
- Because this was a cross-sectional analysis, we cannot rule out whether changes in the causal relations in the mediation model over time may have led to an underestimation of the mediation effect.
- We also cannot rule out potential confounding by genes, such as apolipoprotein E (APOE), or psychosocial factors, such as depression, that influence both AL biomarkers and late-life cognitive outcomes.

more than 30 years of efforts, effective interventions remain elusive and there is growing recognition that brain changes related to the most common cause of dementia may start decades before clinical symptoms emerge.⁶⁻⁸ Consequently, efforts to identify modifiable risk factors that may thwart or delay the onset of late-life cognitive impairment continue to attract considerable scientific interest. Several recent epidemiological studies have reported that the age-adjusted risk of developing dementia in developed countries may be in decline, which has coincided with improvements in education and the reduced prevalence of vascular risk factors at the population level.⁹⁻¹¹ The decline of dementia prevalence and incidence appears to be concentrated in those with higher levels of education, or without a history of stroke. This evidence suggests that better management of a range of cardiovascular risk factors and lifelong learning and its associated socioeconomic benefits may be modifiable pathways affecting risk of cognitive impairment in late life.^{1 12}

Socioeconomic status (SES) as measured by income, education or occupation has been widely associated with cognitive health outcomes in the elderly.^{13 14} Several systematic reviews and meta-analyses have found that lower educational attainment is a risk factor for cognitive decline and dementia.^{15 16} A recent review of potentially modifiable risk factors for Alzheimer's disease (AD) estimated that, out of all the risk factors considered, a reduction in the prevalence of low education would make the largest contribution to a reduction of AD cases worldwide.¹⁷ The main pathways, which have been studied with respect to SES differences in cognitive health in the elderly include differential exposure to greater and higher quality mental and physical stimulation both early and throughout the life course, material conditions (eg, nutrition and living conditions), psychosocial factors (eg, psychological or social stress) and health behaviours (eg, smoking and lack of exercise).^{18–20} Biological pathways have been studied mainly in the context of individual risk parameters and clinically manifest disease. However, less is known about the role of cumulative biologic burden across multiple systems—including subclinical dysregulation—in mediating SES differences in health outcomes in the elderly and particularly cognitive outcomes.

Impaired glucose metabolism, midlife obesity and hypertension, dyslipidaemia and chronic inflammation have all been linked with risk of dementia, cerebrovascular pathological changes associated with vascular dementia and the hallmark neuropathological features associated with AD.^{21–24} A significant feature of the biological dysregulation associated with these risk factors is that it not only predicts cognitive and overall health risks, but it also varies by SES, with lower SES groups exhibiting the highest levels of dysregulation.²⁵ A higher prevalence of these risk factors has also been found as early as early childhood in lower SES groups and this disparity persists throughout life.²⁶ This raises the prospect of a long-term process of cumulative biological 'wear and tear' across multiple physiological systems that may help explain SES disparities in cognitive function in late life.

'Allostatic load' (AL), proposed by McEwen, Stellar, Wingfield and others, is a multisystems view of the cumulative physiological toll that may be exacted on the body over the life course. In response to environmental stressors and the need for adaptation to those stressors, the brain determines appropriate behavioural and physiological responses. These responses occur through the neuroendocrine, autonomic, immune, and metabolic systems and their mediators, which in turn either directly or through epigenetic programmes alter cellular and organ function. Although this process may be adaptive initially, chronic exposure to limited resources, toxic or unhealthy living conditions, negative life events and the chronic activation of physiological responses to these stressors eventually damage the body's ability to turn stress mediators on or off as needed and lead to dysregulation and lasting pathophysiological changes in cardiovascular, metabolic and immune system function.²⁷ The

differential accumulation of this biological dysregulation correlates with differences in exposure to adverse circumstances and is posited to mediate SES-related inequalities in physical and cognitive health. This process may begin in childhood and combine with adult and genetic risk factors to exacerbate risk of age-related disease over the life course. For example, research suggests that exposure to childhood socioeconomic disadvantage, maltreatment or social isolation is associated with elevated risk for depression, inflammation and cardiovascular risk factors in adulthood, all of whom have been associated with risk of cognitive decline in late life.²⁸ These effects appear to be additive to the effects of risk factors and disease mechanisms that emerge in adulthood in the form of poor cardiometabolic health, which may then affect cognition. More likely, AL has a cumulative impact throughout the life course, directly affecting brain development in early life, as well as, indirectly by resulting in poorer overall health across the life span.^{29 30}

The earliest efforts to operationalise AL were reported by the MacArthur Studies of Successful Aging and included primary mediators and secondary markers of physiological health across a range of regulatory systems.³¹ Primary mediators were circulating hormones that play a role in the body's stress response through the hypothalamic–pituitary–adrenal axis and sympathetic nervous system. These mediators interact with each other, body organs and tissue substrates to influence peripheral biological function, which under chronic stress conditions may lead to lasting pathophysiological processes affecting cardiovascular, metabolic, immune and central nervous system function.^{27 32} The main differences between AL and the more traditional focus on individual parameters of biological risk are that it considers overall physiological dysregulation and that it takes into account even relatively modest forms of dysregulation that do not necessarily meet clinically significant thresholds or clinical criteria for disease classification. There exists empirical evidence that such an index of cumulative biological dysregulation can help explain SES-related differences in physical function and mortality better than individual risk parameters.^{33 34} However, to date no studies have assessed the mediating role of cumulative biologic risk in SES disparities in cognitive health in the elderly.

