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RESEARCH ARTICLE

Interrelationships of social determinants with cognition, vascular health, and physical functioning

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The study method, design, and data for the current analysis are from the Midlife in the United States (MIDUS) study. Code for the analysis as it pertains to the current manuscript can be found at https://github.com/PriscillaHo/SDoH-cSEM.git

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Abstract

Objectives: The primary aim of the current analysis was to evaluate the cumulative effect of different social determinants of health (SDoH) factors on vascular burden, cognition, and physical functioning.

Methods: We conducted a secondary data analysis of the Midlife in the United States (MIDUS 2) cross-sectional study using data from participants aged ≥ 55. Measures derived from the Framingham Stroke Risk Profile, Brief Test of Adult Cognition by Telephone, and physical functioning scores from the Medical Outcomes Study 36-item Short Form Health Survey were used to represent vascular burden, cognition, and intermediate activities of daily living, respectively. SDoH variables included education, income, health insurance, stress, and support from family and friends. Associations were evaluated using a composite-based structural equation model (c-SEM) embedded in an overall SEM.

Findings: Among MIDUS 2 participants with no clinical diagnosis of cognitive impairment or neurological disorder ($N = 568$; mean age = 64.6), higher education, less stress, and higher income significantly contributed to the SDoH composite. Positive SDoH was associated with better physical functioning (beta = –0.21, $p < 0.001$) and higher cognition (beta = 0.54, $p < 0.001$). Significant direct effects of SDoH on vascular burden (beta = –0.12, $p < 0.05$) and cognition (beta = 0.51, $p < 0.001$) and of vascular burden on cognition (beta = –0.28, $p < 0.001$) were found. Mediation analysis indicated that the unique effects of SDoH on cognition remained significant after controlling for vascular burden (beta = 0.04, $p < 0.05$). After accounting for vascular burden and cognition, SDoH did not have a significant unique effect on physical functioning.

Conclusion: Our results support the disablement theory, suggesting that factors outside of the disease model (such as SDoH factors) impact diseases that underlie physical and functional limitations.

KEYWORDS
Alzheimer's disease and related dementias, cognition, physical limitations, social determinants of health, vascular burden

1 | INTRODUCTION

Functional (cognitive and physical) decline and limitations are associated with an increased risk of Alzheimer's disease and related dementia (ADRD), falls, hospitalizations, loss of independence, financial capacity impairment, and decreased quality of life in older adults.[1–4] High vascular burden, lower baseline and longitudinal decline of cognitive functioning, and difficulties with performing activities of daily living are all associated with dementia syndromes,[5–7] which includes functional decline. Social determinants of health (SDoH), or conditions in which people are born, live, work, and age,[8–10] are increasingly being recognized for their role in functional decline and ADRD risk factors (including cognition, vascular burden, and physical disability).[11–17] For example, low economic stability is associated with increased vascular disease,[17,18] low cognitive functioning,[15,16] poor physical functional health, and onset and progression of difficulties with activities of daily living.[19] Low educational attainment is associated with low cognition,[20] poor health outcomes,[21] and low health literacy.[21] Likewise, one's community and social context (which inform stress, social integration, support systems, and community engagement) are shown to impact cognitive functioning[22–24] and cerebrovascular health.[25–28] In an analysis of US population health using county health rankings (CHRs), it was found that four determinants of health factors (i.e., health behaviors, clinical care, physical environment, and social and economic factors) accounted for 54% of the overall variance in health outcomes in the United States, with socioeconomic factors and health behaviors as the largest contributors.[29] Likewise, these CHR data showed geographic variation across the United States, with some states having up to 87% of their variance in health outcomes explained by SDoH. In short, SDoH likely significantly affect health outcomes more than direct medical care.

High vascular burden and low cognitive skills are implicated in the onset and progression of ADRD,[1,13,14,30] increased functional impairment,[31,32] and premature mortality.[33] A bi-directional association exists between these two ADRD risk factors, in which vascular health influences cognitive skills and vice versa.[34,35] This is evident in the clinical presentation of patients with vascular risk factors and their performance on neuropsychological assessments (for example, inefficiencies in executive functioning performance).[36–39] Likewise, difficulties with multi-tasking can influence vascular disease management. Neuropathological evaluations also show vascular pathology often co-exists in patients with AD pathology.[40]

The disablement theory[41] is often used to conceptualize the complex interplay among social/environmental factors (like SDoH), vascular and cognitive functioning, and physical limitations (Figure 1). The model posits that environmental factors can influence the disease process, including trajectory and the degree and rate of change of functional abilities. In other words, prolonged exposure to socioeconomic adversity can lead to greater system "wear and tear" over time, increasing the risk for poor health and, ultimately, functional impairment.

The total physiological effect of socioeconomic adversities is often presented as a measure of allostatic load. Allostatic load encompasses cumulative stress, burden, and damage across multiple physiological systems throughout the life course.[42] As the population ages, families, communities, and the health-care system will increasingly face the social and economic burden of ADRD outcomes.[43] A better understanding of the influence of the cumulative and cumulative presence of multiple SDoH on ADRD risk factors (cognitive functioning, vascular burden, and physical functioning) is warranted. Likewise, the recently published aims of Healthy People 2030[8] to achieve health equity and the framework proposed by Alzheimer's Disease Research Centers across the nation for assessing the role of SDoH in ADRD[44] calls for novel ways to evaluate the concurrent combined effect of SDoH on ADRD risk factors and functional abilities.

