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RESEARCH ARTICLE

Association of allostatic load with all-cause and cause-specific dementia: A prospective cohort study

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Abstract

INTRODUCTION: Allostatic load (AL) serves as a valuable tool for objectively assessing the biological impact of chronic stress and has been implicated in dementia risk. This study aims to investigate the association between AL and all-cause dementia, Alzheimer's disease (AD), vascular dementia (VaD), and non-Alzheimer non-vascular dementia (NAVD).

METHODS: This prospective study included 361,920 adults from the UK Biobank, with an observation period extending from March 13, 2006, to October 31, 2022, excluding participants with prior dementia diagnoses. AL was estimated through 10 biomarkers related to the dysregulation of metabolic, cardiovascular, and inflammatory systems. Diagnoses were based on the International Classification of Diseases, 10th Revision (ICD-10). We performed Cox proportional hazards models to assess the relationship between AL and dementia. Additionally, we conducted subgroup analyses for sex, Townsend Deprivation Index (TDI), and smoking, along with sensitivity analyses.

RESULTS: The median follow-up period was 12.88 years. Over the follow-up period, 6155 (1.70%) participants developed all-cause dementia, 2762 (0.76%) developed AD, 1316 (0.36%) developed VaD, and 3790 (1.05%) developed NAVD. In the fully adjusted model, high AL was associated with an increased risk of all-cause dementia (hazard ratio [HR]: 1.269, 95% confidence interval [CI]: 1.159–1.390), VaD (HR: 1.934, 95% CI: 1.569–2.384), and NAVD (HR: 1.253, 95% CI: 1.116–1.408). Women and non-smoking individuals with high AL were vulnerable to VaD, and the associations between AL and all-cause dementia were stronger in people with high TDI.

DISCUSSION: AL is positively associated with an elevated risk of dementia, underscoring its effect as a risk factor in the neurodegenerative process that provokes dementia.

Yifan Gou and Xin Qi contributed equally to this work

KEYWORDS
allostatic load, Alzheimer's disease, dementia, vascular dementia

Highlights

- This study estimated allostatic load (AL) index through 10 biomarkers.
- The associations between AL and all-cause and cause-specific dementia were evaluated.
- Elevated AL is a risk factor for all-cause dementia and vascular dementia.

1 | INTRODUCTION

Dementia poses a significant and growing global health challenge, with the number of cases projected to increase from 57.4 million in 2019 to 152.8 million by 2050.[1] Individuals with dementia often face reduced access to community health care and have difficulty obtaining effective treatment.[2]

Stress, as a reflection of the mind–body interaction, plays a crucial role in the onset and progression of various diseases.[3] The allostatic load (AL) index describes "the 'wear and tear' of the body and its regulatory system" as the result of too much stress or ineffective stress response, characterized by repeated, prolonged, inadequate, or absent adaptation.[3] AL involves multiple interconnected adaptive mediators functioning within a non-linear network.[4] The AL index is a collective measure of cardiovascular, metabolic, neuroendocrine, and immune disorders associated with stress exposure and cognitive function.[5] While some studies have investigated the relationship between individual markers, such as C-reactive protein (CRP), and brain function, comprehensive measurements of AL provide a more holistic understanding of complex brain processes.[6] In recent years, growing evidence has highlighted the impact of comorbidities and additive intraindividual health-related risk factors on cognitive decline.[7,8] Therefore, this study used the AL index to quantify the cumulative physiological burden imposed by stressors over time.

To date, disease biomarkers have been integrated into the prevention for various neurodegenerative diseases, including Alzheimer's disease (AD) and dementia with Lewy bodies.[9–11] The AL index serves as a risk factor for many stress-related health outcomes.[12] Research by Hough et al. demonstrated that AL and metabolic dysregulation may be linked to antidepressant treatment outcomes in patients with major depressive disorder.[13] One study found that individuals with elevated AL showed significantly greater declines in both cognitive and physical function, along with an increased risk of cardiovascular disease.[14] However, research on the relationship between AL and dementia is limited, with only one prospective study assessing the association between AL and AD biomarkers, involving a small sample of 188 participants.[15]

This study aimed to investigate the association between AL and subsequent dementia, including all-cause dementia, AD, vascular dementia (VaD), and non-Alzheimer non-vascular dementia (NAVD) in the UK Biobank (UKB). We explored the relationship between AL and dementia through Cox regression models, and performed a series of sensitivity analyses to judge the robustness of results.

2 | METHOD

2.1 | Study design and participants

The UKB is a large, prospective, population-based study, which recruited ≈ 500,000 participants aged 40 to 69 years.[16] The participants were assessed from 22 assessment centers throughout England, Wales, and Scotland. All participants provided electronic signed consent. Participants underwent a self-completed touch-screen questionnaire; brief computer-assisted interview; a series of physical measurements; and the collection of blood, urine, and saliva for laboratory analysis.[16] The details are described on the official website (https://www.ukbiobank.ac.uk/) and in a previous study.[16] After excluding participants with missing data of baseline and AL index measurements, 361,920 participants were included. The detailed process is shown in Figure 1.