The goal of this study is to evaluate whether AL fully or partially mediates observed SES differences in cognitive function in a nationally representative sample of US elderly. We hypothesised that: (1) without controlling for AL, low SES will be associated with poorer cognitive function; (2) low SES will be associated with higher AL; (3) high AL will be associated with poorer cognitive function, controlling for SES and it will partially mediate the relationship between SES and cognitive function and (4) the mediation effect will be statistically and clinically significant.

METHODS

Study sample

The current research is a secondary data analysis, which combined available data from a cross-sectional, nationally representative sample of elderly (60 years or older) from the National Health and Nutrition Examination Survey (NHANES) 1999–2000 and 2001–2002 cycles.³⁵ The 1999–2002 period is the most recent for which cognitive testing data on the elderly NHANES subsample were available at the start of this analysis. The NHANES programme began in 1959 as a series of periodic health surveys that combine in-home interviews on participant demographics, socioeconomic, dietary, self-reported health, physical and cognitive functioning, household conditions and family information followed by standardised physical examinations and laboratory tests. Since 1999, it has been conducted annually (data are released in 2-year cycles) using a stratified, four stage, probability sampling design to select a nationally representative sample of US households.³⁶ Approximately 30 counties are visited during each 2-year survey cycle (15 on an annual basis) and participants are recruited from all regions of the USA.³⁵ In the 1999–2002 period, certain subgroups of particular public health interest were over-sampled, including low-income persons (beginning in 2000), and persons aged 70 and over, among others.³⁶ Informed consent is obtained during the home interview and all data that are collected and made publically available are deidentified by the National Center for Health Statistics (NCHS) prior to its release.³⁷ For additional information on the NHANES Study design, sampling procedures, study protocols and data collection please see the online supplemental materials: Methods.

Cognitive Function Questionnaire

Cognitive function in this sample of elderly was assessed using the Digit Symbol Substitution Test (DSST)—a component of the Wechsler Adult Intelligence Test (WAIS).³⁸ As a subtest of the WAIS, the DSST has undergone repeated and rigorous psychometric validation such as test–retest reliability and discriminant validity in a range of patient samples.³⁹ It has been found to be a sensitive measure of age, cardiovascular, cerebrovascular and dementia-related changes in motor speed, attention and visuospatial functions with test–retest reliability correlation coefficients in the 0.82–0.88 range in these clinical and normal populations.^{38 39} As such, it has become one of the most commonly used instruments in standardised clinical evaluations in studies of cognitive ageing and dementia.⁴⁰ The test consists of a paper-and-pencil task that requires copying as many novel symbols corresponding to numbers as possible in 120s. Using the key provided at the top of the form, participants draw the symbol under the corresponding number. One point is given for each correctly drawn symbol, with a minimum score of 0 and a maximum—for the version used in the NHANES Survey—of 133, with higher scores indicating better performance. Sample items were provided for

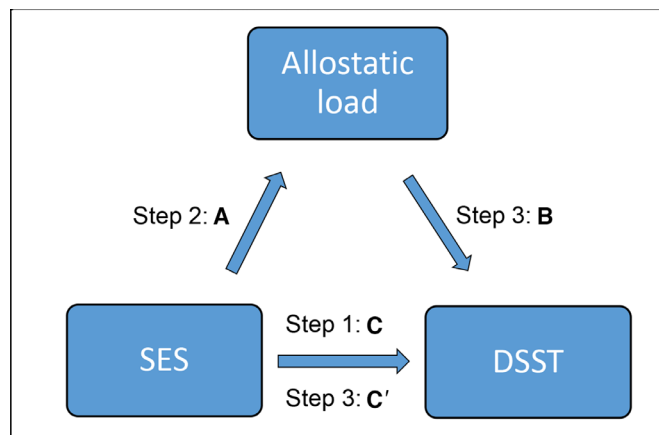


Figure 1 Letters A, B, C and C' represent estimated path parameters. Controlling for participants' age, sex and race/ethnicity: in step 1, DSST was regressed on SES (C); in step 2, AL was regressed on SES (A) and in step 3, DSST was regressed on SES (C') and AL (B) simultaneously. AL, allostatic load; DSST, Digit Symbol Substitution Test; SES, socioeconomic status.

practice and participants who were unable to complete any of the practice items did not continue with the remainder of the exercise. For a copy of the DSST instrument, see figure 1 in the online supplemental materials.