Understanding the associations between SDoH and ADRD risk factors is critical to help identify subpopulations at higher risk for functional decline and inform interventional researchers and clinicians regarding which participants/patients might need additional support to mitigate functional limitations in old age. Likewise, a better understanding of the associations can inform primary and secondary preventive care. Thus, the overarching aim of the current analysis was to evaluate the effect of cumulative multiple SDoH factors from different SDoH domains (i.e., socioeconomic status [SES], educational attainment, health-care access, perceived stress, and community/family support) on vascular burden, cognition, and physical functional abilities as explained by the disablement theory (Figure 1). Using data from a diverse national sample of mid-adult to older adults in the Midlife in the United States (MIDUS 2) cross-sectional study,[45,46] we hypothesized that: (1) positive SDoH would be associated (both directly and indirectly) with fewer physical functional difficulties, less vascular burden, and better cognition; (2) cognition and cumulative vascular risk factors (i.e., vascular burden) would mediate the relationship between SDoH and physical functional abilities; and (3) vascular burden would mediate the relationship between cognition and SDoH.

2 | METHODS AND MATERIALS

The current study conducted a secondary analysis of data from the MIDUS 2 study,[46] using a novel composite-based structural equation model (c-SEM) embedded in an overall SEM to examine the relationship between composite SDoH factors from different SDoH domains, cognitive functioning, vascular burden (as a composite), and physical functional abilities. The MIDUS 2 database is archived at the University of Michigan and holds all data and documentation, which is updated regularly. A complete description of the MIDUS 2 study has been

Highlights

- A composite-based structural equation model was used to create a construct that represented the cumulative impact of multiple determinants of health factors on cognition and vascular health, and physical functioning.
- Aggregate negative standing in key determinants of health—higher stress, lower education, and lower income—was associated with lower baseline cognition, higher vascular burden, and difficulties with physical functioning.
- The results further support the effects of low socioeconomic status, stress, poor social support, and unavailability of health insurance on cognition, vascular risk, and physical functional abilities, consistent with the broader disablement theory.
- The cumulative impact of social determinants of health factors can be theorized to contribute to one's allostatic load. The cumulative stress and burden on various biological and physiological systems over a period of time likely affects cognitive, vascular, and overall health outcomes.

RESEARCH IN CONTEXT

1. **Systematic review**: Social determinants of health (SDoH) are associated with vascular and cognitive outcomes and the risk of Alzheimer's disease and related dementias (ADRDs) among adults and older adults. The disablement theory hypothesizes how cumulative negative SDoH can impact cognitive and physical functioning, ultimately leading to dementia. The authors reviewed the literature using PubMed and archived articles. We found no literature that assessed the combined impact of multiple SDoH on ADRD risk factors—cognition, vascular health, and physical functioning.
2. **Interpretation**: Our findings supported the disablement theory, suggesting that factors outside the disease model (like SDoH) impact physical, cognitive, and vascular outcomes, which can ultimately lead to functional impairments.
3. **Future directions**: Future studies should include other SDoH indicators in a more diverse population and assess how changes in SDoH longitudinally affect functioning. This could increase generalizability, inform policies, and help develop interventions and clinical practices to improve health equity.

published by the Inter-University Consortium for Political and Social Research (ICPSR) at the University of Michigan. Briefly, MIDUS 2 is the first follow-up to a national longitudinal study that assessed the role of behavioral, psychosocial, and social factors in age-related differences in physical and mental health by following adults from early adulthood through old age. In addition, a sample of Black/African Americans (N = 592) from Milwaukee was included in MIDUS 2 to increase the minority participation rate and assess health outcomes. Area probability sampling methods and population counts from the 2000 US Census were used to identify potential participants. All measures used in the Milwaukee sample paralleled those in the MIDUS 2 studies.

2.1 | Consent statement

All study participants signed an informed consent agreeing to collecting and using blinded study-related information (including data for secondary data analysis). All required permissions (i.e., data usage agreement forms) needed to use available datasets were requested and approved, and all procedures for the current study were approved by the University of Florida Institutional Review Board (under an exempt designation) before initiation of study analysis. The current analysis is not a prespecified primary outcome for the MIDUS 2 study.

2.1.1 | Diversity, equity, and inclusion statement

The current analysis is grounded in the principles of diversity, equity, and inclusion. The authors recognize the importance of diverse representation in ADRD and aging studies to ensure that findings are generalizable and beneficial to all populations. To this end, we made diligent attempts to include as much data as possible from underrepresented groups.

2.2 | Participants

Participants for the current analysis were taken from the second cohort of the MIDUS study (i.e., MIDUS 2). Inclusion criteria for the current analysis included: (1) age of ≥ 55 years ("mid" and older adulthood, selected to align the current project's population to the Framingham Stroke Risk Profile [FSRP] score[47]), (2) completion of MIDUS 2 study, and (3) subjective report of no clinical diagnosis of cognitive impairment or neurologic disorder.