2.2 | Assessment of outcomes

The primary outcome of this study was the diagnoses of all-cause dementia and cause-specific dementia. Indeed, the diagnoses of the outcomes were obtained by linking individual medical records from multiple diagnostic data sources, including primary care, hospital admissions, death records, and self-reported medical conditions. Outcomes were coded according to the International Classification of Diseases, 10th Revision (ICD-10) coding system. Specifically, all-cause dementia was defined by codes F00, F01, F02, F03, G30, G310, G311, and G318; AD by F00 and G30; VaD by F01; and NAVD by F02, F03, G310, G311, and G318. Detailed diagnostic codes for each condition are provided in Table S1 in supporting information. Participants were followed up from baseline. The unexposed individuals were defined as those who had no diagnoses of dementia at the date when the

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed sources and meeting abstracts and presentations. Allostatic load (AL) serves as a valuable tool for objectively assessing the biological impact of chronic stress. While the association between AL and dementia is not yet as widely studied, there have been several recent publications describing the effect of AL in mental disorders and cognitive function. These relevant citations were appropriately referenced.
2. **Interpretation**: Our findings lead to a hypothesis describing the positive effect of AL in elevated risk of dementia. This hypothesis is consistent with clinical and non-clinical findings currently in the public domain.
3. **Future directions**: The article proposes a framework for the generation of new hypotheses and the conduct of additional studies. It includes further understanding: (a) possible mechanisms by which elevated AL increases the risk of dementia; (b) if and how interventions to reduce AL can be integrated into the prevention of dementia.

follow-up ended (October 31, 2022). Individuals who did not have a specific date of the outcome event included as follows: the last investigation date was recorded at the date when the follow-up ended, the date of death, or loss to follow-up, whichever came first.

2.3 | Assessment of AL

The AL index was determined by 10 available biomarkers (assessed at the baseline visit) that are associated with disorders of the metabolic, cardiovascular, and inflammatory systems.[17,18] Unfasted serum biomarkers included serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, hemoglobin A1c (HbA1c), insulin-like growth factor 1 (IGF-1), and CRP.[17] Physical measurements, including waist and hip measurements, weight, height, and blood pressure, were collected by trained staff. Specifically, metabolic dysregulation was measured by serum glucose (mmol/L), total cholesterol (mmol/L), HDL cholesterol (mmol/L), HbA1c (mmol/mol), waist-to-hip ratio, and body mass index (BMI). CRP (mg/L) was used to evaluate the inflammatory dysregulation, and cardiovascular dysregulation was assessed by systolic blood pressure (SBP; mmHg) and diastolic blood pressure (DBP; mmHg). The field IDs of variables for the AL construction are shown in Table 1.

Each biomarker was dichotomized into high risk versus low risk based on a sex-specific quartiles.[19] High-risk thresholds were determined for male and female participants, with the high-risk group defined as values above the 75th percentile for serum glucose, total cholesterol, HbA1c, waist-to-hip ratio, BMI, CRP, IGF-1, SBP, and DBP, and below the 25th percentile for HDL cholesterol. Participants were assigned a score of 1 (high risk) or 0 (low risk) for each component based on these sex-specific cut-off points. Descriptive information and high-risk cut-off values are shown in Table 1. The AL score was calculated by summing the 10 dichotomous scores, with higher score indicating more severe physical dysregulation. In the primary analysis, the AL index was converted into a categorical variable, with the tripartite conversion of the initial AL score into "low (0–2)", "medium (3–4)" and "high (5–10)" AL.[18,19]

2.4 | Assessment of covariates

Information on sociodemographic and lifestyle factors was collected through a touch-screen questionnaire. The following covariates were included: age, sex, race (White, Black, Asian, and other), Townsend Deprivation Index (TDI), physical activity, frequency of smoking per day, and frequency of drinking per week. TDI, as an area level socioeconomic status, was defined as "a state of observable and demonstrable disadvantage relative to the local community or wider society to which an individual, family or group belongs," showing its advantage in measuring health inequalities.[20,21] It is a composite score based on four key variables: unemployment, overcrowded households, no car, and no home, with higher scores indicating higher levels of poverty.[21] Physical activity criteria were derived from the UK Biobank Category 100054 and were defined using responses to touchscreen questionnaires regarding walking, moderate physical activity, and vigorous physical activity. Smoking frequency was defined as the maximum number of reported past or current cigarettes (or pipes/cigars) consumed per day, and drinking frequency was defined as the average amount of different types of alcohol per week.

2.5 | Statistical analyses

Data for continuous variables was presented as mean ± standard deviation (SD), and the frequency and percentages were used for categorical variables. We used the Cox proportional hazard model to estimate the association of AL with all-cause and cause-specific dementia (AD, VaD, or NAVD). In Cox proportional hazard models, we defined AL index into three categories including low, middle, and high. We established three models adjusted for an increasing number of covariates: model 1 was adjusted for age and sex; model 2 made additional adjustments for race and TDI; model 3 further adjusted for life factors including physical activity, smoking frequency, and drinking frequency. Previous studies have found that sex, smoking, and socioeconomic status can affect dementia;[2,22] thus, we performed the subgroup analyses of sex, TDI, and ever smoking. TDI was divided into four layers by quartiles. Model in subgroup analyses was adjusted for age, sex, race, TDI, physical activity, smoking frequency, and drinking frequency.