Socioeconomic status

The present study focused on SES as defined by self-reported years of education completed and, separately, as the poverty income ratio (PIR), which reflects reported household income relative to the federally defined poverty level for the participant's area of residence and household size. In the NHANES, education is categorised into less than 9th grade, 9th–11th grade, high school (HS) graduate or general equivalency diploma, some college, and college graduate. Because NHANES uses top coding to protect the anonymity of the highest income participants (PIR of 5 or greater), we categorised PIR into four categories based on the quartile cut offs of its empirical distribution, which consisted of PIR values of <1.3, 1.3–2.39, 2.4–4.18 and >4.18, respectively.

Allostatic load

The set of parameters used consisted of systolic blood pressure and diastolic blood pressure (DBP) (reflecting cardiovascular health), body mass index and the ratio of waist-to-thigh (WTR) circumference (reflecting long-term metabolism and adipose tissue deposition), high-density lipoprotein (HDL), total cholesterol (TC) and the ratio of HDL to TC (reflecting lipid metabolism), glycated haemoglobin (HbA1c) (reflecting glucose metabolism), and C reactive protein (CRP) (as a marker of systemic inflammation). The body measurement and biomarker assay protocols that were used are available on the NHANES website (source: <https://www.cdc.gov/nchs/nhanes/index.htm>).³⁷

Using the empirical distribution of each parameter, an AL Index for each participant was calculated by adding

Table 1 Quartile and clinically defined ‘high-risk’ criteria for allostatic load

| Component | Quartile cut-offs* | Clinical cut-offs |
|----------------------------------|--------------------|-----------------------------------|
| Systolic blood pressure (mm Hg) | 152 | 150 ⁴⁹ |
| Diastolic blood pressure (mm Hg) | 78 | 90 ⁴⁹ |
| TC (mg/dL) | 235 | 240 ⁵⁰ |
| HDL (mg/dL) | <41 | <40 ⁵⁰ |
| TC/HDL ratio | 5 | >5 men, >4.5 women ⁵¹ |
| BMI (kg/m ²)* | 31.3–31.4 | 30 obesity ⁵² |
| Waist to thigh ratio | 2.1 | n/a |
| Waist (cm) | n/a | >102 men, >88 women ⁵³ |
| Glycated haemoglobin (%) | 5.8 | 6.5 ⁵⁴ |
| CRP (mg/dL) | 0.64–0.65 | 0.3 ⁵⁵ |

*Identical across all imputed datasets, except for BMI and CRP for which the range is provided.

BMI, body mass index; CRP, C reactive protein; HDL, high-density lipoprotein; TC, total cholesterol; TC/HDL, the ratio of TC to HDL.

the number of parameters for which the participant’s value fell in the ‘highest risk’ quartile (ie, above the 75th percentile for all parameters except HDL cholesterol for which below the 25th percentile corresponded to the highest risk).³¹ It was postulated that membership in the high-risk quartile would differentiate those exposed to greater dysregulation relative to the rest of the sample. AL scores could range from 0 (ie, none of the participant’s parameters fell in the high-risk quartile) to 9 (ie, all parameters fell in the high-risk quartile). In post hoc analyses, we examined alternative ‘high-risk’ cut-off values derived from commonly accepted clinical practice guidelines (see ‘Post hoc analyses’ section for details). Quartile-based and clinically derived ‘high-risk’ cut-off values are listed in [table 1](#).

Covariates

All mediation analysis models controlled for participants’ age, gender and race/ethnicity. Because NHANES uses top coding to protect the anonymity of participants who are 85 or older, age was categorised into 60–69, 70–79 and 80 or older. Moreover, due to low cell counts, all 68 observations in the other/multiracial category of the race/ethnicity variable were excluded from the analysis, leaving 3166 participants in the dataset.

Statistical analysis

Of the 4976 elderly who were selected for NHANES 1999–2002, 3706 agreed to participate in the household interview (74.5% response rate) and 3234 participated in

the medical examination (65% response rate). NHANES participants are assigned individual weights that account for factors that are correlated with propensity for non-response to the household and medical examinations (ie, unit non-response), such as age, race, gender, household size, education, self-reported health status and activity level.³⁶ Of the 3234 elderly who participated in the household and medical exam interviews, 1280 (39.5%) had missing data on at least one of the variables that were to be used in the mediation analysis (ie, item non-response). Participants with missing data were significantly different with respect to age, race/ethnicity, SES, AL components and cognitive function. As such, 10 multiple imputations using fully conditional specification were used to address potential biases arising from item non-response.⁴¹

Once the imputation step was completed, the mediation analysis was performed separately in each of the 10 imputed datasets using the SURVEYREG procedure in SAS V.9.4, which takes into account the effect of stratification, cluster sampling and unequal survey weights on the estimation of regression coefficients and variance parameters. The mediation analysis consisted of the multistep procedure of multiple regressions outlined by Baron and Kenny,⁴² which was used to assess whether the mediation model was correctly specified and to estimate the mediating effect of AL. [Figure 1](#) illustrates the recursive structural equation model that was used in steps 1–3 of the mediation analysis. In the first step, performance on the DSST was regressed on SES, controlling for the covariates, but not the mediator (path C). In the second step, AL was regressed on SES, controlling for the covariates (path A). In the third step, cognitive performance on the DSST was regressed on SES (path C’) and AL (path B) simultaneously, controlling for the covariates. The indirect effect, which is a measure of the mediation effect, was estimated by taking the product of the coefficients for paths a and b and the Sobel Test was used to determine its statistical significance.⁴³ The estimated regression coefficients and associated standard errors obtained from fitting the linear models in steps 1–3 were synthesised into single sets of statistics using the MIANALYZE procedure in SAS V.9.4. Taken together the SURVEYREG and MIANALYZE procedures produced variance estimates that were fully corrected for the complex sample design of the NHANES Survey, as well as, the additional variability introduced by the multiple imputations.

