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Associations of Vestibular Disorders With Risk of All-Cause and Cause-Specific Dementia: A Longitudinal Cohort Study in UK Biobank

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ABSTRACT

To explore associations of vestibular disorders with all-cause and cause-specific dementia and underlying biological mechanisms/neuroimaging changes. A population-based cohort study of 406,348 UK Biobank participants was conducted. Inverse probability of treatment weighting (IPTW) balanced baseline covariates, and Cox proportional hazards models estimated hazard ratios (HRs) for dementia outcomes. Inflammatory markers, plasma metabolites, and brain structure changes were analyzed. During 13.9 (SD 2.1) years of follow-up, 6702 dementia cases occurred. Vestibular disorders were linked to higher risks of all-cause dementia (HR 1.86 and 95% CI 1.04–3.30), Alzheimer's disease (AD, 2.36, and 1.01–5.51), and vascular dementia (VD, 3.35, and 1.48–7.59). Eight metabolites (e.g., VLDL cholesterol, and histidine) mediated the vestibular disorder-dementia association. Vestibular disorders also correlated with alterations in dementia-related brain structures (cortex, subcortical regions, and white matter tracts). Vestibular disorders increase all-cause and cause-specific dementia risk. This modifiable factor should be incorporated into dementia prevention initiatives.

Xiaofei Li, Fan Jiang and Qiuyue Dong contributed equally.

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Highlights

- In this large prospective cohort, vestibular disorders were associated with a significantly increased risk of all-cause dementia, Alzheimer's disease, and vascular dementia.
- The association between vestibular disorders and dementia was partially mediated by specific plasma metabolites, including VLDL cholesterol subclasses and histidine.
- Vestibular disorders were linked to structural changes in dementia-related brain regions, such as the hippocampus, entorhinal cortex, and temporal lobe.
- These findings identify vestibular disorders as a potentially modifiable risk factor, suggesting a new target for dementia prevention initiatives.

1 | Introduction

Dementia remains a serious challenge for healthcare systems worldwide [1]. By the year 2050, dementia is predicted to affect 150 million people worldwide, contributing to 115.8 million disability-adjusted life years [2]. Pharmaceutical approaches that target neuropathological processes, such as Alzheimer's disease (AD), offer limited benefits beyond symptom modification [3]. Preventive strategy that reduces risk factors of dementia may be more beneficial than pharmacologic therapy after clinical expression of neuropathology changes [4]. Studies estimate that more than one-third of dementia cases could be prevented by taking precautionary measures that address modifiable risk factors [2]. Recent research has suggested that vestibular disorders, which affect the inner ear and balance system, may be associated with an increased risk of cognitive decline and dementia [5–7]. The lifetime prevalence of vestibular disorders is approximately 7.4%, which increased with age from 6% in participants of 18–29 years to 35% among adults 80 years or older [8, 9]. Given their high prevalence, particularly among older adults, vestibular disorders represent a potentially modifiable risk factor for dementia [8, 9]. However, limited by the cross-sectional design and relatively small samples of previous studies, the association of vestibular disorders and dementia remain unclear [10–16].

The mechanism through which vestibular disorders might predispose an individual to dementia remain poorly understood. Plasma metabolomics has been used to depict alterations in circulating metabolites that could reflect the interaction of genetic and environmental factors, which benefits for understanding the pathophysiology of dementia [17–19]. Moreover, evidence suggests that peripheral immunity and inflammatory responses play significant roles in dementia onset. Given the accumulating evidence that inflammation and circulating metabolites are disturbed in people with vestibular disorders [20–23], we included systematic inflammatory markers and all metabolites detected by untargeted high-throughput nuclear magnetic resonance (NMR) spectroscopy to investigate the biological mechanism underlying the associations between vestibular disorders and dementia. In addition, vestibular disorders are likely to exacerbate brain atrophy, and even project

erroneous information to the hippocampus, retrosplenial cortex and visual cortex, and thus may be one of the mechanisms affecting dementia risks [24, 25]. However, current evidence on the associations of vestibular disorders with brain structure is sparse and inconclusive and are based on relatively small numbers of participants. Benefitting from the collected large-scale brain imaging data in UK Biobank (UKB), we are able to investigate the neuroimaging alterations between vestibular disorders and dementia.

In this study, we used the inverse probability of treatment weighting (IPTW) and propensity score matching to explore the associations between vestibular disorders with the risk of all-cause dementia and its subtypes, including AD, vascular dementia (VD), and non-AD non-VD (NAVD), using longitudinal data from the UK Biobank. Furthermore, we explored the potential mediation effect of inflammation and metabolites between vestibular disorders and all-cause dementia. Last, neuroimaging findings support the hypothesis that vestibular disorders and dementia share an overlapping neurobiological basis.

2 | Methods

2.1 | Study Design and Participants

The UKB is a longitudinal population-based cohort, recruited over 500,000 volunteers aged 40–69 years between 2006 and 2010. Individuals were invited to attend one of the 22 centers across England, Scotland, and Wales for baseline assessment. Written informed consent was obtained for collection of questionnaire and biological data. Since 2014, a subsample of participants was invited back for imaging assessment. UKB was undertaken with ethical approval from the North West Multi-Center Research Ethics Committee of the UK (ref11/NW/0382). This research was conducted under UKB application number 107217. We excluded those with missing data on vestibular disorders status or covariates, a prior diagnosis of dementia at baseline, resulting in 406,348 participants in formal analyses. All participants were followed until the date of first reported dementia diagnosis censored at date of death or lost to follow-up. Supporting Information S1: Table S1 presents a comparison of baseline characteristics between enrolled participants and excluded individuals. The detailed participant selection process is displayed in Supporting Information S1: Figure S1. This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supporting Information S1: Appendix 1). Figure 1 shows an overview of analyses performed in the current study.

2.2 | Assessment of Exposure, Outcome, and Covariates

Vestibular disorders cases were defined using hospital inpatient recorders (Hospital Episode Statistics for England, Morbidity Record for Scotland, and Patient Episode Database for Wales). International Classification of Diseases-10th (ICD-10) codes H81.0, H81.1, H81.2, H81.3, H81.4, H81.8, H81.9, H83.0, H83.1,