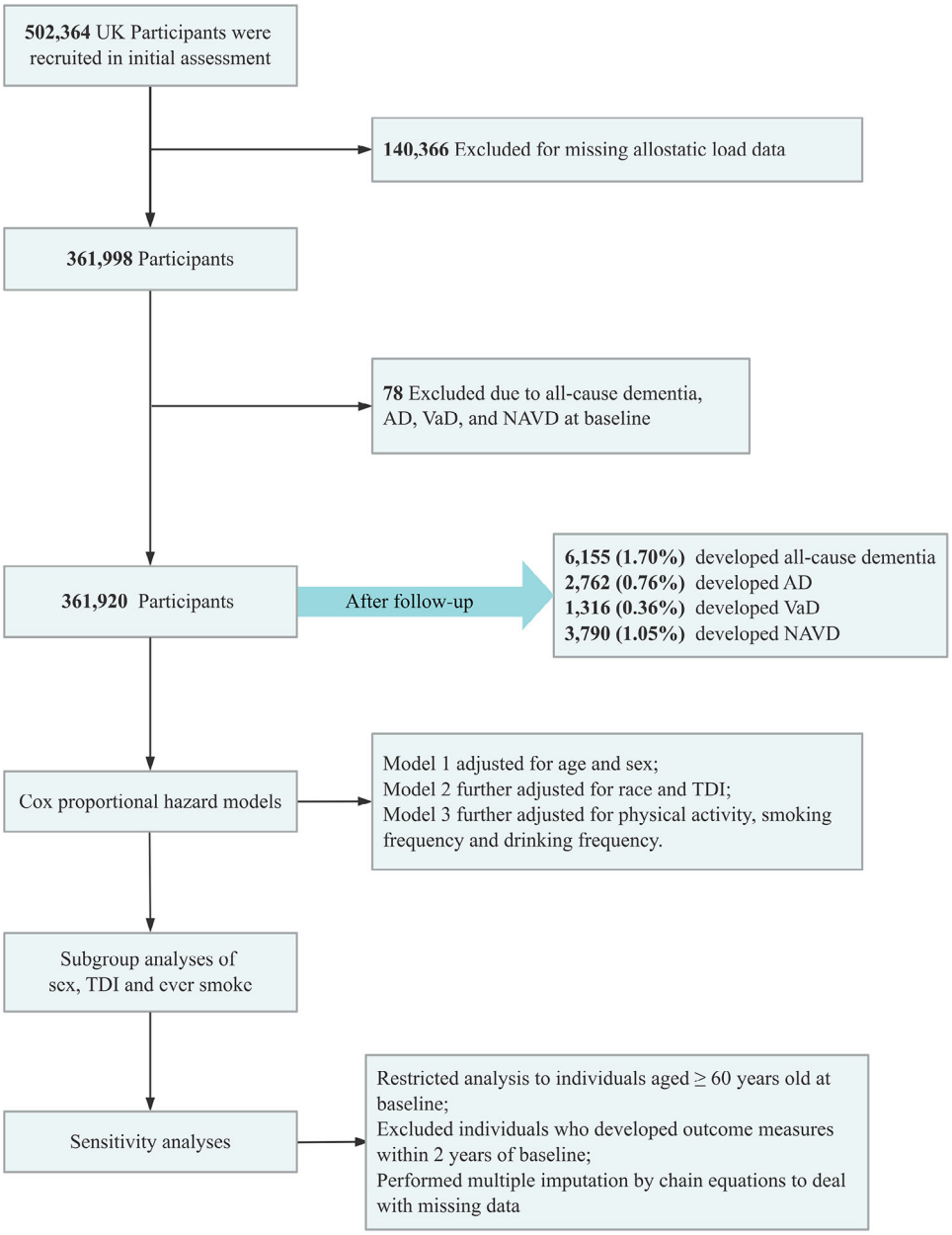

FIGURE 1 The flowchart of the study. AD, Alzheimer's disease; NAVD, non-Alzheimer, non-vascular dementia; TDI, Townsend Deprivation Index; VaD, vascular dementia

2.6 | Sensitivity analyses

We performed a series of sensitivity analyses to test the robustness of our findings. First, given that dementia typically occurs in older people, we restricted analysis to individuals aged at least 60 years at baseline. Moreover, we excluded individuals who developed outcome measures within 2 years of baseline assessment to minimize the possibility of reverse causality. Finally, we performed multiple interpolation using chain equations to deal with missing variables and reduce the possibility of inference bias using the "mice" package in R. The mice function used the predictive mean matching method to perform multiple imputations. We set the parameter "$m = 5$" to generate five different input datasets, thereby estimating the inherent uncertainty of the missing value. To ensure repeatability of the imputation process, we set a random seed (seed = 123). The Bonferroni method was used to correct for multiple testing, and $P<0.05$ was considered statistically significant. All analyses were performed in R v. 4.3.0.

3 | RESULTS

3.1 | Baseline characteristics of participants

This study included 361,920 participants and the median follow-up period was 12.88 years. Over the follow-up period, 6155 (1.70%) par-

TABLE 1 Field IDs and high-risk cut-off values of variables for the construction of allostatic load.

Domain	Labels in the current study	Full name in UK Biobank data dictionary	Field ID	Cut-points	
				Male	Female
Metabolic	Glucose (mmol/L)	Glucose	30740	5.36	5.28
	Total cholesterol (mmol/L)	Cholesterol	30690	6.22	6.59
	HDL (mmol/L)	HDL cholesterol	30760	1.06	1.33
	HbA1c (mmol/mol)	Glycated hemoglobin (HbA1c)	30750	38.10	37.70
	IGF-1(nmol/L)	IGF-1	30770	25.20	24.40
	Waist-to-hip ratio	Waist circumference/hip circumference	48, 49	0.98	0.86
	BMI (kg/m^2)	Weight/(height)^2	21002, 12144	30.00	29.70
Inflammatory	C-reactive protein (mg/L)	C-reactive protein	30710	2.53	2.96
Cardiovascular	SBP (mm Hg)	Systolic blood pressure (SBP)	4080	152.00	147.00
	DBP (mm Hg)	Diastolic blood pressure (DBP)	4079	90.50	87.00

Note: High-risk group was defined as below the 25th percentile for HDL and above the 75th percentile for glucose, total cholesterol, HbA1c, IGF-1, waist-to-hip ratio, BMI, C-reactive protein, SBP, DBP.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IGF, insulin-like growth factor; SBP, systolic blood pressure.

ticipants developed all-cause dementia, 2762 (0.76%) developed AD, 1316 (0.36%) developed VaD, and 3790 (1.05%) developed NAVD. Table 2 demonstrates the baseline characteristics of included participants by incident disease status.