Post hoc analyses

A series of post hoc analyses considered the role of individual AL components, separately, as mediators of SES effects on cognitive performance and examined a number of alternative AL indices. Specifically, an alternative scoring algorithm considered subjects’ self-reported medication use for diabetes, hypertension or high cholesterol, by assigning a point to their AL Score for each medication used, even if these participants’ biomarker values for HbA1c, blood pressure or TC did not fall into the ‘high-risk’ quartile range.⁴⁴ Moreover, consistent

with previous scoring methods, we also examined alternative ‘high-risk’ cut-off values derived from commonly accepted clinical practice guidelines. Although the clinically defined “high-risk” criteria were very similar to the quartile-based cut-offs for most parameters, there were notable exceptions for DBP, HbA1c and CRP. Moreover, because evidence-based clinical guidelines for defining high-risk thresholds for WTR do not exist, WHO waist circumference guidelines for men and women were used as an alternative.

Patient and public involvement

Although, the public was not directly involved in the design of this study, the development of the research question was informed by the needs of patients, caregivers and society to identify potentially modifiable pathways affecting the risk of cognitive impairment in late life. Identifying factors that help explain SES inequalities in the distribution of reduced cognitive function in old age allow government agencies and private sector organisations to establish policies and plan research, education and health promotion programmes that can directly benefit elderly participants in the USA and worldwide.

RESULTS

Table 2 displays descriptive statistics for the non-multiply imputed sample and the univariate regression of DSST on all analytic variables. Participants who were older, male, non-white, had lower level of education or income, and higher AL had significantly lower DSST scores.

SES and cognitive function

To test whether SES has an effect on cognitive function that may be mediated by AL (ie, total effect), performance on the DSST was regressed on SES, controlling for the covariates. As expected, level of education and PIR was significantly positively associated with performance on the DSST. As shown in [figure 2A,B](#), relative to participants with the lowest level of education or family income, participants who were college graduates or in the highest PIR quartile had the highest DSST scores ($\beta=24.4$, 95% CI 22 to 26.8 and $\beta=17.3$, 95% CI 15.2 to 19.4; $p<0.0001$, respectively), followed by participants with some college or who were in the third PIR quartile ($\beta=18.6$, 95% CI 16.4 to 21 and $\beta=12.5$, 95% CI 10.2 to 14.8; $p<0.0001$, respectively) and participants who were HS graduates or in the second PIR quartile ($\beta=15.5$, 95% CI 13 to 18 and $\beta=6$, 95% CI 3.5 to 8.5; $p<0.0001$, respectively). Moreover, the DSST Score of participants who completed 9th–11th grade was also significantly higher than that of participants with the lowest level of education ($\beta=8.9$, 95% CI 6.6 to 11.3, $p<0.0001$). [Table 1](#), Hypothesis 1 model, in the online supplemental materials lists the synthesised parameter estimates (over all imputations) for the regression of DSST on SES.

SES and allostatic load

The first hypothesised pathway of the indirect effect of SES on cognitive function postulates that AL changes

Table 2 Descriptive statistics and univariate regression of DSST on analytic variables

| Variables | % or mean (SE) | β (SE) |
|--|----------------|--------------|
| Age | | |
| Age 60–69* | 46.3 | 17 (0.9) |
| Age 70–79* | 35.6 | 8.6 (1.2) |
| Age 80+ | 18.1 | – |
| Sex | | |
| Female† | 56.6 | 1.9 (0.8) |
| Male | 43.4 | – |
| Race/Ethnicity | | |
| Black* | 8.5 | –16 (1.1) |
| Hispanic* | 8.5 | –15.6 (1.4) |
| White | 83 | – |
| Education (nmiss=13) | | |
| <9th grade | 15 | – |
| 9th–11th grade* | 17 | 12.6 (1.3) |
| High school/general equivalency diploma* | 29 | 20.5 (1.3) |
| Some college* | 21.5 | 23.2 (1.1) |
| College graduate* | 17.5 | 29.7 (1.4) |
| PIR (nmiss=416) | | |
| PIR<1.3 | 24.2 | – |
| PIR 1.3–2.39* | 25.4 | 7.2 (1.5) |
| PIR 2.4–4.18* | 25.1 | 15.7 (1.3) |
| PIR>4.18* | 25.3 | 21.2 (1.2) |
| DSST (nmiss=511) | 46.3 (0.6) | – |
| Allostatic load* (nmiss=630) | 2.4 (0.0) | –1.7 (0.3) |

* $p<0.0001$.