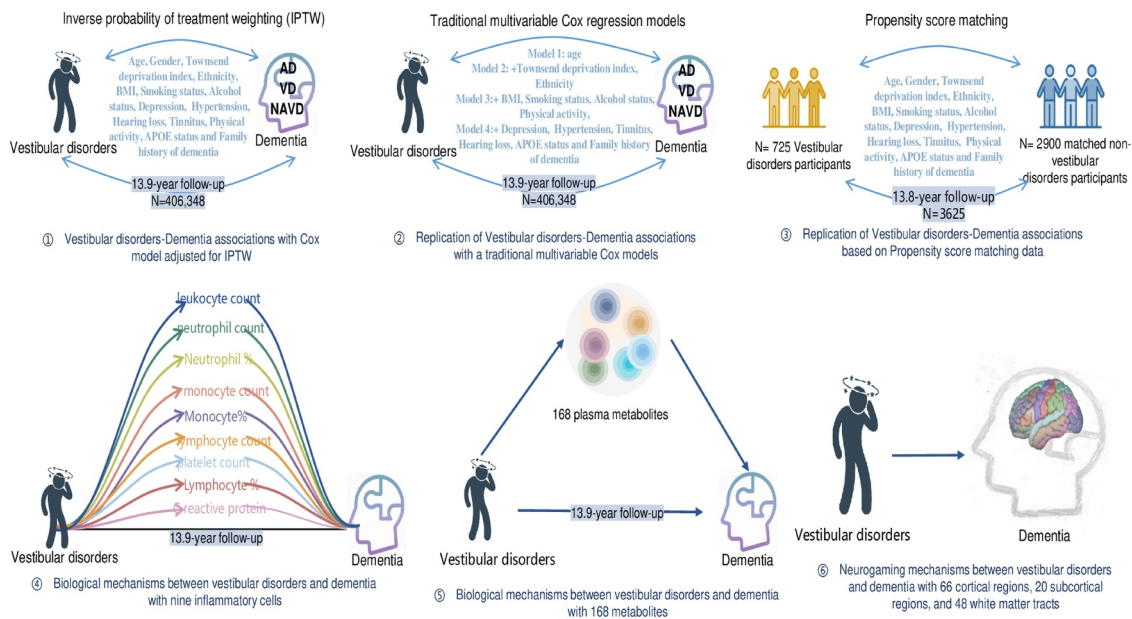


FIGURE 1 | Overview of analyses performed in the current study. Leveraging data from the UK Biobank, this study investigates the longitudinal association of vestibular disorders and all-cause and cause-specific dementia and the possible biological mechanisms and neuroimaging changes underlying these associations. First, Cox proportional hazards models adjusted for inverse probability of treatment weighting (IPTW) to estimate the hazard ratios and 95% confidence intervals between vestibular disorders at baseline and the risks of all-cause dementia and its subtypes. These analyses are subsequently replicated used traditional multivariable Cox regression models and based on matched vestibular disorders and nonvestibular disorders samples using a propensity score matching procedure to validate the main results. Second, the study investigated the mediating effects of inflammatory markers and plasma metabolites on the association between vestibular disorders and dementia in IPTW-adjusted cohort. Finally, the changed of brain structures were also analyzed in IPTW-adjusted cohort.

and H83. Two were used to identify participants with vestibular disorders if one or more of these codes were recorded as a primary or secondary diagnosis in the health records.

Dementia diagnoses were ascertained using hospital inpatient recorders and death register data (NHS Digital, NHS Central Register, and National Records). Hospital inpatient data were censored on 30 October 2022 (England), 31 August 2022 (Scotland), and 31 May 2022 (Wales). ICD-10 codes F00, F01, F02, F03, G30, G31.0, G31.1, and G31.8 were used to identify participants with all-cause dementia if one or more of these codes were recorded as a primary or secondary diagnosis in the health records. Incident AD was defined by ICD-10 codes F00 and G30. Incident VD was defined by ICD-10 code F01. Incident NAVD was defined by ICD-10 codes F02, F03, G31.0, G31.1, and G31.8. As AD is the most common type of dementia, in the present study, mixed dementia as atypical AD were classified in to AD. Outcome adjudication for incident dementia was conducted by the UKB Outcome Adjudication team.

We included the following factors in the analyses as covariates according to evidence from previous studies: age at baseline, sex, ethnicity, Townsend index of deprivation, smoking status, alcohol intakes, BMI, hypertension status, cardiovascular diseases (CVD) status, hearing loss status, tinnitus, depressive symptoms, apolipoprotein E (APOE) allele status, and family history of dementia [8, 13]. Detailed information on covariates was presented in Supporting Information S1: Appendix 2.

Supporting Information S1: Table S2 provided the field ID of vestibular disorders, dementia outcome, and covariates above.

2.3 | Assessment of Plasma Metabolites and Inflammatory Markers

Inflammatory biomarkers included leukocyte count, neutrophil count and percentage, monocyte count and percentage, lymphocyte count and percentage, platelet count, and C reactive protein (CRP). For metabolites, we included all metabolites available in absolute levels ($n = 168$) obtained with NMR. The mean concentration for inflammatory markers and plasma metabolites can be seen in Supporting Information S1: Tables S3 and S4. More detailed information of the assessment of blood biomarkers was provided in Supporting Information S1: Appendix 3.

2.4 | Assessment of Brain Imaging Data

Brain magnetic resonance imaging (MRI) data were acquired and processed by the UK Biobank team and made available to approved researchers as image-derived phenotypes (IDP). IDPs used in this study included volume, area, and thickness of 66 cortical regions, volume and intensity of 20 subcortical regions, and tract-specific fractional anisotropy (FA) and mean

diffusivity (MD) values of 48 white matter tracts. Detailed variable IDs and parameter meanings of brain imaging data were described in Supporting Information S1: Appendix 4 and Tables S5–S7.

2.5 | Statistical Analysis

2.5.1 | Longitudinal Association Between Vestibular Disorders and Dementia

Baseline summary statistics are presented as proportions for categorical data and means with standard deviations (SDs) for continuous variables. The inverse probability of treatment weighting (IPTW) was adopted to balance baseline participant characteristics. All the baseline variables presented in Table 1 were included in calculating the weights for IPTW and Cox proportional hazards regression models with robust standard error. After IPTW, covariates that were considered prognostically significant as well as those that might have influenced differences between exposure groups were considered insignificant if the standard mean difference (SMD) < 0.2 [26]. The Cox models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) between baseline vestibular disorders status and the risk of all-cause dementia, followed by separate analyses with dementia subtypes of AD, VD, and NAVD. Individuals with normal vestibular function were used as the reference group. The proportional hazards (pH) assumption was tested graphically using a plot of the log cumulative hazard, where the logarithm of time is plotted against the estimated log cumulative hazard. The curves for compared groups were approximately parallel; thus, the pH assumption was deemed reasonable. We estimated the 13.9-year cumulative incidence adjusted for IPTW.

Subgroup analyses were conducted by sex, age, Townsend deprivation index, smoking status, alcohol status, physical activity level, BMI, CVD status, hearing loss status, depression symptoms, and APOE allele status to assess potential effect modification. The interactions of vestibular disorders and stratification factors on dementia risk were assessed by adding product terms to the Cox models and tested using likelihood ratio tests.

We also conducted several sensitivity analyses to assess the robustness of the findings, including: (i) a traditional multivariable Cox proportional hazards regression model without accounting for IPTW; (ii) an alternative 1:3 propensity score matching instead of IPTW; (iii) excluding those who occurred dementia within 5 years of follow-up to minimize potential reverse causation; (iv) performing competing risk analysis with all-cause mortality defined as the competing event; and (v) covariates with missing values were imputed using the multiple imputations by the chained equations method (“mice” package in R software).

All analyses were performed using SAS (version 9.4; Institution Inc., Cary, NC) and R (version 4.1.2). A two-tailed $p < 0.05$ was regarded as statistically significant.

2.5.2 | Biological Mediators and Neuroimaging Analyses Between Vestibular Disorders and Dementia

We performed metabolic and inflammatory mechanism analyses based on IPTW-adjusted cohort. First, linear regression models were applied to evaluate the association of vestibular disorders with inflammatory markers or metabolites, with inflammatory markers or metabolites as dependent variable. Second, Cox regression models were implemented to examine the relationship between vestibular disorders, inflammatory markers/metabolites, and dementia, with the dementia as the outcome and inflammatory markers or metabolites as the independent variables. Biomarkers that simultaneously exhibited significance in the aforementioned steps would be considered as potential mediators for subsequent mediation analyses. All analyses were corrected using the Benjamini–Hochberg false discovery rate (FDR) method. The proportion mediated (PM) was estimated via the “mediation” package in R, and the nonparametric bootstrap method (1000 sampling) was used to calculate 95% CIs of the mediation effect. Inflammatory markers or metabolites were standardized (Z-score).

Mean MD in superior fronto-occipital fasciculus on FA skeleton was log-transformed due to its skewness. All brain morphometric measures were standardized (Z-score) prior to the analysis. Linear-mixed effect model was applied to investigate the association of vestibular disorders and dementia with brain morphometric measures. Vestibular disorders (dementia) were fitted as a fixed effect, UK Biobank assessment center as a random effect, and each of the brain morphometric measures was set as the dependent variable in separate models. All analyses were corrected using the Benjamini–Hochberg FDR method.

All analyses were performed using R (version 4.1.2) and an FDR adjusted $p < 0.05$ was regarded as statistically significant.

2.5.3 | Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of this study.

3 | Results

3.1 | Study Participants

A total of 406,348 participants with a mean (SD) age of 56.4 (8.1) years were included, of which 53.3% were female, the majority (95.2%) were white, and 725 (0.2%) had vestibular disorders. Prevalence of vestibular disorders increased with age and was more common in females. Participants with vestibular disorders were more likely to have lower socioeconomic status and unhealthier lifestyle behaviors, including less physical activity, have obesity and depressive symptoms, and have comorbidities such as hearing loss, hypertension, and CVD (Table 1). After IPTW, covariates were generally well-balanced with SMD < 0.2,

TABLE 1 | Characteristics of participants by vestibular disorders and dementia status, *n* (%).