3.2 | Associations of AL with all-cause and cause-specific dementia

Figure 2 illustrates the cumulative morbidity risk for dementia with low, middle, and high AL. Overall, morbidity risk for all-cause and specific dementia were found to be significantly higher in individuals with higher AL than in those with lower AL (log-rank test, $P < 0.001$).

The results of model 3 showed that, compared to participants with low AL, those with medium AL had a significantly increased risk of all-cause dementia (hazard ratio [HR]: 1.142, 95% confidence interval [CI]: 1.048–1.245), VaD (HR: 1.524, 95% CI: 1.242–1.871), and NAVD (HR: 1.124, 95% CI: 1.006–1.254). Participants with high AL had an even greater risk of all-cause dementia (HR: 1.269, 95% CI: 1.159–1.390), VaD (HR: 1.934, 95% CI: 1.569–2.384), and NAVD (HR: 1.253, 95% CI: 1.116–1.408), suggesting that high AL is a risk factor for all-cause dementia, VaD, and NAVD. In addition, the three models of all-cause dementia and cause-specific dementia all revealed a trend that the higher the AL, larger the HR value. The results are shown in Figure 3.

3.3 | Results of subgroup analyses

In subgroup analyses, compared to those with low AL, men with high AL exhibited a higher risk of all-cause dementia (HR: 1.275, 95% CI: 1.131–1.437) than women (HR: 1.256, 95% CI: 1.092–1.444). Conversely, women with high AL exhibited a significantly increased risk of VaD and NAVD (HR $_{VaD}$: 2.086, 95% CI: 1.457–2.986; HR $_{NAVD}$: 1.285, 95% CI: 1.070–1.542) than men (HR $_{VaD}$: 1.828, 95% CI: 1.411–2.368; HR $_{NAVD}$: 1.237, 95% CI: 1.064–1.439). Compared to the smoking group (HR $_{all\text{-}cause\ dementia}$: 1.156, 95% CI: 1.036–1.290; HR $_{VaD}$: 1.575, 95% CI: 1.243–1.995), the non-smoking group showed higher HRs (HR $_{all\text{-}cause\ dementia}$ 1.324, 95% CI: 1.173–1.495; HR $_{VaD}$: 2.213, 95% CI: 1.644–2.979). These findings are presented in Tables S2 and S3 in supporting information. Additionally, Table S4 in supporting information shows that in the high TDI group, high AL has a positive association with all-cause dementia (HR $_{TDI\_Q3}$: 1.335, 95% CI: 1.111–1.604; HR $_{TDI\_Q4}$:1.547, 95% CI: 1.284–1.864).

3.4 | Results of sensitivity analyses

After we restricted analysis to individuals aged at least 60 years at baseline, we found the association did not materially change (Table S5 in supporting information). After we excluded individuals who developed outcome measures within 2 years of baseline assessment,

TABLE 2 Basic characteristics of individuals included in this study.