† $p<0.05$.

DSST, Digit Symbol Substitution Test; nmiss, number missing; PIR, poverty-to-income ratio.

with SES (ie, path a). As hypothesised, SES, as measured either by participants’ education or PIR, was significantly negatively associated with AL. [Figure 3A,B](#) shows that relative to participants with the lowest level of education or family income, participants who were college graduates or in the highest PIR quartile had the least AL burden ($\beta=-0.72$, 95% CI -0.98 to -0.47 and $\beta=-0.82$, 95% CI -1 to -0.57 ; $p<0.0001$, respectively), followed by participants with some college or who were in the third PIR quartile ($\beta=-0.37$, 95% CI -0.6 to -0.13 , $p<0.01$; and $\beta=-0.37$, 95% CI -0.67 to -0.06 , $p<0.05$) and participants who were HS graduates or in the second PIR quartile ($\beta=-0.19$, 95% CI -0.44 to 0.04 , $p=0.11$; and $\beta=-0.17$, 95% CI -0.42 to 0.07 , $p=0.17$). The AL burden of participants who completed 9th–11th grade was virtually the same as that of participants with the lowest level of education ($\beta=0.03$, 95% CI -0.19 to 0.25 , $p=0.79$). [Table 1](#), Hypothesis 2

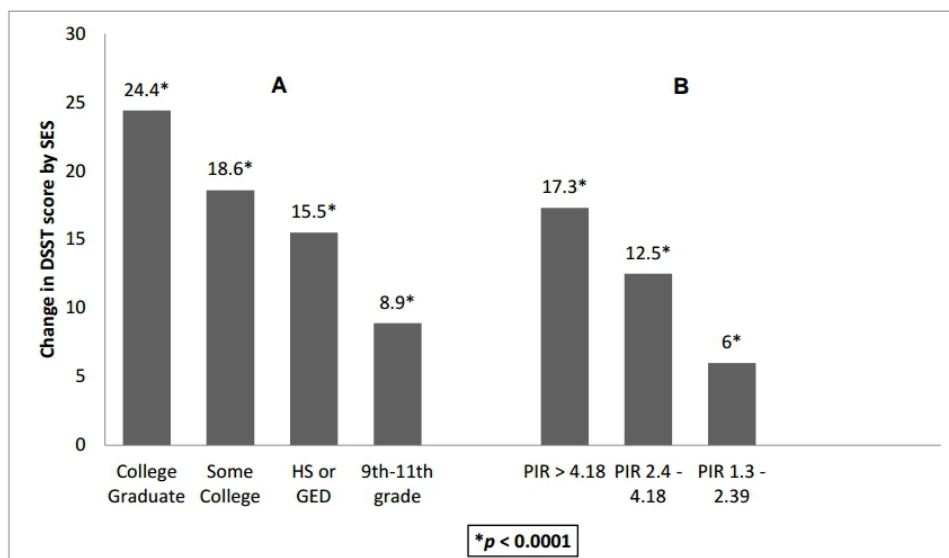


Figure 2 Age, gender and race/ethnicity adjusted change in DSST by SES. DSST, Digit Symbol Substitution Test; GED, general equivalency diploma; HS, high school; PIR, poverty-to-income ratio; SES, socioeconomic status.

model, in the online supplemental materials lists the synthesised parameter estimates (over all imputations) for the regression of AL on SES.

Allostatic load and cognitive function

To test the second hypothesised pathway through which the indirect effect of SES is postulated to affect cognitive function (ie, path b), performance on the DSST was regressed on SES and AL simultaneously, controlling for the covariates. As postulated, AL was significantly negatively associated with cognitive performance (see figure 4). The magnitude of the association was similar when SES was measured either by participants' education ($\beta = -0.99$, 95% CI -1.4 to -0.5) or PIR ($\beta = -0.96$, 95% CI -1.3 to -0.5) at $p < 0.0001$, respectively. Table 1, Hypothesis 3 model, in the online supplemental materials lists the synthesised parameter estimates (over all imputations) for the regression of DSST on SES, controlling for AL.

Allostatic load as mediator of SES differences in DSST performance

Controlling for AL attenuated the effect of SES on cognitive performance, although marginally. As shown in figure 5A,B, the parameter estimates for college graduates and those in the highest PIR quartile were reduced by 0.72 and 0.79 DSST points (or by 2.9% and 4.5%), respectively. Parameter estimates for participants with some college and those in the third PIR quartile were reduced by 0.36 and 0.35 DSST points (or by 1.9% and 2.8%), respectively; and for HS graduates and those in the second PIR quartile, parameter estimates were reduced by 0.19 and 0.16 points (or by 1.2% and 2.7%), respectively. The regression coefficient for participants who completed 9th–11th grade was virtually unchanged after controlling for AL. Although the absolute change in the magnitude of the effect of SES on cognitive performance