Characteristics	All (<i>N</i> = 406,348)	Vestibular disorders (%)		SMD before IPTW	SMD after IPTW
		No (<i>N</i> = 405,623)	Yes (<i>N</i> = 725)		
Age at baseline				0.378	0.075
< 50	96,093	96,007 (23.7)	86 (11.9)		
50–60	156,082	155,833 (38.4)	249 (34.3)		
> 60	154,173	153,783 (37.9)	390 (53.8)		
Sex				0.002	0.053
Female	216,554	216,167 (53.3)	387 (53.4)		
Male	189,794	189,456 (46.7)	338 (46.6)		
Ethnicity				0.043	0.051
White	386,895	386,203 (95.2)	692 (95.5)		
Asian or Asian British	7562	7547 (1.9)	15 (2.1)		
Black or Black British	5527	5517 (1.4)	10 (1.4)		
Other	6364	6356 (1.6)	8 (1.1)		
Townsend deprivation index (quartiles)				0.056	0.038
Q1: Least deprived	105,338	105,160 (25.9)	178 (24.6)		
Q2	102,631	102,453 (25.3)	178 (24.6)		
Q3	101,869	101,689 (25.1)	180 (24.8)		
Q4: Most deprived	96,510	96,321 (23.8)	189 (26.1)		
Body mass index (kg/m ²)				0.283	0.014
< 25 kg/m ²	137,539	137,373 (33.9)	166 (22.9)		
25–29.9 kg/m ²	174,067	173,750 (42.8)	317 (43.7)		
≥ 30 kg/m ²	94,742	94,500 (23.3)	242 (33.4)		
Smoking status				0.087	0.044
Never	163,513	163,209 (40.2)	304 (41.9)		
Past	202,174	201,808 (49.8)	366 (50.5)		
Current	40,661	40,606 (10.0)	55 (7.6)		
Alcohol intake				0.293	0.156
Daily or almost daily	86,028	85,912 (21.2)	116 (16.0)		
3–4 times a week	97,275	97,126 (23.9)	149 (20.6)		
1–2 times a week	105,281	105,119 (25.9)	162 (22.3)		
Occasionally	88,242	88,050 (21.7)	192 (26.5)		
Never	29,522	29,416 (7.3)	106 (14.6)		
Physical activity level				0.086	0.039
Low	27,922	27,856 (6.9)	66 (9.1)		
Moderate	238,761	238,337 (58.8)	424 (58.5)		
High	139,665	139,430 (34.4)	235 (32.4)		
Hypertension				0.188	0.076
No	307,320	306,833 (75.6)	487 (67.2)		
Yes	99,028	98,790 (24.4)	238 (32.8)		
Hearing loss				0.561	0.014
No	303,238	302,887 (74.7)	351 (48.4)		
Yes	103,110	102,736 (25.3)	374 (51.6)		

(Continues)

TABLE 1 | (Continued)

Characteristics	All (N = 406,348)	Vestibular disorders (%)		SMD before IPTW	SMD after IPTW
		No (N = 405,623)	Yes (N = 725)		
Depressive symptoms				0.104	0.043
Several days or not at all	387,725	387,048 (95.4)	677 (93.4)		
More than half the days	11,512	11,488 (2.8)	24 (3.3)		
Nearly every day	7111	7087 (1.8)	24 (3.3)		
Tinnitus				0.361	0.082
No	382,774	382,173 (94.2)	601 (82.9)		
Yes	23,574	23,450 (5.8)	124 (17.1)		
APOE e4				0.016	0.070
No APOE e4	308,228	307,677 (75.9)	551 (76.0)		
One APOE e4	89,947	89,786 (22.1)	161 (22.2)		
Two APOE e4	8173	8160 (2.0)	13 (1.8)		
Family history of dementia				0.026	0.006
No	358,846	358,212 (88.3)	634 (87.5)		
Yes	47,502	47,411 (11.7)	91 (12.6)		

Abbreviations: APOE, apolipoprotein E; IPTW, inverse probability of treatment weighting; SMD, standard mean difference.

although participants with vestibular disorders still had a higher propensity for alcohol intake. The baseline characteristics of the weighted cohort were described in Supporting Information S1: Table S8. After 13.9 (SD 2.1) years of follow-up, 6702 study participants were diagnosed with dementia, including 3059 cases of AD, 1426 VD, and 4075 NAVD.

3.2 | Longitudinal Associations Between Vestibular Disorders and All-Cause and Cause-Specific Dementia

The 13.9-year cumulative incidence of all-cause dementia was 2.9% in participants with normal vestibular function and 5.8% in participants with vestibular disorders. Participants with vestibular disorders had 1.86-times higher risk of all-cause dementia (HR 1.86 and 95% CI 1.04–3.30) than participants with normal vestibular function (Figure 2A). Regarding subtypes of dementia, participants with vestibular disorders consistently increased the risk of AD and VD. For AD, the 13.9-year cumulative incidence was 1.3% among participants with normal vestibular function and 2.9% among participants with vestibular disorders. Participants with vestibular disorders had a 2.36-times increased risk of AD than health control (HR 2.36 and 95% CI 1.01–5.51). The 13.9-year cumulative incidence of VD was 0.6% among participants with normal vestibular function and 2.0% among participants with vestibular disorders. Participants with vestibular disorders had a 3.35-times increased risk of VD than participants without vestibular disorders (HR 3.35 and 95% CI 1.48–7.59) (Figure 2A).

No interaction effect between vestibular disorders and covariates on the risk of all cause dementia, AD, and VD were observed (Supporting Information S1: Tables S9–S11). Several

sensitivity analyses did not affect the robustness of the findings (Figure 2B,C, Supporting Information S1: Table S12).

3.3 | The Mediation Analysis of Vestibular Disorders and Dementia Based on Metabolites and Inflammatory Cells

After correcting for multiplicity, most inflammatory cells were significantly associated vestibular disorders but none with dementia (Supporting Information S1: Table S13). Therefore, no inflammatory cells were available as potential mediators of the association between vestibular disorders and dementia. Although all selected metabolites except total fatty acids, glycine, valine, glucose, and lactate were significant associated with vestibular disorders, only 46 were predictors of dementia risk (FDR < 0.05) (Supporting Information S1: Table S14). Figure 3 exhibits the PM of these potential metabolites that were simultaneously associated with both vestibular disorders and dementia. We found that the relationship between vestibular disorders and dementia was mediated by VLDL cholesterol, cholesteryl esters in VLDL, histidine, concentration of medium VLDL particles, cholesterol in small VLDL, cholesteryl esters in small VLDL, cholesterol in very small VLDL, and free cholesterol in very small VLDL. Full results can be found in Supporting Information S1: Table S15.