	All-cause dementia (*N* = 361,920)		AD (*N* = 361,920)		VaD (*N* = 361,920)		NAVD (*N* = 361,920)	
Basic characteristics	**Case (*N* = 6155)**	**Control (*N* = 355,765)**	**Case (*N* = 2762)**	**Control (*N* = 359,158)**	**Case (*N* = 1316)**	**Control (*N* = 360,604)**	**Case (*N* = 3790)**	**Control (*N* = 358,130)**
Sex (female)	2915 (47.36%)	191,567 (53.85%)	1424 (51.56%)	193,058 (53.75%)	525 (39.89%)	193,957 (53.79%)	1754 (46.28%)	192,728 (53.82%)
Age (years)	64.26 (4.72)	56.40 (8.07)	64.67 (4.28)	56.47 (8.08)	64.76 (4.18)	56.50 (8.08)	64.11 (4.90)	56.45 (8.08)
Race (White)	5873 (95.42%)	335,719 (94.37%)	2642 (95.66%)	338,950 (94.37%)	1258 (95.59%)	340,334 (94.38%)	3595 (94.85%)	337,997 (94.38%)
TDI	−1.07 (3.22)	−1.35 (3.04)	−1.23 (3.17)	−1.35 (3.05)	−0.83 (3.33)	−1.35 (3.05)	−0.97 (3.25)	−1.35 (3.05)
Alcohol frequency weekly	9.99 (11.26)	10.13 (10.13)	9.28 (9.97)	10.14 (10.15)	10.71 (13.57)	10.13 (10.14)	10.15 (11.89)	10.13 (10.13)
Smoking frequency daily	8.47 (12.43)	6.37 (10.50)	7.54 (11.65)	6.40 (10.53)	9.94 (13.25)	6.40 (10.53)	8.56 (12.69)	6.39 (10.51)
Physical activity	49.93 (68.10)	48.72 (64.24)	53.12 (72.70)	48.71 (64.23)	48.00 (60.88)	48.74 (64.32)	48.89 (66.64)	48.74 (64.28)
AL biomarkers (dysregulated)								
Glucose (mmol/L)	5.47 (1.80)	5.12 (1.20)	5.38 (1.52)	5.12 (1.21)	5.78 (2.27)	5.12 (1.21)	5.47 (1.81)	5.12 (1.21)
Total cholesterol (mmol/L)	5.56 (1.29)	5.70 (1.14)	5.67 (1.29)	5.70 (1.14)	5.35 (1.35)	5.70 (1.14)	5.51 (1.25)	5.70 (1.14)
HDL (mmol/L)	1.42 (0.40)	1.45 (0.38)	1.45 (0.39)	1.45 (0.38)	1.36 (0.39)	1.45 (0.38)	1.42 (0.40)	1.45 (0.38)
HbA1c (mmol/mol)	38.65 (9.14)	36.04 (6.63)	38.15 (8.15)	36.07 (6.68)	40.98 (11.32)	36.07 (6.66)	38.55 (9.25)	36.06 (6.66)
IGF-1 (nmol/L)	20.27 (5.68)	21.43 (5.66)	20.15 (5.49)	21.42 (5.66)	20.13 (6.12)	21.41 (5.66)	20.36 (5.78)	21.42 (5.66)
Waist-to-hip ratio	0.90 (0.09)	0.87 (0.09)	0.89 (0.09)	0.87 (0.09)	0.92 (0.09)	0.87 (0.09)	0.90 (0.09)	0.87 (0.09)
BMI (kg/m^2)	27.74 (4.84)	27.39 (4.72)	27.34 (4.60)	27.40 (4.73)	28.65 (5.09)	27.39 (4.72)	27.76 (4.90)	27.39 (4.72)
C-reactive protein (mg/L)	2.86 (4.91)	2.57 (4.29)	2.64 (4.75)	2.58 (4.29)	3.11 (4.60)	2.58 (4.30)	3.00 (5.23)	2.57 (4.29)
SBP (mm Hg)	143.90 (19.07)	137.72 (18.55)	144.22 (18.88)	137.77 (18.57)	145.73 (19.81)	137.79 (18.57)	143.52 (19.30)	137.76 (18.56)
DBP (mm Hg)	81.75 (10.15)	82.26 (10.10)	81.63 (9.96)	82.25 (10.10)	82.36 (10.58)	82.25 (10.10)	81.67 (10.25)	82.26 (10.10)

Abbreviation: AD, Alzheimer's disease; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IGF, insulin-like growth factor; NAVD, non-Alzheimer, non-vascular dementia; SBP, systolic blood pressure; TDI, Townsend Deprivation Index; VaD, vascular dementia.

361,816 participants were included in the all-cause dementia cohort, 361,897 participants in the AD cohort, 361,902 participants in the VaD cohort, 361,850 participants in the NAVD cohort, and the association did not materially change (Table S6 in supporting information). Additionally, when we conducted interpolation to address missing values of variables, the results were not much different from the original analysis (Table S7 in supporting information).

4 | DISCUSSION

This study assessed the association between AL and dementia, revealing that elevated AL was positively associated with increased risk of all-cause dementia, VaD, and NAVD. Furthermore, women and non-smoking individuals with high AL were vulnerable to VaD, and the associations between AL and all-cause dementia were stronger in people with high TDI.

One study used UK Biobank data to construct an AL index and demonstrated that elevated AL is positively associated with increased risks of depression, anxiety, and suicide, underscoring its harmful effects on mental health.[18] Chronic stress and AL may contribute to cognitive decline and dementia risk.[23] A meta-analysis found a significant association between high AL and poorer cognition.[24] Insulin resistance, a key component of AL, mediates cognitive dysfunction, while AL itself induces insulin resistance.[25] This bidirectional association promotes conditions including diabetes, depression, and cardio-