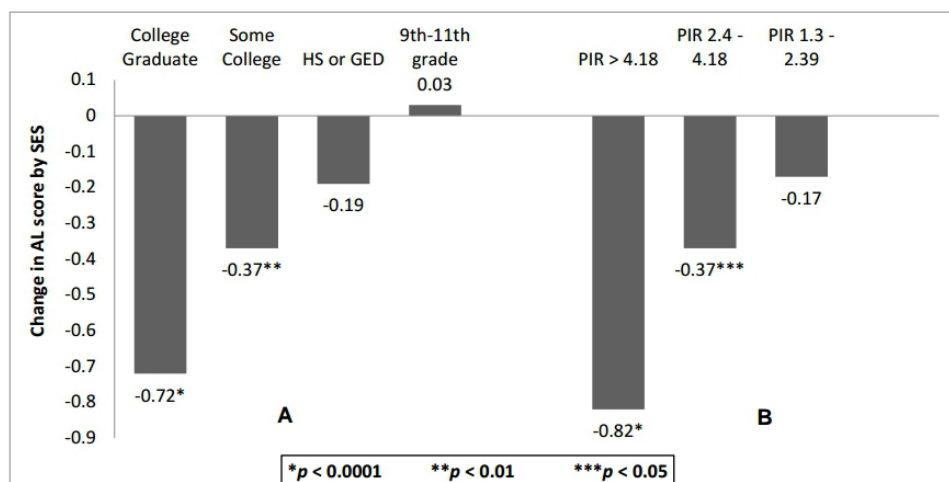


Figure 3 Age, gender and race/ethnicity adjusted change in AL by SES. AL, allostatic load; GED, general equivalency diploma; HS, high school; PIR, poverty-to-income ratio; SES, socioeconomic status.

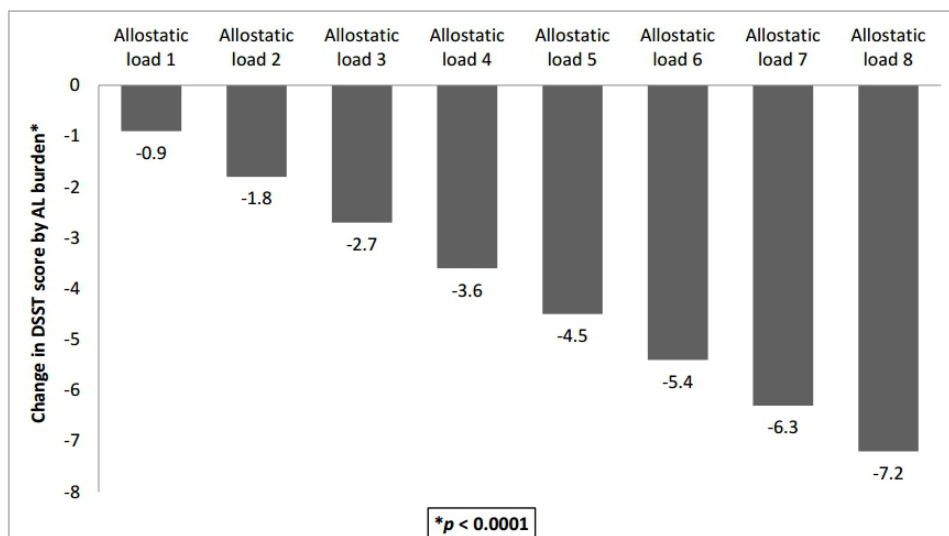


Figure 4 Age, gender and race/ethnicity adjusted change in DSST Score by AL burden. AL, allostatic load; DSST, Digit Symbol Substitution Test.

after controlling for AL was relatively small, Sobel Tests of the indirect effects were statistically significant for college graduates ($ab=0.72$, 95% CI 0.31 to 1.13, $p=0.0006$) and participants with some college ($ab=0.36$, 95% CI 0.09 to 0.63, $p=0.011$) and for participants in the top two PIR quartiles ($ab=0.79$, 95% CI 0.38 to 1.2, $p=0.0002$ and $ab=0.35$, 95% CI 0.04 to 0.66, $p=0.033$; respectively). All other Sobel Tests were not statistically significant.

Post hoc analyses

Although, changes in the magnitude of the observed effect of SES on DSST performance after controlling for

most individual AL components were marginal, the Sobel Test was statistically significant for WTR and HbA1c. WTR mediated between 2.6% and 3.2% of the effect for participants with HS or greater education and 4.0% of the effect for those in the highest PIR quartile. HbA1c mediated approximately 2% of the effect in college educated participants and 3.0% of the effect for participants in the top PIR quartile. Because WTR alone appeared to mediate a similar or greater proportion of SES effects on DSST performance than AL, we examined an alternative AL Index that did not include WTR to ascertain whether