3.4 | Associations Between Vestibular Disorders and Dementia-Related Brain Structure

The results revealed significant associations between vestibular disorders and dementia-related cortical regions (FDR_{dementia} < 0.05 and FDR_{vestibular disorders} < 0.05), including

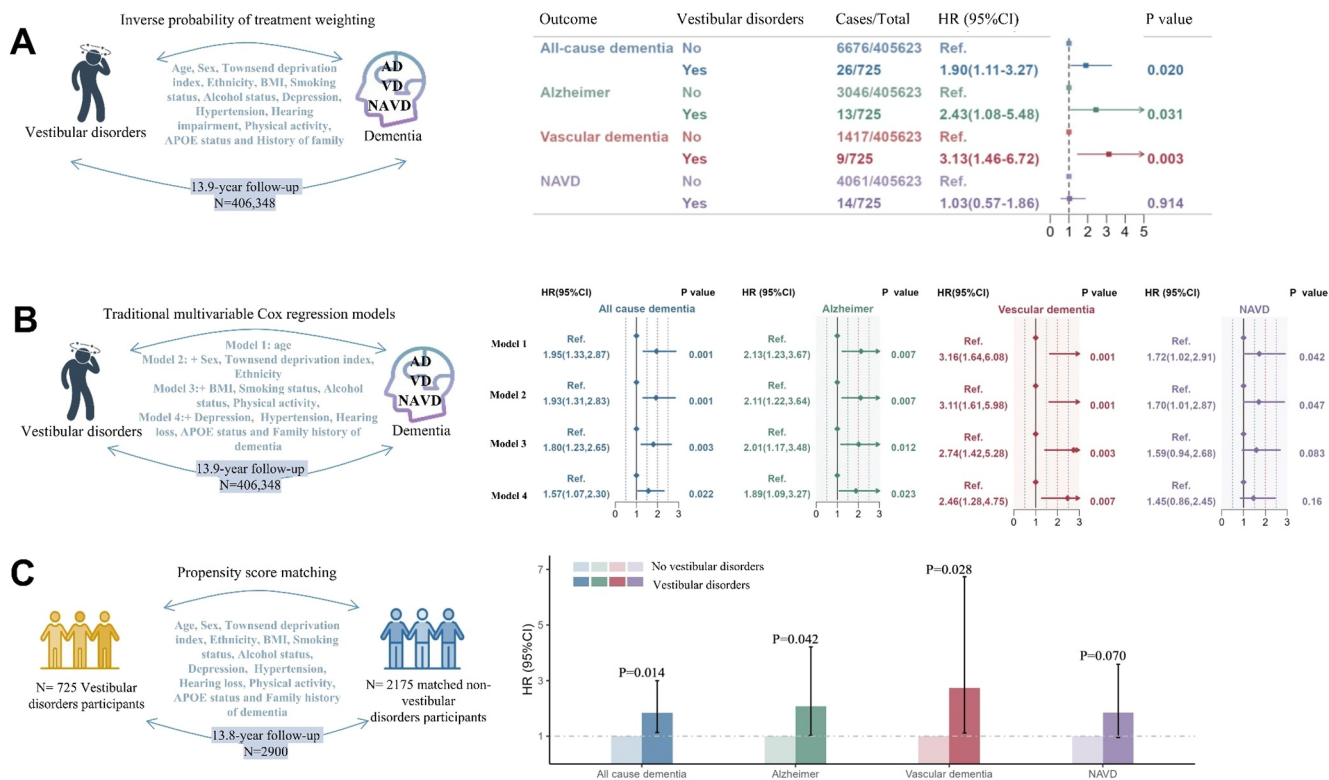


FIGURE 2 | The longitudinal associations between vestibular disorders and dementia. Panel (A) shows the results of Cox proportional hazards models adjusted for inverse probability of treatment weighting (IPTW); panel (B) shows the results based on traditional multivariable Cox proportional regression models which adjusted covariates step by step. In model 1, age was adjusted; in model 2, sex, ethnicity, and Townsend index of deprivation were further adjusted based on model 1; in model 3, smoking status, alcohol intake, physical activity level, and BMI were further adjusted based on model 2; and in model 4, diseases histories of hypertension status, hearing loss status, depression symptoms, APOE allele status, and family history of dementia were further adjusted based on model 3; panel (C) shows the results based on matched vestibular disorders and nonvestibular disorders samples using a propensity score matching procedure. The propensity score matching procedure generated two groups of 3625 vestibular impaired and nonvestibular impaired participants who were matched on all covariates. AD, Alzheimer; APOE, apolipoprotein E; NAVD, non-AD-non-VD; VD, vascular dementia. Lcons were made from <https://www.logosc.cn/make.com/>.

volume of superior, middle, and inferior temporal cortex (left hemisphere and right hemisphere), superior and inferior parietal cortex (left hemisphere and right hemisphere), superior frontal cortex (left hemisphere and right hemisphere), and entorhinal cortex (left hemisphere) (Figure 4, Supporting Information S1: Table S16). Dementia-related subcortical regions demonstrating significant associations with vestibular disorders ($FDR_{dementia} < 0.05$ and $FDR_{vestibular\ disorders} < 0.05$) included the hippocampus (left hemisphere and right hemisphere), amygdala (left hemisphere and right hemisphere), accumbens area (left hemisphere and right hemisphere), cerebellum (left hemisphere and right hemisphere), pallidum (left hemisphere), and thalamus (left hemisphere and right hemisphere) (Figure 4, Supporting Information S1: Table S17). Significantly associations were found between vestibular disorders and FA and MD values in the majority of the white matter tracts, including superior fronto-occipital fasciculus, fornix, fornix cres and stria terminalis, corpus callosum, cingulum cingulate gyrus, and superior longitudinal fasciculus (Supporting Information S1: Table S18).

4 | Discussion

This study systematically explored the association between vestibular disorders and dementia in a large longitudinal cohort for the first time. Our findings indicated that vestibular disorders were associated with 1.86-times, 2.36-times, and 3.35-times increased risk of all-cause dementia, AD, and VD, respectively. In subsequent mediation analysis of metabolic and inflammatory analyses, we identified eight metabolites that mediated vestibular disorders and dementia, providing clues to underlying biological mechanisms. Moreover, vestibular disorders were strongly associated with alterations in brain structure that has also been observed in dementia pathophysiology, giving a hint of underlying brain structure changes. This suggests that there may be underlying brain structural changes associated with vestibular disorders that increase the risk of dementia.

Previous studies mainly focus on the association between vestibular function and cognitive function of specific domains (e.g., executive function, visual-spatial abilities, attention, and

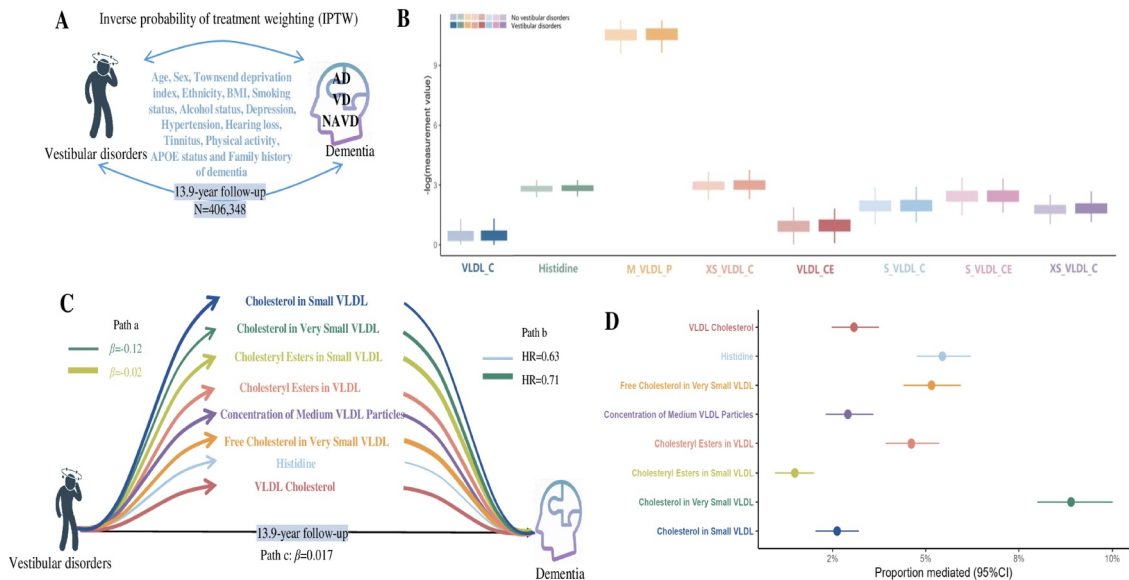


FIGURE 3 | Mediation analysis with plasma metabolites between the association of vestibular disorders and dementia. Panel (A) shows all analyses were based the IPTW-adjusted cohort; panel (B) shows significant differences between vestibular impaired and nonvestibular impaired individuals in 8 metabolites (two-sided *t*-test); VLDL_C, VLDL cholesterol; VLDL_CE, cholesteryl esters in VLDL; M_VLDL_P, concentration of medium VLDL Particles; S_VLDL_C, cholesterol in small VLDL, S_VLDL_CE, cholesteryl esters in small VLDL; XS_VLDL_C, cholesterol in very small VLDL; and XS_VLDL_FC, free cholesterol in very small VLDL; panel (C) shows 8 metabolites significantly mediated the longitudinal association between vestibular disorders and dementia. Path thickness indicates the strength of associations, and numerical values for the largest and smallest effect sizes are provided for reference; panel (D) shows the proportion mediated of each significant plasma metabolites. The nonparametric bootstrap method (1000 draws) was used to calculate 95% CIs of the proportion mediated; dots, mean HRs; horizontal line, 95% CI; HR, hazard ratios; and Lcons were made from <https://www.logosc.cn/make.com/>.