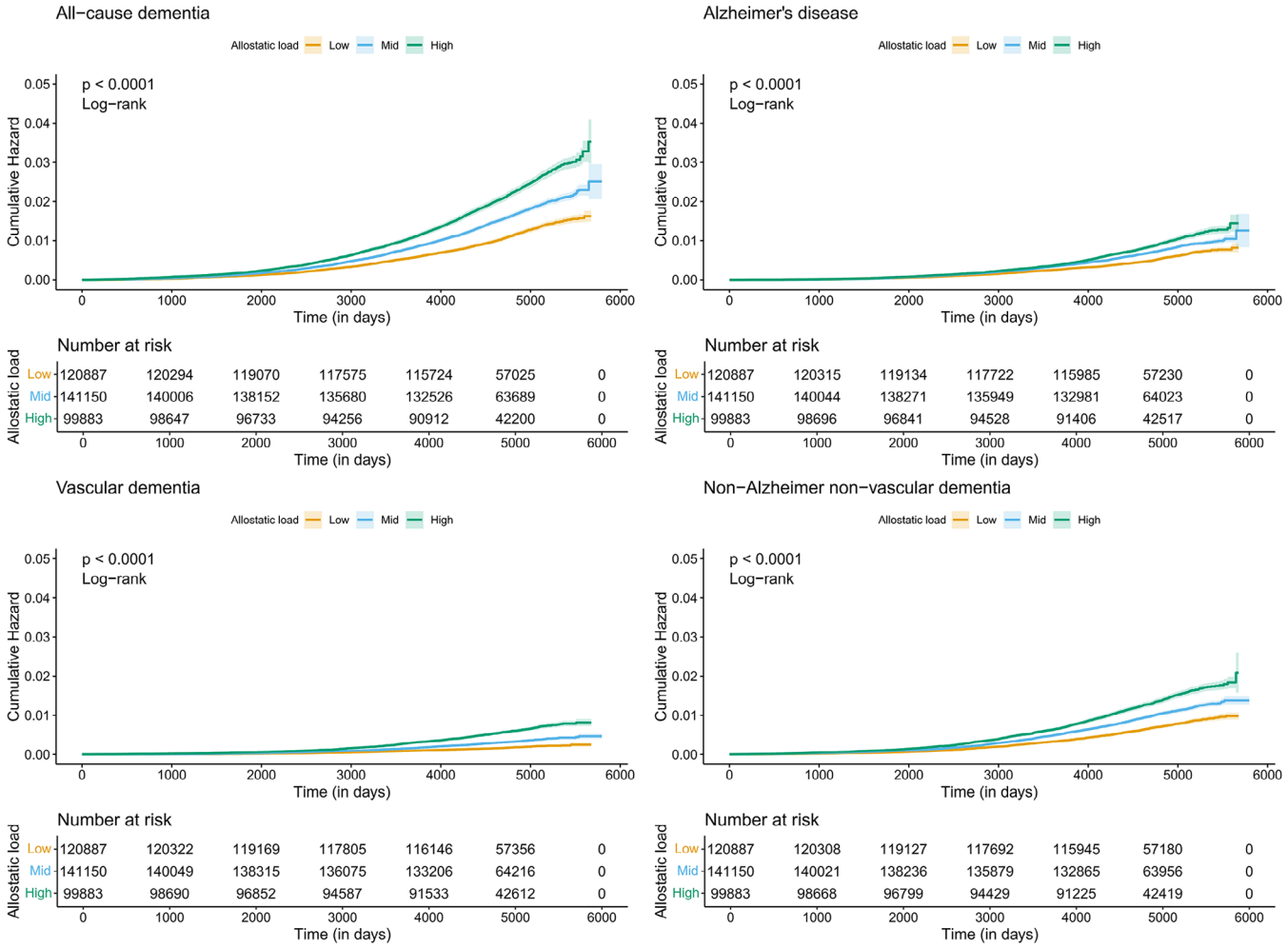

FIGURE 2 Kaplan–Meier probability of the cumulative morbidity risk for common mental disorders with allostatic load. Cumulative mortality is shown for the "low," "middle," and "high" allostatic load index

vascular and cerebrovascular diseases, that increase dementia risk.[23] Our findings further support the link between AL and dementia.

Systolic and diastolic blood pressure were key components of the AL index. Hypertension increases the risk of VaD through mechanisms such as compromised vasoreactivity and hypoperfusion, damage to the blood–brain barrier, oxidative stress, and cerebral capillary degeneration.[26] Additionally, dyslipidemia interacts with cerebral hypoperfusion, promoting brain inflammation and cognitive decline.[27] Elevated levels of oxidized low-density lipoprotein increase oxidative stress, triggering neuroinflammation and contributing to dementia progression.[28,29] Insulin resistance was also a key factor in VaD, as both insulin resistance and hyperinsulinemia were linked to cognitive impairment.[30] Emerging evidence suggests that insulin and its receptors regulate cognitive function by modulating postsynaptic receptor activity and activating specific signaling pathways.[31–33]

AD is a neurodegenerative disorder characterized by amyloid plaques and neurofibrillary tangles, resulting in memory impairment and cognitive decline.[34] In contrast, the AL index used in this study primarily reflected the cumulative physiological burden of chronic stress on the cardiovascular, metabolic, and immune systems rather than specific neurodegenerative processes. As AD is primarily driven by neuronal pathology, its association with the AL index may be weaker.

A recent study has found that the association between vascular risk factors and poor cognitive ability in women is stronger than that in men, consistent with our study.[35] In our study, high AL was more strongly linked to dementia in individuals with high TDI. A previous study proposed that lower socioeconomic status throughout the life course may be associated with higher AL.[36] From the ages 20 to 60 years old, biological risk increases due to the stress of poverty and reaches its highest level in middle age.[37] In addition, we found AL was more significantly associated with dementia in non-smokers. Nicotine temporarily affects the cholinergic system, potentially enhancing cognitive function or offering neuroprotection under certain conditions.[38,39] However, some studies have suggested that smoking increases the risk of dementia[40] or that it had nothing to do with dementia,[41] requiring further investigation.

Our findings suggested that AL biomarkers may be a significant risk factor in dementia, possibly promoting the neurodegenerative process, which provokes dementia. Therefore, our study underscores that reducing AL may help prevent the occurrence of dementia or alleviate