2.3 | Measures

2.3.1 | SDoH measures/indicators

The SDoH composite was developed using participant demographic characteristics (i.e., years of education, annual household income), availability of health insurance, perceived stress, and perceived availability of social support. Perceived stress (Perceived Stress Scale [PSS])[46,48] was assessed by asking participants to answer 10 questions

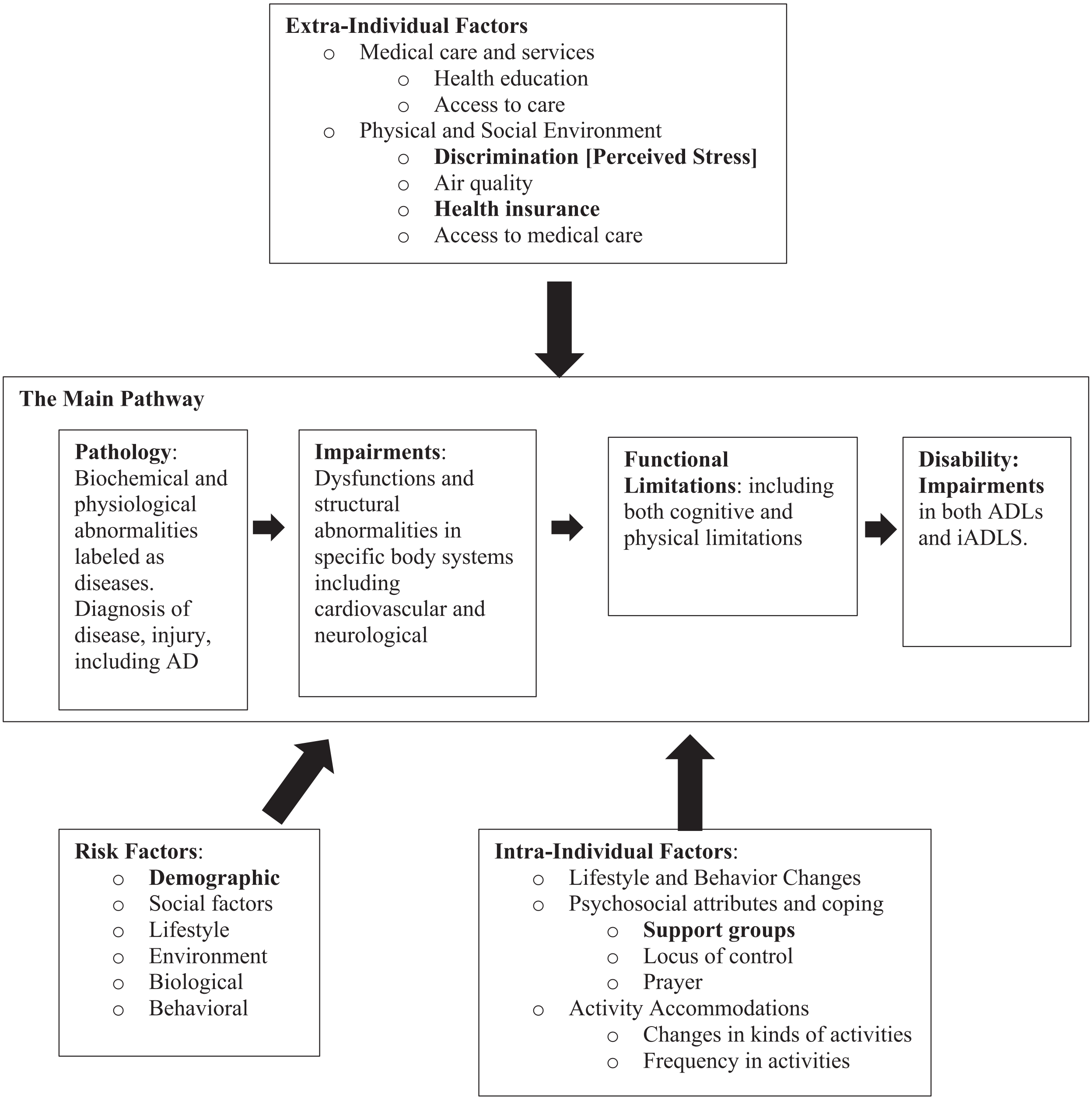

FIGURE 1 Theoretical model (modified disablement theory). AD, Alzheimer's disease; ADLs, activities of daily living; iADLs, instrumental activities of daily living.

regarding how stressful they perceived their lives and daily activities to be (e.g., In the last month, how often have you been upset because of something that happened unexpectedly; In the last month, how often have you felt nervous and stressed) on a 5-point scale (1 = never to 5 = very often). Pre-existing PSS composite scores for each participant were available in the MIDUS 2 dataset, with higher scores reflecting higher perceived stress. Social support was assessed using four questions (e.g., How much do members of your family/friends really care about you; How much do they understand the way you feel about things), querying support from both family and friends.[46] Social support was assessed on a 4-point scale (1 = not at all to 4 = a lot) with higher scores reflecting most support.