short-term memory) [14, 16]. A previous study, including 33 adults aged > 50 years older, showed that participants with chronic vestibular failure performed worse than the health control on tests of visuospatial abilities, rapid processing, memory, and executive function [15]. In another study involving 1303 participants from 1999 to 2002 National Health and Nutrition Examination Surveys, Yevgeny R. Semenov et al. found vestibular dysfunction was associated with a significant lower score of digit symbol substitution score test [27]. Giving growing evidence that vestibular function contributes to cognitive function, researches have investigated whether vestibular loss increases the odds of clinical syndromes of cognitive impairment, notably mild cognitive impairment (MCI) and AD [11, 28]. Aisha Harun et al. used data from the Baltimore Longitudinal Study of Aging to explore the prevalence of vestibular impairment in 47 patients with AD or MCI and found that vestibular impairment was two-fold more common in AD patients (~50% prevalence) relative to cognitively-normal age-matched controls (~25%) [29]. However, another study in 97 participants from the same dataset did not find a significant association between vestibular function and A β deposition [30]. The inconsistent results might be due to the limited sample size and misclassification of vestibular disorders [30]. A recent study using the South Korean National Health Information Database found that vestibular loss increases the risk of developing dementia (HR 1.084 and 95% CI 1.059–1.110). However, according to the retrospective cross-sectional design of this study, the relationship between vestibular disorders and dementia has not yet been validated [10].

In contrast to previous studies, which were carried out in cross-sectional design or had limited samples, we used the UKB cohort, with its large sample size ($n > 400,000$), prolonged follow-up (mean duration of 13.9 years, with specific event dates), and precise diagnosis of vestibular disorders and all-cause and cause-specific dementia (relying on inpatient hospital records and death registers), substantially reinforced the validity of our findings. In particular, we included in our analyses genetic susceptibility factors, a critical determinant of dementia incidence that will limit inference, which most previous studies have not considered [2]. Importantly, our findings were independent of hearing loss, a major known risk factor for dementia. Statistical adjustment for hearing loss, as well as tinnitus, did not attenuate the association, suggesting that the vestibular system's contribution to dementia risk is distinct from that of hearing and tinnitus. Additionally, a key concern in studies that investigate risk factors for dementia is reverse causation bias. Dementia pathology progresses several years prior to a formal dementia diagnosis, and this progression can affect other behavioral and physical measure [31]. It is also well established that neurodegeneration caused by the pathophysiological progression of AD occurs several years prior to clinical manifestation of the disease [32, 33]. In the context of the current study, preclinical dementia could adversely affect performance on a sensory processing, which in turn would be associated with a future diagnosis of dementia [34]. To address this, we investigated whether associations differed by length of follow-up period in our sensitivity analyses. We found that the associations remained similar to the main findings when restricting to cases that occurred over longer follow-up periods.

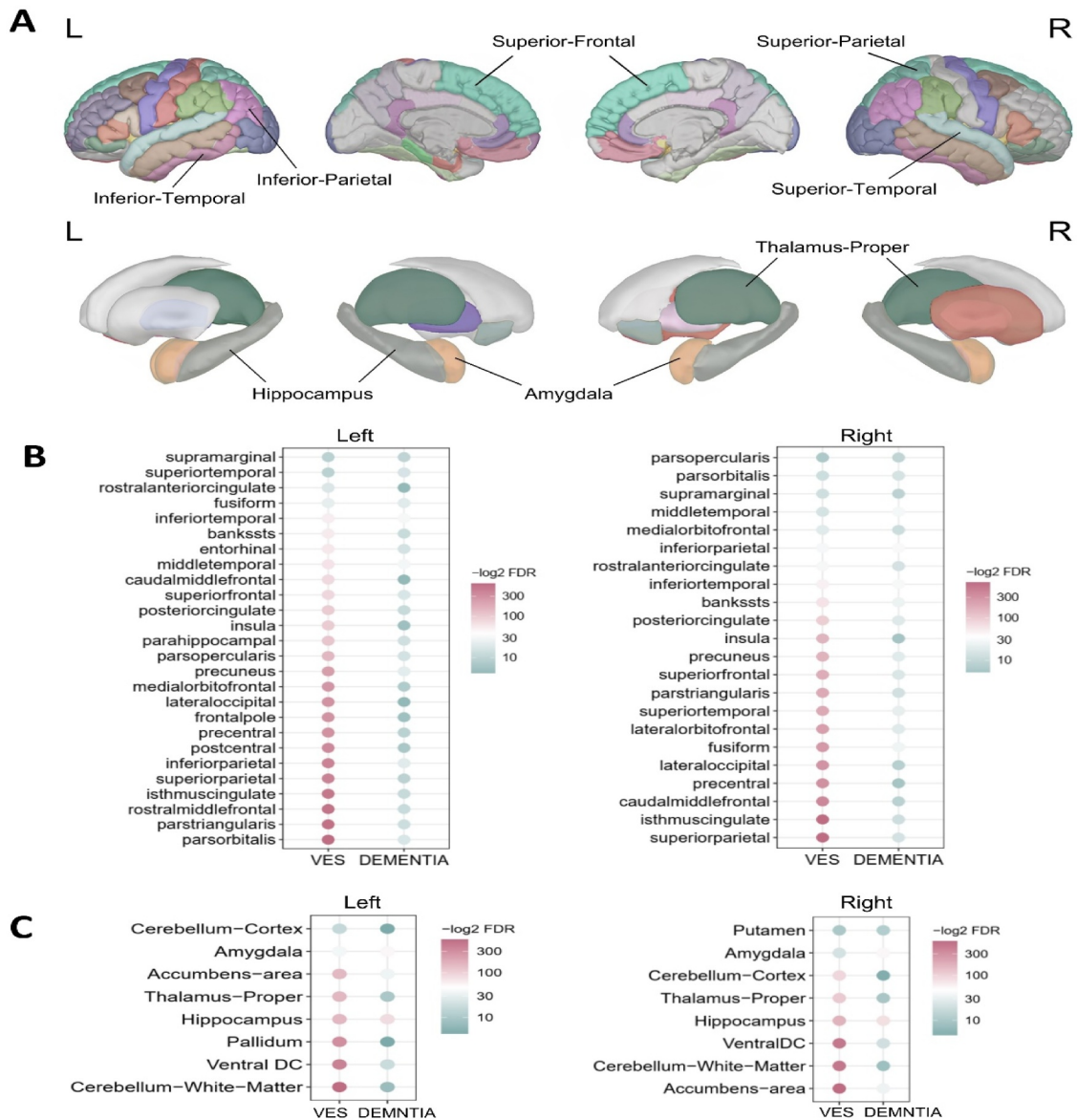


FIGURE 4 | Associations between vestibular disorders and brain structure. Panel (A) shows vestibular disorders was significantly associated with the volume of dementia related cortical and subcortical areas (FDR < 0.05); here, we colored the areas of the brain associated with both dementia and vestibular disease. L, left and R, right. Panels (B and C) show the FDR values for the associations between dementia and vestibular disorders with brain structures. FDR, Benjamini-Hochberg false discovery rate and VES, vestibular disorders.