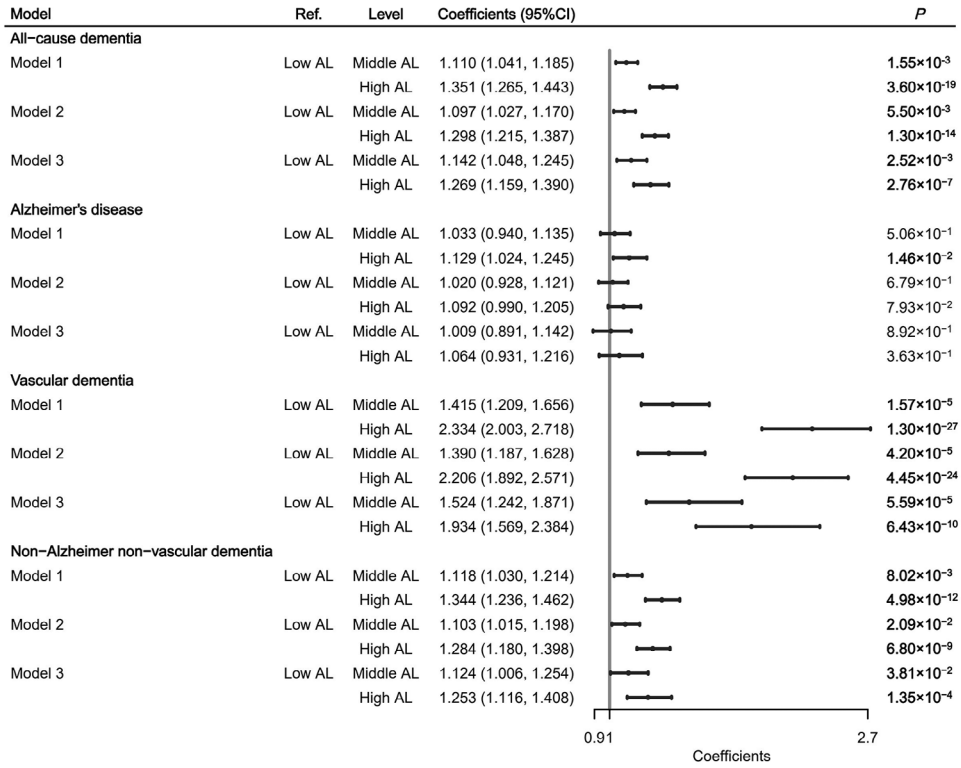

FIGURE 3 Forest plots for associations of allostatic load with all-cause and cause-specific dementia. The plots show the Cox proportional hazard models 1, 2, and 3. The dots are point estimations and the error bars are the 95% confidence limits. AL, allostatic load

its symptoms. A number of pieces of evidence suggest that AL can be modifiable through lifestyle interventions such as balanced nutrition, adequate sleep, and regular exercise.[12]

This study had some strengths in design and analysis. First, biomarker measurements from the UKB are standardized and follow a consistent protocol, minimizing measurement bias. Second, we decided to analyze an AL index rather than separate measures, which is helpful for assessing the effect of AL on dementia comprehensively. However, there are some limitations to the study. The construct of AL was limited to biomarkers available in UKB. Data on covariates were self-reported and may lead to recall bias. In addition, the strength of the HR may be affected by selection bias and incomplete control of confounding factors. Finally, only the primary care data of the majority of participants were available, which might lead to insufficient diagnosis of mild or early dementia. Therefore, our research may better represent cases of moderate to severe dementia.

In conclusion, our study provides strong evidence for the harmful effect of AL on all-cause dementia and VaD. Notably, women and non-smoking individuals with high AL were vulnerable to VaD, and we found the association between AL and all-cause dementia was stronger in people with high TDI. These findings suggest that AL biomarkers may serve as a risk factor for dementia, possibly playing a key role in the pathological pathways that cause the neurodegenerative processes of dementia.

AUTHOR CONTRIBUTIONS

Yifan Gou and Feng Zhang collected the data and conceived the study; Yifan Gou carried out the statistical analyses and wrote the manuscript; Xin Qi and Feng Zhang helped revise the manuscript; Chen Liu, Jingni Hui, Ye Liu and Meijuan Kang conducted the literature review and helped write the initial manuscript; Ruixue Zhou, Bingyi Wang and Panxing Shi improved the grammar and language of the manuscript. All authors reviewed and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have stated that they have no conflicts of interest. Author disclosures are available in supporting information.

DATA AVAILABILITY STATEMENT

The UK Biobank data are available through the UK Biobank Access Management System (https://www.ukbiobank.ac.uk/). We will return the derived data fields following UKB policy; in due course, they will be available through the UK Biobank Access Management System.

ETHICS STATEMENT

Ethical approval of the UKB study was granted by the National Health Service National Research Ethics Service (reference 11/NW/0382).

CONSENT STATEMENT

We confirm that all human subjects provided informed consent.