2.3.2 | Cognitive functioning

Cognitive abilities were assessed with cognitive measures from the Brief Test of Adult Cognition by Telephone (BTACT).[49,50] Prior exploratory and confirmatory factor analyses identified two underlying cognitive factors assessed with the BTACT: episodic memory and executive functioning.[51] In the MIDUS 2 dataset, canonical cognitive composite scores were previously calculated for each participant by the MIDUS 2 research team as standardized means of z scores for the corresponding cognitive variables. The full sample (MIDAS and Milwaukee subsamples) was included when computing z scores. Accordingly, the episodic memory composite scores consisted of the standardized means of z scores for word list immediate and word list delayed, and the executive function composite scores consisted of the standardized means of z scores for digits backward, categorical fluency, number series, backward counting, and mean of switch-and-no switch trails. These two cognitive domains (i.e., episodic memory and executive functioning), as computed by the MIDUS study, were used in the current analysis (age adjusted). It is worth noting that the MIDUS 2 dataset also includes a previously calculated *overall* cognitive composite score consisting of the standardized means of z scores for each cognitive test. However, we opted to load the two cognitive domain composites on an overall cognition factor within the SEM, so as not to presume equal loadings for the distinct domains. Indeed, exploratory analyses indicated that fit substantially worsened when using the pre-existing overall cognition composite (root mean square error of approximation [RMSEA] = 0.12 vs. RMSEA = 0.08).

2.3.3 | Vascular risk factors

Vascular burden was assessed with the FSRP.[47] Vascular risk factor scores were calculated for each participant using the FSRP equation developed by Dufouil et al.[47] This score was computed for each participant using the following individual-specific risk factor values present in the MIDUS 2 dataset: antihypertensive medications, prevalent cardiovascular disease, current smoking status, current or previous atrial fibrillation, and diabetes mellitus. Risk scores were calculated accordingly per participant's age and sex, as specified by the FSRP equation. In the context of the current analysis, the FSRP served as a measure of aggregate vascular burden detrimental to the brain.

2.3.4 | Intermediate activities of daily living/physical functioning

In MIDUS 2, seven adapted questions from the Medical Outcomes Study 36-item Short Form Health Survey (MOS SF-36)[52] were used to assess intermediate activities of daily living (proxy for physical functioning). Participants rated, on a 4-point scale, the extent to which physical health limited their ability to complete various activities of daily living (e.g., carrying groceries, walking several blocks). Higher scores reflected a greater difficulty in performing physical functioning. A pre-existing composite score of these 7 items was available for each participant in the MIDUS 2 dataset.

2.4 | Analysis

Statistical analyses for the current project were performed using R Programming Language,[53] using packages lavaan,[54] cSEM,[55] Amelia,[56] and mice.[57]

2.4.1 | SDoH construct

An SDoH composite score was created by clustering individual SDoH factors from various SDoH domains. This SDoH composite was created as a formative/composite-based latent variable, which was then embedded in a c-SEM as explained by Bollen and Davis[58] and Diamantopoulos.[59] An c-SEM–based mediation model was fit, including the SDoH composite and the observed outcomes (cognitive, vascular, and functional abilities). Model fit was assessed and the contribution of each SDoH indicator to the formative composite was evaluated using a y-coefficient ($t > 1.96$). Bootstrapping (500 samples) was used to estimate standard errors.

Preliminary descriptive statistics were performed to examine variable distributions; distributions not meeting normality assumptions were transformed prior to performing any study-related analyses. Data was also screened for outliers ($z > 3.29$) and missing data. Patterns of missing data were assessed with the Little missing completely at random (MCAR) test.[60]

Multiple imputation was performed (prior to the computation of any composite variables) to account for missing data while preserving data characteristics and statistical power. Fifty imputed datasets were used for the c-SEM mediation model analysis. c-SEM results were pooled across imputations using the Rubin rules.[61] For fit indices and effect sizes, the mean and standard deviation (SD) of the statistic across imputations were reported

3 | RESULTS

A detailed breakdown of participant demographics is found in Table 1. In brief, there were 568 MIDUS 2 participants, with a mean age of 64.6. There were slightly more women than men (55.3% vs. 44.7%, respectively). Education was categorized into 12 groups, with the mean years of education falling within the group: "≥ 3 years of college with no degree." Approximately 15% of participants identified as Black and 85% identified as White. The average systolic blood pressure was 135 mmHg, 17.5% of participants smoked cigarettes, 8.8% had a diagnosis of diabetes, 29.6% had a history of cardiovascular disease, 52.5% were taking antihypertension medications, and 6.8% had a history of atrial fibrillation. On average, participants reported mild to moderate difficulties with physical functioning (mean = 1.88, range 1–4).

Mean and SD of fit indices across imputations can be found in Table S1 in supporting information. A preponderance of all indices indicated acceptable model fit; chi-square was not significant; comparative fit index, goodness of fit index, incremental fit index, and normed fit index were between 0.85 and 0.97; standardized root mean squared residual was 0.05; and RMSEA was 0.08. Evaluation of patterns of missing data with the Little test of missing data indicated that data were not MCAR ($p < 0.001$). Multiple imputation was carried out under the default assumption of missing at random, as this is preferable to listwise deletion. Variables included in the model were

TABLE 1 Participant demographics.