The precise mechanisms underlying the vestibular disorders and cognitive impairment or dementia are not yet fully understood. A cognitive load hypothesis theorizes that increased gaze and postural instability associated with vestibular loss may require increased attentional resources allocated to maintaining balance and decreased resources available for cognitive tasks [14]. Additionally, a common cause hypothesis states that the high comorbidity of affective disorders in individuals with vestibular impairment may also contribute to cognitive dysfunction [35]. To our knowledge, few studies have established a molecular hypothesis between the possible relationship between vestibular disorders and cognitive impairment. Our exploratory analysis examined potential metabolite and inflammatory mediators that could help us gain a deeper understanding of the increased risk of dementia associated with vestibular disorders. We observed cholesteryl esters, cholesterol,

cholesterol in VLDL subclasses, and concentration of medium VLDL particles as well as VLDL cholesterol were inversely associated with future risk of dementia. These findings are aligned with some previous studies [36, 37], although it has been historically conflicting [38–41]. The specific mechanisms by which these lipoprotein subclasses and cholesterol mediate the vestibular disease and risk of dementia have not been fully elucidated as they do not appear to directly penetrate the blood-brain barrier. That means, the lipid environment in the brain and the periphery may be very different. Further research is needed to fully understand the role of lipoproteins in these conditions. Nevertheless, the amino acid metabolites we identified are beneficial in shedding light on the mediating role of vestibular disorders and dementia risk. Histidine have been verified to play an important role in protein aggregation, inhibiting α -synuclein and Tau protein aggregation [42–44].

Both proteins are known to form abnormal clumps in the brain, which can disrupt normal cellular function and contribute to neurodegeneration, including dementia [45]. Thus, vestibular disorders could increase dementia risk by downregulating histidine.

This study revealed significant associations between vestibular disorders and a number of dementia-related brain regions, including entorhinal cortex, temporal cortex, superior frontal cortex, hippocampus, thalamus, and amygdala. Our findings were in accordance with previous studies, which demonstrated the importance of these brain regions in dementia pathology [46–48]. The pathological changes of temporal cortex involved in impaired memory and cognitive decline [49]. Changes of superior frontal cortex contribute to cognitive deficits in attention, and executive function, which are common symptoms of dementia [50]. Previous studies have shown that vestibular stimulation activates a large multisensory cortex and subcortical network, including insula, temporoparietal junction, somatosensory cortex, hippocampus, medial entorhinal cortex, and thalamus [51], suggesting that vestibular projection to the cortex and subcortex is extensive, and vestibular diseases can affect cognition through these broad pathways. Notably, vestibular disorders significantly affected the hippocampus and entorhinal cortex, which are markers of AD [52–55]. Additionally, our finding indicated that the white matter tracts were widely affected by vestibular disorders and involve various functions including emotion and memory (e.g., cingulum cingulate gyrus, fornix cres/stria terminalis, tapetum, and uncinate fasciculus), perception (e.g., medial lemniscus, posterior thalamic radiation, and posterior limb of internal capsule), motor control (e.g., corticospinal tract, anterior limb of internal capsule, and superior and inferior cerebellar peduncle), and information processing (e.g., corona radiata, corpus callosum, superior longitudinal fasciculus, and sagittal stratum). These widespread impairments may partially mediate the pathway of vestibular disorders to dementia [56, 57]. Overall, our findings provide evidence for how vestibular disorders may mediate the risk of dementia through structural changes in the brain.

The identification of metabolic abnormalities (e.g., histidine downregulation) and brain structural changes in this study provides dual targets for early intervention. Going forward, the development of screening tools based on blood metabolomic profiles, combined with neuroimaging assessments, will enable stratified management of individuals with vestibular disorders. High-risk individuals should be prioritized for balance training or pharmacological interventions (e.g., therapies regulating cholesterol metabolism) to interrupt or delay dementia progression. These findings provide new evidence for clinical guidelines, recommending the integration of vestibular function assessments into routine health checks for older adults, with subsequent metabolomic and neuroimaging monitoring for those with abnormalities.

Strengths of the present study include the large sample size, long follow-up, and extensive measurement of covariates as well as the available biological markers and brain imaging data, which allow us examining the distant effect of vestibular disorders on dementia and exploring underlying mechanisms. Also, this is the first study to examine the association of

vestibular disorders and dementia in a large longitudinal cohort. The study also has several limitations. First, it was an observational study, therefore, reverse causality might exist. However, the study rigorously adjusted for confounding factors and performed sensitivity analysis, thereby addressing this issue to the best extent possible. Second, information on date of onset and severity of vestibular disorders were unavailable. Thus, some quantitative relationships between vestibular disorders and risk of dementia could not be analyzed. In addition, we did not take into account possible changes in vestibular disorders over time. Although we consider the found associations valid and reliable, we cannot completely rule out undiscovered mechanisms between increasingly declining vestibular performance and longitudinal dementia. Third, although the UKB has strict quality control measures in place for data collection and measurements, some measurement errors are inevitable, particularly for fluctuating biological indicators. In addition, our study grouped various vestibular disorders into a single exposure category due to the small number of incident dementia cases within each specific subtype, which precluded a statistically powered stratified analysis. These conditions have different pathophysiological mechanisms, and future research, perhaps through large-scale meta-analyses or in cohorts with higher prevalence of specific vestibular diagnoses, is needed to disentangle their individual contributions to dementia risk. Last, the majority of UK Biobank participants are white, which may limit the generalizability of the findings to other races.

5 | Conclusion

In conclusion, this large population-based cohort study found that vestibular disorders are associated with an increased risk of all-cause and cause-specific dementia, and that abnormalities in brain structure and metabolites may play a key role in this relationship. Early intervention targeting individuals with vestibular disorders, particularly before significant cognitive decline, may be more effective for reducing dementia risk.

Author Contributions

Prof. Haibo Wang attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Qiuyue Dong, Fan Jiang, Hongkai Li have directly accessed and verified the underlying data. All the authors were responsible for the decision to submit the manuscript. Concept and design: Haibo Wang, Shanquan Chen, Daogong Zhang, Fan Jiang, Xiaofei Li, Hong Kai Li. Acquisition of data: Qiuyue Dong, Guorong Li (UKB cohort study). Formal analysis and Interpretation of data: Qiuyue Dong, Fan Jiang, Xiaofei Li, Hongkai Li, Daogong Zhang, Haibo Wang. Statistical analysis: Qiuyue Dong, Guorong Li. Drafting of the manuscript: Fan Jiang, Xiaofei Li, Daogong Zhang. Critical revision of the manuscript for important intellectual content: Shanquan Chen, Alimu Dalimu, Daogong Zhang, Na Li, Qi Jing.

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Ethics Statement

UKB was undertaken with ethical approval from the North West Multi-Center Research Ethics Committee of the UK (ref11/NW/0382). This research was conducted under UKB application number 107217.

Conflicts of Interest

Haibo Wang, Daogong Zhang, and Na Li report being members of the editorial board of the journal.

Data Availability Statement

UK Biobank data are available via www.ukbiobank.ac.uk. Syntax for the generation of derived variables and for the analysis used for this study will be submitted to UKB for record.