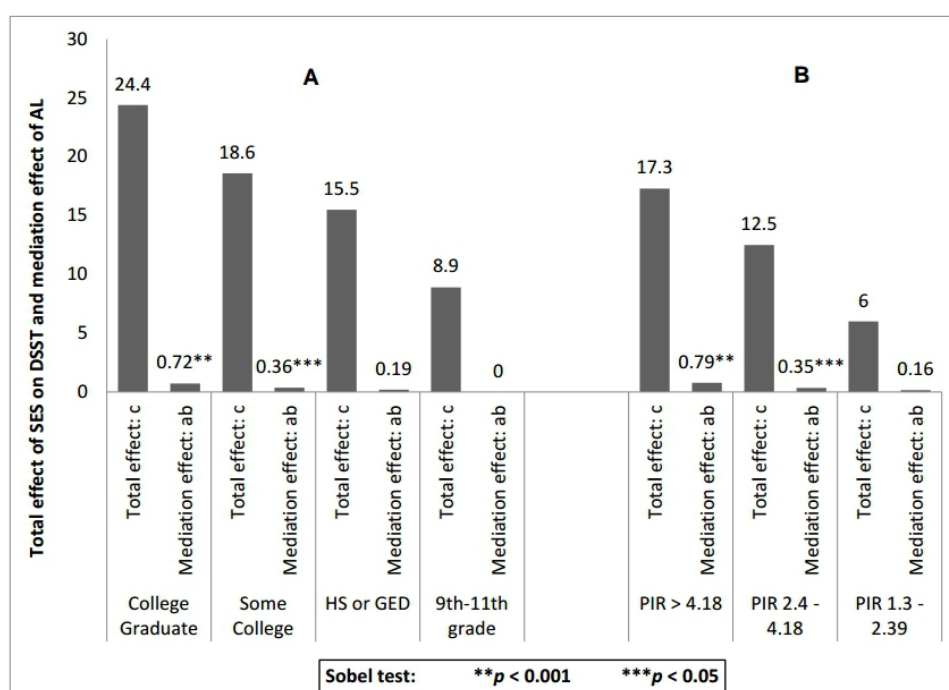


Figure 5 Age, gender and race/ethnicity adjusted change in DSST by SES and mediation effect of AL. AL, allostatic load; DSST, Digit Symbol Substitution Test; GED, general equivalency diploma; HS, high school; PIR, poverty-to-income ratio; SES, socioeconomic status.



the earlier statistically significant AL findings were due to the effect of WTR. We also examined a second alternative AL Index, which did not include HbA1c. After excluding WTR, or HbA1c, the proportion of the total effect of SES on DSST performance, which was mediated by AL, was now reduced. However, both alternative AL Indices were still found to mediate over 2% of the effect for college educated participants and between 2.3% and 3.5% of the effect for participants in the higher PIR quartiles. In sum, the largest percent mediation of PIR effects was explained by the most comprehensive AL Index, while the largest percent mediation for education effects was explained by WTR alone.

The addition of points for self-reported current medication use to the AL Score led to a small increase (i.e. <0.7%) in the proportion of the total effect for college educated participants and for all PIR quartiles, which was mediated by the index. On the other hand, the use of clinically derived cut-offs led to a marginal decrease in the proportion of the total effect for college educated participants (~0.5%) and for all PIR quartiles (~1%), which was mediated by the index. In sum, none of the alternative indices altered the results substantially.

In a final set of post hoc analyses, we used data from the NHANES Medical Conditions Questionnaire to examine whether self-reported 'doctor-diagnosed' morbidity modified our findings. We split our sample into a group of 'healthy' participants who had no self-reported doctor-diagnosed conditions (n=659) and a 'morbidity' group who reported at least one medical condition (n=2507) and repeated the Hypothesis 3 analysis separately, within each group. Although in the 'healthy' group, the parameter estimates for the effect of AL on DSST (path b) and for the total and indirect effects of PIR were reduced, in the 'morbidity' group all findings were very similar to those of our main analysis, which did not take medical history into account. See online supplemental table 2 and Post hoc analyses of participants with a medical history section for details.

DISCUSSION

Overall, changes in DSST Score were strongly positively associated with level of SES and occurred in a nearly linear and dose-dependent fashion. Most notably, even after controlling for participants' age, gender and race/ethnicity, the DSST Score of college graduates was on the average more than 24 points higher than the score of participants with less than ninth grade education. Similarly, relative to participants with the lowest level of education, the DSST Score was more than 18 points higher for participants with some college education, more than 15 points higher for those who graduated HS and almost 9 points higher for those who completed 9th–11th grade. A comparable pattern was observed with respect to DSST scores and participants' family income. These findings show that there is a sizeable SES effect on cognition that may be mediated and they are consistent with several

other community-based and population-based studies that have found a strong link between SES, cognitive performance and the risk of dementia and cognitive decline in late life.¹⁶

The effect of SES on DSST performance was partially mediated by the AL Index, which explained between 1.2% and 2.9% of the total effect on cognitive performance for those with HS or greater education and between 2.7% and 4.5% for those in the top three PIR quartiles. Although, the null hypothesis concerning the indirect effect was rejected for college educated participants and for those in the top two PIR quartiles, in absolute terms the amount of mediation was relatively small. After controlling for the postulated AL mediator, the DSST Score for college graduates was attenuated by less than 1 point from 24.4 to 23.7, whereas, the DSST Score for those in the highest PIR quartile was reduced from 17.3 to 16.5. For all other SES levels, the reduction was even smaller still at less than half a point. Alternative scoring algorithms for summarising AL burden that took into account participants' prescribed medication use (for diabetes, hypertension and hypercholesterolaemia) and clinical cut-offs as a criterion for 'high risk' did not alter these findings.