Variable	*N*	Mean (SD), range, (median)
Age	568	64.6 (7.7), 55–84
Sex	568	–
Men (%)	254 (44.7%)	–
Women (%)	314 (55.3%)	–
Education	565	7.414, 1–12, (7 median)
Race	556	–
Black (%)	83 (14.9%)	–
White (%)	473 (85.1%)	–
Physical function score from MOS SF-36	566	1.878 (0.872), 1–4
Covered by health insurance	565	–
Yes (%)	536 (94.9%)	–
No (%)	29 (5.1%)	–
Total support	559	6.96 (1.0)
Total household income	557	63,749.67 (56,981.7), 0–300,000
Perceived stress	564	20.75 (5.64)
Cognition	–	–
BTACT composite score	523	−0.185 (0.88)
BTACT episodic memory score	538	−0.137 (0.93)
BTACT executive function score	540	−0.132 (0.87)
Other health measures/conditions	–	–
Average 2nd and 3rd systolic blood pressure	568	135.48 (0.5)
Cigarettes status	302	–
Yes (%)	53 (17.5%)	–
No (%)	249 (82.5%)	–
Diagnosis of diabetes	559	–
Yes (%)	49 (8.8%)	–
No (%)	510 (91.2%)	–
History of CVD	568	–
Yes (%)	168 (29.6%)	–
No (%)	400 (70.4%)	–
Taking antihypertension meds	474	–
Yes (%)	249 (52.5%)	–
No (%)	225 (47.5%)	–
History of atrial fibrillation	482	–
Yes (%)	33 (6.8%)	–
No (%)	449 (93.2%)	–

Note: Education was categorized into 12 groups: 1 = no school/some grade school (1–6 years; 0.2%); 2 = eighth grade/junior high school (7–8 years; 1.4%); 3 = some high school (9–12 years, no diploma or GED; 5.5%); 4 = GED (0.9%); 5 = graduated from high school (21.1%); 6 = 1–2 years of college, no degree (18.2%); 7 = 3 or more years of college, no degree (4.4%); 8 = graduated from a 2-year college or vocational school or associate's degree (8.3%); 9 = graduated from a 4- or 5-year college or bachelor degree (16.6%); 10 = some graduate school (5.3%); 11 = master's degree (13.3%); 12 = PhD, EdD, MD, DDS, LLB, LLD, JD, or other professional degree (4.8%). Physical Function Score: higher scores reflect greater difficulty in performing activities; Total support from family and friends: higher scores indicate higher support; Total household income: in public release, this is top-coded at 300,000; Perceived Stress: higher scores indicate higher perceived stress; Cognition: *z* scores for the composite BTACT battery, episodic memory, and executive functioning; mean of 0 and SD of 1.
Abbreviation: BTACT, Brief Test of Adult Cognition by Telephone; CVD, cardiovascular disease; GED, General Education Diploma; MOS SF-26, Medical Outcomes Study 36-item Short Form Health Survey; SD, standard deviation.

approximately normal (absolute skewness < 2) with the exceptions of the dichotomous variable indicating whether participants currently had health insurance coverage (skewness = 4.04) and the FSRP (skewness = 2.87).

3.1 | SDoH composite

Education (weight = 0.68, standard error [SE] = 0.08, t = 8.21, $p < 0.001$), total household income (weight = 0.44, SE = 0.11, t stat = 4.07, $p < 0.001$), and total perceived stress (weight = –0.27, SE = 0.13, t stat = –2.12, $p < 0.05$) were all significant contributors to the SDoH composite. Current enrollment in health insurance (weight = 0.11, SE = 0.10, t stat = 1.11, $p = 0.2$) and total support from family and friends (weight = 0.11, SE = 0.09, t stat = 1.22, $p = 0.2$) were not significant contributors but contributed to the SDoH composite. Assessment of the correlation between indicators showed a significant correlation between education and income ($r = 0.3$, $p < 0.001$), education and perceived stress ($r = -0.11$, $p < 0.05$), health insurance and income ($r = -0.13$, $p < 0.001$), support and perceived stress ($r = -0.28$, $p < 0.001$), and total income and perceived stress ($r = -0.14$, $p < 0.005$). Variance inflation factor, a measure of multicollinearity, was < 2.5 for all indicators on each outcome variable indicating no significant multicollinearity among the indicators used (Table S2 in supporting information).

3.2 | Factor loadings for cognitive score

Both executive functioning (weight = 0.77, SE = 0.06, t = 12.26, $p < 0.001$) and episodic memory (weight = 0.43, SE = 0.05, t = 8.78, $p < 0.001$) significantly contributed to the cognition factor.

3.3 | Mediation model

3.3.1 | Total effects of SDoH on outcomes

The total effect of SDoH on physical functioning was small yet significant (beta = –0.21, SE = 0.05, $p < 0.001$, Cohen $f^2 = 0.01$), such that positive SDoH predicted less difficulty with physical functioning. Likewise, the total effect of SDoH on cognitive functioning was large and significant (beta = 0.54, SE = 0.05, $p < 0.001$, Cohen $f^2 = 0.41$), such that positive SDoH predicted better cognitive functioning.

3.3.2 | Direct effects

The direct effects of SDoH on both vascular burden (beta = –0.12, SE = 0.05, $p = 0.01$, Cohen $f^2 = 0.02$ [small]) and cognitive functioning (beta = 0.51, SE = 0.05, $p < 0.001$, Cohen $f^2 = 0.41$ [large]) were significant. The direct effect of vascular burden on cognition was also significant and negative (beta = –0.29, SE = 0.06, $p < 0.001$, Cohen $f^2 = 0.13$, [medium]). However, neither vascular burden (beta = 0.03, SE = 0.05, $p = 0.53$) nor cognition (beta = –0.16, SE = 0.09, $p = 0.10$) had significant direct effects on physical function. Furthermore, SDoH also did not have a significant direct effect on physical function (beta = –0.12, SE = 0.08, $p = 0.16$, Cohen $f^2 = 0.01$ [small]).