References

1. J. Yates, M. Stanyon, R. Samra, and L. Clare, "Challenges in Disclosing and Receiving a Diagnosis of Dementia: A Systematic Review of Practice From the Perspectives of People With Dementia, Carers, and Healthcare Professionals," *International Psychogeriatrics* 33, no. 11 (2021): 1161–1192, <https://doi.org/10.1017/S1041610221000119>.
2. G. Livingston, J. Huntley, A. Sommerlad, et al., "Dementia Prevention, Intervention, and Care: 2020 Report of the Lancet Commission," *Lancet* 396, no. 10248 (2020): 413–446, [https://doi.org/10.1016/S0140-6736\(20\)30367-6](https://doi.org/10.1016/S0140-6736(20)30367-6).
3. S. H. Lai, T. Tsoi, C. T. Tang, et al., "An Integrated, Collaborative Healthcare Model for the Early Diagnosis and Management of Dementia: Preliminary Audit Results From the First Transdisciplinary Service Integrating Family Medicine and Geriatric Psychiatry Services to the Heart of Patients' Homes," *BMC Psychiatry* 19, no. 1 (2019): 61, <https://doi.org/10.1186/s12888-019-2033-7>.
4. G. B. Frisoni, J. L. Molinuevo, D. Altomare, et al., "Precision Prevention of Alzheimer's and Other Dementias: Anticipating Future Needs in the Control of Risk Factors and Implementation of Disease-Modifying Therapies," *Alzheimer's & Dementia* 16, no. 10 (2020): 1457–1468, <https://doi.org/10.1002/alz.12132>.
5. J. H. Baek, Y. Zheng, C. L. Darlington, and P. F. Smith, "Evidence That Spatial Memory Deficits Following Bilateral Vestibular Deafferentation in Rats Are Probably Permanent," *Neurobiology of Learning and Memory* 94, no. 3 (2010): 402–413, <https://doi.org/10.1016/j.nlm.2010.08.007>.
6. B. Dobbels, O. Peetermans, B. Boon, G. Mertens, P. Van de Heyning, and V. Van Rompaey, "Impact of Bilateral Vestibulopathy on Spatial and Nonspatial Cognition: A Systematic Review," *Ear and Hearing* 40, no. 4 (2019): 757–765, <https://doi.org/10.1097/AUD.0000000000000679>.
7. T. Brandt, F. Schautzer, D. A. Hamilton, et al., "Vestibular Loss Causes Hippocampal Atrophy and Impaired Spatial Memory in Humans," *Brain* 128, no. 11 (2005): 2732–2741, <https://doi.org/10.1093/brain/awh617>.
8. H. K. Neuhauser, M. von Brevern, A. Radtke, et al., "Epidemiology of Vestibular Vertigo: A Neurologic Survey of the General Population," *Neurology* 65, no. 6 (2005): 898–904, <https://doi.org/10.1212/01.wnl.0000175987.59991.3d>.
9. R. Hulse, A. Biesdorf, K. Hörmann, et al., "Peripheral Vestibular Disorders: An Epidemiologic Survey in 70 Million Individuals," *Otology & Neurotology* 40, no. 1 (2019): 88–95, <https://doi.org/10.1097/MAO.0000000000002013>.

10. S. J. Lim, S. Son, Y. Chung, S. Y. Kim, H. Choi, and J. Choi, "Relationship Between Vestibular Loss and the Risk of Dementia Using the 2002–2019 National Insurance Service Survey in South Korea," *Scientific Reports* 13, no. 1 (2023): 16746, <https://doi.org/10.1038/s41598-023-42598-w>.
11. Y. Agrawal, P. F. Smith, and P. B. Rosenberg, "Vestibular Impairment, Cognitive Decline and Alzheimer's Disease: Balancing the Evidence," *Aging & Mental Health* 24, no. 5 (2020): 705–708, <https://doi.org/10.1080/13607863.2019.1566813>.
12. R. J. Kamil, M. Bilgel, D. F. Wong, S. M. Resnick, and Y. Agrawal, "Vestibular Function and Beta-Amyloid Deposition in the Baltimore Longitudinal Study of Aging," *Frontiers in Aging Neuroscience* 10 (2018): 408, <https://doi.org/10.3389/fnagi.2018.00408>.
13. J. Y. Lee, "Relationship Between Vestibular Dysfunction and Dementia in Elderly Patients: Peripheral Vertigo or Central Vertigo," supplement *Alzheimer's & Dementia* 16, no. S2 (2020): S040102, <https://doi.org/10.1002/alz.040102>.
14. R. T. Bigelow and Y. Agrawal, "Vestibular Involvement in Cognition: Visuospatial Ability, Attention, Executive Function, and Memory," *Journal of Vestibular Research* 25, no. 2 (2015): 73–89, <https://doi.org/10.3233/VES-150544>.
15. M. Obermann, A. Gebauer, D. Arweiler-Harbeck, et al., "Cognitive Deficits in Patients With Peripheral Vestibular Dysfunction," *European Journal of Neurology* 32, no. 1 (2023): e15907, <https://doi.org/10.1111/ene.15907>.
16. C. Aedo-Sanchez, P. Riquelme-Contreras, F. Henriquez, and E. Aguilar-Vidal, "Vestibular Dysfunction and Its Association With Cognitive Impairment and Dementia," *Frontiers in Neuroscience* 18 (2024): 1304810, <https://doi.org/10.3389/fnins.2024.1304810>.
17. R. Kaddurah-Daouk, B. S. Kristal, and R. M. Weinshilboum, "Metabolomics: A Global Biochemical Approach to Drug Response and Disease," *Annual Review of Pharmacology and Toxicology* 48, no. 1 (2008): 653–683, <https://doi.org/10.1146/annurev.pharmtox.48.113006.094715>.
18. E. Trushina and M. M. Mielke, "Recent Advances in the Application of Metabolomics to Alzheimer's Disease," *Biochimica et Biophysica Acta* 1842, no. 8 (2014): 1232–1239, <https://doi.org/10.1016/j.bbadis.2013.06.014>.
19. X. H. Xu, Y. Huang, G. Wang, and S. D. Chen, "Metabolomics: A Novel Approach to Identify Potential Diagnostic Biomarkers and Pathogenesis in Alzheimer's Disease," *Neuroscience Bulletin* 28, no. 5 (2012): 641–648, <https://doi.org/10.1007/s12264-012-1272-0>.
20. I. Ozbay, C. Kahraman, H. H. Balıkcı, et al., "Neutrophil-to-Lymphocyte Ratio in Patients With Peripheral Vertigo: A Prospective Controlled Clinical Study," *American Journal of Otolaryngology* 35, no. 6 (2014): 699–702, <https://doi.org/10.1016/j.amjoto.2014.08.004>.
21. S. Shushan, S. Shemesh, O. Ungar, et al., "Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio Among Patients With Vestibular Neuritis," *ORL: Journal for Otorhinolaryngology and Its Related Specialties* 81, no. 5–6 (2019): 304–308, <https://doi.org/10.1159/000502152>.
22. B. Fattori, A. Nacci, P. L. Ghilardi, L. Bruschini, F. Matteucci, and F. Ursino, "Acute Peripheral Vertigo: Involvement of the Hemostatic System," *International Tinnitus Journal* 9, no. 2 (2003): 124–129, <https://pubmed.ncbi.nlm.nih.gov/15106288/>.
23. K. H. Xie, L. L. Liu, C. Y. Su, et al., "Low Antioxidant Status of Serum Uric Acid, Bilirubin, Albumin, and Creatinine in Patients With Benign Paroxysmal Positional Vertigo," *Frontiers in Neurology* 11 (2020): 601695, <https://doi.org/10.3389/fneur.2020.601695>.
24. H. Jian, S. Wang, X. Li, et al., "Effect of Late-Stage Meniere's Disease and Vestibular Functional Impairment on Hippocampal Atrophy," *Laryngoscope* 134, no. 1 (2024): 410–418, <https://doi.org/10.1002/lary.30816>.