Our findings suggest that SES, as measured by educational attainment or family income, is a strong predictor of performance on a test that is sensitive to age and dementia-related cognitive changes in the elderly. However, only a small proportion of this relationship was mediated by AL. Although, the parameter estimates for the two postulated pathways, through which SES predicts AL and in turn AL predicts performance on the DSST, were statistically significant, their magnitude was modest and their product—reflecting the amount of mediation—was not large enough to account for the substantial impact of SES on cognitive function, which remained largely unaffected after adjusting for AL. Similar findings were obtained when individual components of AL were substituted in place of the summary index. Parameter estimates for paths a and b associated with each component were generally not of such magnitude as to be considered clinically significant and only WTR and HbA1c were found to have statistically significant mediation effects, although, not of sufficient magnitude to be considered clinically meaningful. Indeed the findings reported here suggest that for a nationally representative sample of US elderly 60 years of age or older, neither cumulative nor individual dysregulations in cardiovascular, metabolic and immune system parameters provide additional information regarding biological pathways through which SES may affect cognitive function. These findings suggest that despite evidence of significant SES-related differentials in biological dysregulation and the likely cumulative nature of these dysregulations across the life course, further efforts are required to elucidate the exact physiological pathways and mechanisms through which SES impacts cognitive function in late life.

Our study used a large, nationally representative sample of elderly, who were assessed through in-person interviews

and physical examinations, using validated instruments and standardised protocols that remained consistent throughout the 1999–2002 NHANES period. Missing data were multiply imputed using available predictors and a methodology that is well suited to the complex survey design of the NHANES. Moreover, the analyses used a comprehensive index of cumulative biological risk, simultaneous measurements of SES and cognitive function, and controlled for a number of important demographic confounders.

The current study has some important limitations. Because this was a cross-sectional study, we cannot rule out reverse causation, whereby lower cognitive ability may have preceded and was the cause of both lower SES and higher AL scores. Moreover, it is possible that substantive changes in the causal relations in the current mediation model over time could have led to an underestimation of the indirect effect.⁴⁵ For example, studies have found that abnormal values for some of the metabolic and cardiovascular biomarkers used in our AL Index are detrimental in midlife, but not in late life.¹⁷ A related potential concern for any cross-sectional study on the elderly is that of survivor bias. That is, participants who were eligible and were ultimately enrolled in NHANES may consist of a generally healthier and more resilient cohort of elderly. Therefore, the absence of a stronger link between SES and AL and of AL and cognitive function may reflect such a bias.⁴⁶

We also cannot rule out potential confounding by genes, such as APOE, or psychosocial factors, such as depression, that influence both AL biomarkers and late-life cognitive outcomes.^{17 47} However, confounding by such factors is unlikely given the strength of the SES and DSST relationship. Moreover, the 1999–2002 NHANES did not measure endocrine activity markers, which are hypothesised to play a role in the assessment of AL.³¹ However, even if additional biomarker data was available, currently there is no gold standard approach to measuring AL and the comparative analyses of AL measurement approaches which have been conducted to date, have shown only modest predictive ability differences among the various indices.⁴⁸ Our study used a single test for cognitive function. A more detailed battery that included additional tests for language, memory, attention and executive function could have provided greater statistical power to detect any AL mediated SES-differences in cognitive function. Lastly, we could not include non-community-dwelling elderly in our analysis, because by design the NHANES excludes all persons in supervised care or custody in institutional settings. Non-community-dwelling elderly individuals would, presumably be more cognitively and physically impaired. As such, their exclusion from our analysis may have biased our findings towards the null.

Despite these potential limitations, the findings reported here suggest that the potential value of the AL Index in mediating SES differences in cognitive function in the elderly is limited. Although numerous studies have shown that individual parameters of cardiovascular,

metabolic and immune system function play a role in late-life cognitive function,²¹ our findings suggest that cumulative profiles of biological risk, based on these parameters, do not mediate SES differences in performance on a test that is sensitive to age and dementia-related changes. Given that SES-related adversity affects human health through a multitude of physiological pathways, a more comprehensive view of biological risk may be important in explaining SES differences in mortality or physical health outcomes.²⁵ However, our findings do not support the hypothesis that AL is a significant mediator of SES-related disparities in late-life cognitive function.

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Patient consent for publication Not required.

Ethics approval This study was conducted using National Health and Nutrition Examination Survey (NHANES) data. All NHANES protocols are approved by the National Center for Health Statistics Research Ethics Review Board.

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Data availability statement Data are available in a public, open access repository at <https://www.cdc.gov/nchs/nhanes/index.htm>

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