3.3.3 | Indirect effects

The indirect effect of SDoH on cognition (through vascular burden) was significant (beta = 0.04, SE = 0.02, t stat = 2.33, $p = 0.02$). As such, the association between SDoH and cognitive functioning was partially mediated by vascular burden. On the other hand, the indirect effect of vascular burden on physical function (through cognition) was not significant (beta = 0.04, SE = 0.03, t stat = 1.49, $p = 0.14$). Thus, the relationship between vascular burden and physical function was not significantly mediated by cognition. Finally, the total *indirect* effect of SDoH on physical function (through vascular burden, through cognition, and through vascular burden *and* cognition) was trending toward significance (beta = –0.09, SE = 0.05, t stat = –1.78, $p = 0.08$), while (as noted above) the *direct* effect was not significant. Considering that the direct effect was insignificant and the total indirect effect was trending toward significance, we may conclude that a substantial portion of the significant association between positive SDoH and physical function is mediated by vascular burden and cognition. See Figure 2 for the SEM model.

4 | DISCUSSION

The present analysis indicates that in a diverse adult population ages ≥ 55 who reported no clinical diagnosis of cognitive impairment or neurological disorders, SDoH had a significant total effect on physical functioning and a significant direct effect on cognition and vascular burden. Additionally, SDoH affected cognition indirectly through vascular burden. The association between vascular burden and physical functioning (through cognition) was insignificant. Overall, neither the direct effect nor indirect effect of SDoH on physical functioning reached significance. However, the indirect effect trended toward significance, inferring that a substantial portion of the relationship between SDoH and physical functioning was attributable to SDOH's effect on cognition and vascular burden. Examination of the individual SDoH indicators showed that years of education, perceived stress, and income contributed most substantially to the SDoH composite.

Various determinants of health factors are proposed to affect ADRD risk factors, including cognitive and vascular health. The current analysis showed the negative effects of stress and SES proxies (i.e., education and income) on cognition, vascular burden, and difficulties with physical functioning. Likewise, the results allude to the possibility that factors like support from family and friends and the availability of health insurance play a minor role in vascular health, cognition, and physical functioning, especially in the presence of low education, high stress, and low income. Although these SDoH factors might not play a

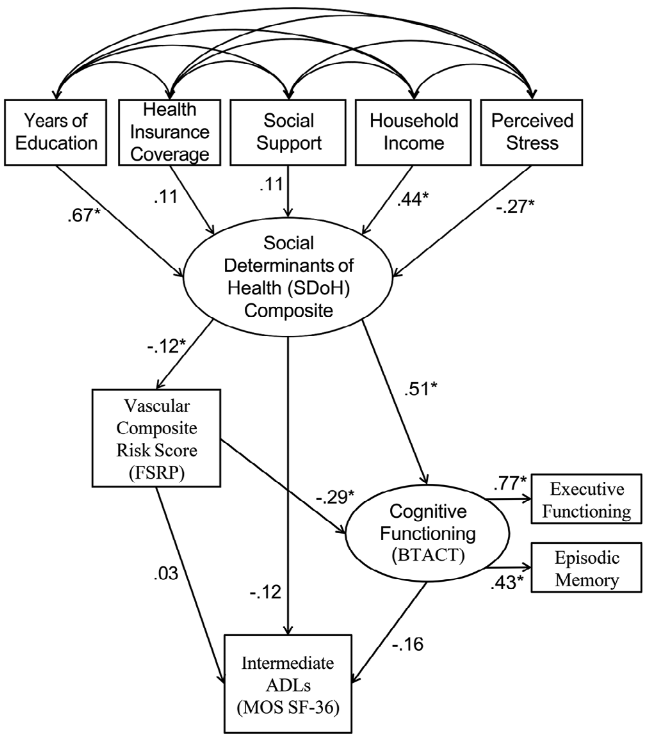

FIGURE 2 Composite-based structural equation model results for the primary dataset. ADLs, activities of daily living; BTACT, Brief Test of Adult Cognition by Telephone; FSRP, Framingham Stroke Risk Profile; MOS SF-26, Medical Outcomes Study 36-item Short Form Health Survey.

significant individual role in functioning, they might cumulatively exacerbate the impact on functioning. Clinically, assessing the cumulative impact of multiple SDoH factors helps us better understand how interlaced these indicators can be while also helping us identify the magnitude of individual indicators for intervention and preventive care purposes.

In the analysis of the SDoH composite, years of education had the greatest weight among the indicators, followed by total family income, perceived stress, support, and availability of health insurance. For the cognitive construct, executive functioning had a greater weight than episodic memory. One can infer then that when considering these five SDoH indicators in their relationship with cognition, vascular burden, and physical functional abilities, education, income, and stress individually play a significant role in the presence of vascular diseases (and, as such, increase vascular burden) and cognitive functioning (with a significant magnitude of impact on executive functioning). That is to say that education, income, and stress individually significantly impacted executive functioning more than episodic memory. The literature on the effects of SES proxies (e.g., income and education) on cognition[15,16,44,62] and stress on memory[23,24,44] is vast. However, the data on the relationship between stress and executive functioning are limited and inconsistent, and the relationship is proposed to be bi-directional. In one direction, high executive functioning mitigates the effects of stress by facilitating cognitive regulation and cognitive appraisal, reducing stress's perceived severity.[63,64] As such, individuals with better executive functioning skills may perceive stressful situations as less stressful, increasing resilience to stress and improving health outcomes. In the other direction, acute and chronic stress impair executive functioning[23,65] with a potential moderating effect of sex.[66,67] Results from the current analysis support the potential relationship between higher stress and poor episodic memory and executive functioning, in the presence of higher education and income. These findings are clinically meaningful as they add to the literature on the effects of stress on episodic memory, executive functioning, vascular burden, and physical functioning. The findings also suggest a greater association between stress and executive functioning than stress and memory.