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REFERENCES

1. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7(2):e105-e125.
2. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446.
3. McEwen BS. Protective and damaging effects of stress mediators: central role of the brain. *Dialogues Clin Neurosci*. 2006;8(4):367-381.
4. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med*. 1998;338(3):171-179.
5. Ganzel BL, Morris PA, Wethington E. Allostasis and the human brain: integrating models of stress from the social and life sciences. *Psychol Rev*. 2010;117(1):134-174.
6. Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C. Circulating IL-6 and CRP are associated with MRI findings in the elderly: the 3C-Dijon Study. *Neurology*. 2012;78(10):720-727.
7. Morrow LA, Snitz BE, Rodriquez EG, Huber KA, Saxton JA. High medical co-morbidity and family history of dementia is associated with lower cognitive function in older patients. *Fam Pract*. 2009;26(5):339-343.
8. Peters R, Booth A, Rockwood K, Peters J, D'Este C, Anstey KJ. Combining modifiable risk factors and risk of dementia: a systematic review and meta-analysis. *BMJ Open*. 2019;9(1):e022846.
9. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014;13(6):614-29.
10. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology*. 2017;89(1):88-100.
11. Larner AJ. Diagnosis of dementia and cognitive impairment. *Diagnostics*. 2019;9(4).
12. McEwen BS. Mood disorders and allostatic load. *Biol Psychiatry*. 2003;54(3):200-207.
13. Hough CM, Bersani FS, Mellon SH, et al. Pre-treatment allostatic load and metabolic dysregulation predict SSRI response in major depressive disorder: a preliminary report. *Psychol Med*. 2021;51(12):2117-2125.
14. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci Biobehav Rev*. 2010;35(1):2-16.
15. Adedeji DO, Holleman J, Juster RP, et al. Longitudinal study of Alzheimer's disease biomarkers, allostatic load, and cognition among memory clinic patients. *Brain Behav Immun Health*. 2023;28:100592.
16. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779.
17. Jakubowski D, Peterson CE, Sun J, Hoskins K, Rauscher GH, Argos M. Association between adverse childhood experiences and later-life allostatic load in UK Biobank female participants. *Womens Health*. 2023;19:17455057231184325.
18. Gou Y, Cheng S, Kang M, et al. Association of allostatic load with depression, anxiety, and suicide: a prospective cohort study. *Biol Psychiatry*. 2024.
19. Castagné R, Garès V, Karimi M, et al. Allostatic load and subsequent all-cause mortality: which biological markers drive the relationship? Findings from a UK birth cohort. *Eur J Epidemiol*. 2018;33(5):441-458.
20. Ye J, Wen Y, Sun X, et al. Socioeconomic deprivation index is associated with psychiatric disorders: an observational and genome-wide gene-by-environment interaction analysis in the UK biobank cohort. *Biol Psychiatry*. 2021;89(9):888-895.
21. Townsend P, Phillimore P, Beattie A. Health and deprivation. Inequality and the North*. *Revista Cubana De Higiene Y Epidemiología*. 2004;35(1):48-50.
22. Podcasy JL, Epperson CN. Considering sex and gender in Alzheimer disease and other dementias. *Dialogues Clin Neurosci*. 2016;18(4):437-446.
23. De Felice FG, Gonçalves RA, Ferreira ST. Impaired insulin signalling and allostatic load in Alzheimer disease. *Nat Rev Neurosci*. 2022;23(4):215-230.
24. D'Amico D, Amestoy ME, Fiocco AJ. The association between allostatic load and cognitive function: a systematic and meta-analytic review. *Psychoneuroendocrinology*. 2020;121:104849.
25. Biessels GJ, Reagan LP. Hippocampal insulin resistance and cognitive dysfunction. *Nat Rev Neurosci*. 2015;16(11):660-671.
26. Peters R. Blood pressure, smoking and alcohol use, association with vascular dementia. *Exp Gerontol*. 2012;47(11):865-872.
27. Nordestgaard LT, Christoffersen M, Afzal S, Nordestgaard BG, Tybjærg-Hansen A, Frikke-Schmidt R. Triglycerides as a shared risk factor between dementia and atherosclerotic cardiovascular disease: a study of 125 727 individuals. *Clin Chem*. 2021;67(1):245-255.
28. Liang YQ, Kakino A, Matsuzaka Y, et al. LOX-1 (lectin-like oxidized low-density lipoprotein receptor-1) deletion has protective effects on stroke in the genetic background of stroke-prone spontaneously hypertensive rat. *Stroke*. 2020;51(6):1835-1843.
29. Chang HC, Tai YT, Cherng YG, et al. Resveratrol attenuates high-fat diet-induced disruption of the blood-brain barrier and protects brain neurons from apoptotic insults. *J Agric Food Chem*. 2014;62(15):3466-3475.
30. Ninomiya T. Diabetes mellitus and dementia. *Curr Diab Rep*. 2014;14(5):487.
31. Zhao WQ, Alkon DL. Role of insulin and insulin receptor in learning and memory. *Mol Cell Endocrinol*. 2001;177(1-2):125-134.
32. Zemva J, Schubert M. Central insulin and insulin-like growth factor-1 signaling: implications for diabetes associated dementia. *Curr Diabetes Rev*. 2011;7(5):356-366.
33. Salkovic-Petrisic M, Osmanovic J, Grünblatt E, Riederer P, Hoyer S. Modeling sporadic Alzheimer's disease: the insulin resistant brain state generates multiple long-term morphobiological abnormalities including hyperphosphorylated tau protein and amyloid-beta. *J Alzheimers Dis*. 2009;18(4):729-750.
34. Herrup K. Reimagining Alzheimer's disease–an age-based hypothesis. *J Neurosci*. 2010;30(50):16755-16762.
35. Tarraf W, Kaplan R, Daviglus M, et al. Cardiovascular risk and cognitive function in middle-aged and older Hispanics/Latinos: results from the Hispanic community health study/study of latinos (HCHS/SOL). *J Alzheimers Dis*. 2020;73(1):103-116.
36. Gruenewald TL, Karlamangla AS, Hu P, et al. History of socioeconomic disadvantage and allostatic load in later life. *Soc Sci Med*. 2012;74(1):75-83.
37. Crimmins EM, Kim JK, Seeman TE. Poverty and biological risk: the earlier "aging" of the poor. *J Gerontol A Biol Sci Med Sci*. 2009;64(2):286-292.
38. Brody AL. Functional brain imaging of tobacco use and dependence. *J Psychiatr Res*. 2006;40(5):404-418.

39. Swan GE, Lessov-Schlaggar CN. The effects of tobacco smoke and nicotine on cognition and the brain. *Neuropsychol Rev*. 2007;17(3):259-273.
40. Meyer JS, Rauch G, Rauch RA, Haque A. Risk factors for cerebral hypoperfusion, mild cognitive impairment, and dementia. *Neurobiol Aging*. 2000;21(2):161-169.
41. Kalmijn S, Foley D, White L, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. *Arterioscler Thromb Vasc Biol*. 2000;20(10):2255-2560.

SUPPORTING INFORMATION

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

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