The direct association between vascular burden and physical functional abilities was positive (i.e., higher vascular burden and increased physical limitations) but non-significant in the current analysis. Significant evidence exists in the literature on the association between poor vascular and physical health. Possible mechanisms include cerebrovascular accidents and other vascular diseases causing profound limitations on physical and functional abilities.[68–70] Although the current findings confirmed this association, it was not significant. Using the FSRP allows one to evaluate cumulative effects and the impact of various vascular risk factors on physical limitations. Given that the current analysis used a measure that directly assesses physical limitations, and the FSRP combines risk factors with a direct negative association with physical limitations (e.g., cardiovascular disease, smoking, atrial fibrillation, diabetes), it was surprising that the assessed relationship in the current analysis was not significant. A potential explanation could be the few physical limitations the study sample reported. Also, in the FSRP, smoking carries a large weight. Our original sample had ≈ 18% smokers, potentially restricting the range of FSRP scores in this relatively young and healthy sample. Clinically, the result from the current analysis adds to the current literature in that, even in a presumed cognitively healthy sample, increased vascular burden can impact one's physical functioning. This further emphasizes the importance of controlling vascular risk factors even in mid-adulthood.

Consistent with our hypotheses, cognition and vascular burden fully mediated the relationship between SDoH and physical functional abilities. The results of the current analyses further support the effects of SDoH on everyday functioning, consistent with the broader disablement theory.[41] The cumulative evaluation of these SDoH factors points to how different systems outside the disease model can collectively affect functioning, potentially leading to functional impairment. Although not formally evaluated (due to the cross-sectional nature of the current analysis), the current results showcase how suboptimal functioning (secondary to SDoH factors) can lead to clinically significant functional impairment over time. In other words, prolonged cumulative stress and burden on various biological and physiological systems over a period of time due to negative SDoH likely contribute to functional impairments. Clinically, it might be helpful to perceive the cumulative negative different SDoH indicators as a potential indirect increase in allostatic load, given SDoH association with increased allostatic load.[71–73] This can facilitate the use of a broader systems approach to develop treatment plans and recommendations. In clinical research, we can also evaluate whether manipulating or improving one factor can rebalance the burden on the system and ultimately reduce the detrimental effect on health.

The current analyses observed a negative significant indirect association between SDoH and cognitive functioning (through vascular burden). It is well established that increasing vascular risk factors and their associated vascular burden negatively affect cognition.[68–70] Likewise, different SDoH factors affect vascular health and cognition negatively.[14,15,17,18,21–24,27,74] As such, a significant association between these factors was expected to be observed in the current analysis. Surprisingly, our results showed that SDoH and vascular burden might be independent of (albeit adding to) the associations between SDoH and cognition among this population of adults. As explained earlier, the relationship and magnitude of impact between the individual SDoH indicators and vascular health and cognition might differ. It is possible that either the individual indicators or their combined effect impact vascular burden and cognition differently. One potential difference might be the effect of the indicators on a cognitive construct with a higher executive function weight. This result is new and important in that SDoH factors might impact vascular health and cognition differently. Clinically, different interventions and policies might be needed to improve health equity within these health outcomes. Focusing on interventions or policies that improve health equity in vascular health might not completely improve cognition. As evidenced by the results (i.e., reduced variance in the mediation analysis), it is also possible that targeting poor vascular health due to adversities in SDoH might indirectly improve cognition. However, additional interventions might be needed given the continued unique effects of SDoH on cognitive health.

4.1 | Strengths and limitations

One of the significant strengths of the current analysis is the success in creating a combined effect of five SDoH factors from multiple SDoH domains and using this to assess the interplay with vascular burden, cognition, and physical functional. This is the first analysis of this type, as prior analyses have only examined associations of individual SDoH with ADRD risk factors (cognitive, vascular, and physical functioning). Additionally, the unique benefit of the current statistical model and analysis (i.e., the use of c-SEM) is that one can evaluate both cumulative effect and individual contributing weights on different outcome factors. As such, one is truly evaluating the unique association between each significant formative indicator and observed and latent variables while simultaneously looking at the combined effects. The current study is the first to test a proposed theory of the co-occurring effects of different SDoH factors (again from different SDoH domains) on ADRD risk factors and outcomes among participants without clinically diagnosed neurologic disorders. This paves the way to evaluate different combinations of SDoH factors and their impact on different health outcomes or in a sample with a more balanced cognitive diagnosis (i.e., cognitively healthy, mild cognitive impairment, and dementia). The current analysis also included a diverse national sample in terms of SES, education, race, and sex.

The recently proposed framework for evaluating the role of SDoH in ADRD across Alzheimer's Disease Research Centers identified seven domains of SDoH to watch: perceived stress, social support, education, occupation, social positioning, social environment/neighborhood, and social identity.[44] While measures from most of these proposed domains were included in the current analysis, measures on occupation and social environment were not included. Variations in validated measures existed between the proposed measures and those used in the current study (although these were minimal). Nevertheless, the current project coincidently tested this recently proposed framework in a diverse national sample of adults. To our knowledge, this is the first evaluation of the co-occurring impact of different SDoH factors (i.e., indicators from different SDoH domains) on ADRD outcomes and risk factors. The present study adds to the literature by providing a window into the individual and cumulative magnitudes of the effects of SDoH factors and their interplay with cognitive functioning, vascular burden, and everyday functional status. The results also provide a multi-system approach to evaluating and creating interventions to decrease ADRD outcomes.

The current study possesses a few limitations. For one, the analysis was conservative in the number of formative indicators added to create the SDoH construct. The novelty of the statistical method/model and the availability of indicators in the available dataset limited our ability to expand the number of indicators included in the analysis. Likewise, the addition of more indicators introduces the possibility of multicollinearity, as the c-SEM model cannot be used with indicators that are highly correlated with one another. Also, although the model fit for the current analysis is good, it is not "great." As such, it is possible that the model could be improved with the addition or substitution of other SDoH variables (i.e., formative indicators).

In addition, the interpretation of results was limited by using a cross-sectional dataset, precluding our ability to test the directionality or causality of effects. Longitudinal analysis would be informative in evaluating trends in cognitive, vascular, and physical functional abilities secondary to changes/transitions in the SDoH factors.

Although the overall MIDUS study is diverse and the percentage of Black Americans included was at the national makeup of Black Americans, the study sample was still predominantly White. Additionally, the study participants were generally healthy, with higher education and positive SDoH factors, compared to individuals experiencing poor health equity. Although this is an observational study with a nationally representative sample, the sample of participants may echo what is commonly seen in other research studies: those with resources are the most able to participate in research.

In terms of limiting study measures, the tool used in the MIDUS study for everyday functional abilities predominantly assessed physical difficulties, with no evaluation of the impact of cognitive difficulties on everyday functioning. As such, the current results cannot be generalized to overall instrumental activities of daily living (ADLs), and might be more applicable to disability and physical limitations. Substituting the current intermediate ADL (proxy for physical functional abilities) measure with a more commonly used (and appropriate) measure of instrumental ADL, like the Functional Activities Questionnaire (FAQ) or the Everyday Cognition (ECog) battery, might have yielded different results. As explained earlier, the direct effect of cognition on intermediate ADLs might have been significant if a measure that accounts for cognitive functioning (like the ECog) was used instead. Knowing that cognition can interfere with both basic and instrumental ADLs, substituting the current intermediate ADL measure with the FAQ, for example, (which does not directly account for the impact of cognitive functioning on completing ADLs) would have still provided different results.

5 | CONCLUSION

Healthy People 2030 aims to eliminate health disparities, achieve health equity, and attain health literacy to improve health and well-being for all.[8,10] Further evaluation of cumulative effects with a model like c-SEM could help create multisystem interventions and policies to reach that goal. The current article explains that cardiovascular health is vital to cognitive and everyday physical functioning. The Lancet Commission on Diabetes and the World Health Organization Global Diabetes Compact recommends multifaceted perspectives to address the challenges and burden of cardiovascular diseases like diabetes.[75] In addressing this, Walker et al.[75] proposed multilayered approaches that connect the ecosystem (i.e., policies, social systems, and the environment) and frameworks within public health and social sciences to direct interventions and inform clinical practices. By so doing, we can improve health equity. The statistical approach used in the current article attempts to follow this recommendation by testing the association between different theoretical social constructs and various health outcomes. Future studies should consider including other SDoH indicators in a more diverse population. This could help address the generalizability of findings, inform policies, and move researchers closer to developing interventions and implementing clinical practices to improve health equity.

The current analysis found that higher perceived stress, lower education, and lower income contributed substantially to the SDoH composite and were associated with lower baseline cognition, higher vascular burden, and poor physical functioning in mid-adulthood. A broader systems approach to developing treatment plans and recommendations is warranted, especially among individuals with multiple adversities.

AUTHOR CONTRIBUTIONS

PAAH: contributed to the conceptualization, data curation, formal analysis, methodology, validation, visualization, and writing of the original draft and review/editing. JAF: contributed to formal analysis and review/editing of the written manuscript. SAL: contributed to visualization, supervision, and review/editing of the written manuscript. KMR: contributed to visualization, supervision, and review/editing of the written manuscript. AFW: contributed to supervision and review/editing of the written manuscript. GES: contributed to supervision and review/editing of the written manuscript.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report. Author disclosures are available in the supporting information.

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CONSENT STATEMENT

All study participants signed an informed consent agreeing to collecting and using blinded study-related information (including data for secondary data analysis). All required permissions (i.e., data usage agreement forms) needed to use available datasets were requested and approved, and all procedures for the current study were approved by the University of Florida Institutional Review Board (under an exempt designation) before initiation of study analysis. The current analysis was not prespecified primary outcomes for the MIDUS 2 study.

LEXI-DATA USED IN MIDUS

Lexi-Data is a drug data solution offered by Wolters Kluwer Clinical Drug Information. Certain information about therapeutic effects and active ingredients of generic medications identified in the MIDUS (Midlife in the U.S.) or MIDJA study is derived from the Lexi-Data database and used under license from Lexi-Comp, Inc., which reserves all rights in that information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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