25. S. Balabhadrapatruni, Y. Zheng, R. Napper, and P. F. Smith, "Basal Dendritic Length Is Reduced in the Rat Hippocampus Following Bilateral Vestibular Deafferentation," *Neurobiology of Learning and Memory* 131 (2016): 56–60, <https://doi.org/10.1016/j.nlm.2016.03.009>.
26. Q. W. Ren, T. H. Katherine Teng, Y. K. Tse, et al., "Statins and Risks of Dementia Among Patients With Heart Failure: A Population-Based Retrospective Cohort Study in Hong Kong," *Lancet Regional Health. Western Pacific* 44 (2024): 101006, <https://doi.org/10.1016/j.lanwpc.2023.101006>.
27. Y. R. Semenov, R. T. Bigelow, Q. L. Xue, S. du Lac, and Y. Agrawal, "Association Between Vestibular and Cognitive Function in U.S. Adults: Data From the National Health and Nutrition Examination Survey," *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 71, no. 2 (2016): 243–250, <https://doi.org/10.1093/gerona/glv069>.
28. F. H. Previc, "Vestibular Loss as a Contributor to Alzheimer's Disease," *Medical Hypotheses* 80, no. 4 (2013): 360–367, <https://doi.org/10.1016/j.mehy.2012.12.023>.
29. A. Harun, E. S. Oh, R. T. Bigelow, S. Studenski, and Y. Agrawal, "Vestibular Impairment in Dementia," *Otology & Neurotology* 37, no. 8 (2016): 1137–1142, <https://doi.org/10.1097/MAO.0000000000001157>.
30. L. Yesantharao, Y. Cai, J. A. Schrack, et al., "Sensory Impairment and Beta-Amyloid Deposition in the Baltimore Longitudinal Study of Aging," *Alzheimer's & Dementia* 15, no. 2 (2023): e12407, <https://doi.org/10.1002/dad2.12407>.
31. Z. Arvanitakis, R. C. Shah, and D. A. Bennett, "Diagnosis and Management of Dementia: Review," *JAMA* 322, no. 16 (2019): 1589–1599, <https://doi.org/10.1001/jama.2019.4782>.
32. C. Murphy, "Olfactory and Other Sensory Impairments in Alzheimer Disease," *Nature Reviews Neurology* 15, no. 1 (2019): 11–24, <https://doi.org/10.1038/s41582-018-0097-5>.
33. R. A. Sperling, P. S. Aisen, L. A. Beckett, et al., "Toward Defining the Preclinical Stages of Alzheimer's Disease: Recommendations From the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease," *Alzheimer's & Dementia* 7, no. 3 (2011): 280–292, <https://doi.org/10.1016/j.jalz.2011.03.003>.
34. J. S. Stevenson, L. Clifton, E. Kuzma, and T. J. Littlejohns, "Speech-in-Noise Hearing Impairment Is Associated With an Increased Risk of Incident Dementia in 82,039 UK Biobank Participants," *Alzheimer's & Dementia* 18, no. 3 (2022): 445–456, <https://doi.org/10.1002/alz.12416>.
35. C. Gurvich, J. J. Maller, B. Lithgow, S. Haghgooye, and J. Kulkarni, "Vestibular Insights Into Cognition and Psychiatry," *Brain Research* 1537 (2013): 244–259, <https://doi.org/10.1016/j.brainres.2013.08.058>.
36. J. Tynkynen, V. Chouraki, S. J. van der Lee, et al., "Association of Branched-Chain Amino Acids and Other Circulating Metabolites With Risk of Incident Dementia and Alzheimer's Disease: A Prospective Study in Eight Cohorts," *Alzheimer's & Dementia* 14, no. 6 (2018): 723–733, <https://doi.org/10.1016/j.jalz.2018.01.003>.
37. V. P. Lara, P. Caramelli, A. L. Teixeira, et al., "Cortisol, HDL-c, VLDL-c, and APOE Polymorphisms as Laboratorial Parameters Associated to Cognitive Impairment No Dementia (CIND) and Dementia," *Journal of Clinical Laboratory Analysis* 30, no. 5 (2016): 374–380, <https://doi.org/10.1002/jcla.21865>.
38. A. Zaciragic, A. Valjevac, A. Dervisevic, et al., "Traditional and Non-Traditional Lipid Profiles in Bosnian Patients With Probable Alzheimer's Disease and Vascular Dementia," *Medical Archives* 76, no. 4 (2022): 267–272, <https://doi.org/10.5455/medarh.2022.76.267-272>.
39. O. Lepara, A. Valjevac, A. Alajbegovic, A. Zaciragic, and E. Nakas-Icindic, "Decreased Serum Lipids in Patients With Probable Alzheimer's Disease," *Bosnian Journal of Basic Medical Sciences* 9, no. 3 (2009): 215–220, <https://doi.org/10.17305/bjbms.2009.2809>.
40. Y. Zhu, X. Liu, R. Zhu, J. Zhao, and Q. Wang, "Lipid Levels and the Risk of Dementia: A Dose-Response Meta-Analysis of Prospective Cohort Studies," *Annals of Clinical and Translational Neurology* 9, no. 3 (2022): 296–311, <https://doi.org/10.1002/acn3.51516>.
41. M. Benn, B. G. Nordestgaard, R. Frikke-Schmidt, and A. Tybjaerg-Hansen, "Low LDL Cholesterol, PCSK9 and HMGCR Genetic Variation, and Risk of Alzheimer's Disease and Parkinson's Disease: Mendelian Randomisation Study," *BMJ* 357 (2017): j1648, <https://doi.org/10.1136/bmj.j1648>.
42. K. Kondo, T. Ikura, H. Tanaka, et al., "Hepta-Histidine Inhibits Tau Aggregation," *ACS Chemical Neuroscience* 12, no. 16 (2021): 3015–3027, <https://doi.org/10.1021/acscchemneuro.1c00164>.
43. R. Nakamura, I. Tomizawa, A. Iwai, et al., "Photo-Oxygenation of Histidine Residue Inhibits Alpha-Synuclein Aggregation," *FASEB Journal* 37, no. 12 (2023): e23311, <https://doi.org/10.1096/fj.202301533R>.
44. H. Li, E. Joo, and J. Y. Lee, "Theoretical Insights Into Mutation and Histidine Tautomerism Effects on Tau Proteins," *ACS Chemical Neuroscience* 12, no. 22 (2021): 4361–4366, <https://doi.org/10.1021/acscchemneuro.1c00594>.
45. J. Song, L. Yang, D. Nan, Q. He, Y. Wan, and H. Guo, "Histidine Alleviates Impairments Induced by Chronic Cerebral Hypoperfusion in Mice," *Frontiers in Physiology* 9 (2018): 662, <https://doi.org/10.3389/fphys.2018.00662>.
46. L. Pini, M. Pievani, M. Bocchetta, et al., "Brain Atrophy in Alzheimer's Disease and Aging," *Ageing Research Reviews* 30 (2016): 25–48, <https://doi.org/10.1016/j.arr.2016.01.002>.
47. S. Y. Huang, Y. Z. Li, Y. R. Zhang, et al., "Sleep, Physical Activity, Sedentary Behavior, and Risk of Incident Dementia: A Prospective Cohort Study of 431,924 UK Biobank Participants," *Molecular Psychiatry* 27, no. 10 (2022): 4343–4354, <https://doi.org/10.1038/s41380-022-01655-y>.
48. Y. T. Deng, Y. Z. Li, S. Y. Huang, et al., "Association of Life Course Adiposity With Risk of Incident Dementia: A Prospective Cohort Study of 322,336 Participants," *Molecular Psychiatry* 27, no. 8 (2022): 3385–3395, <https://doi.org/10.1038/s41380-022-01604-9>.
49. P. Scheltens, N. Fox, F. Barkhof, and C. De Carli, "Structural Magnetic Resonance Imaging in the Practical Assessment of Dementia: Beyond Exclusion," *Lancet Neurology* 1 (2002): 13–21, [https://doi.org/10.1016/s1474-4422\(02\)00002-9](https://doi.org/10.1016/s1474-4422(02)00002-9).
50. M. P. Laakso, H. Soininen, K. Partanen, et al., "Volumes of Hippocampus, Amygdala and Frontal Lobes in the MRI-Based Diagnosis of Early Alzheimer's Disease: Correlation With Memory Functions," *Journal of Neural Transmission-Parkinson's Disease and Dementia Section* 9, no. 1 (1995): 73–86, <https://doi.org/10.1007/BF02252964>.
51. A. Jacob, D. J. Tward, S. Resnick, et al., "Vestibular Function and Cortical and Sub-Cortical Alterations in an Aging Population," *Heliyon* 6, no. 8 (2020): e04728, <https://doi.org/10.1016/j.heliyon.2020.e04728>.
52. C. R. Jack Jr., F. Barkhof, M. A. Bernstein, et al., "Steps to Standardization and Validation of Hippocampal Volumetry as a Biomarker in Clinical Trials and Diagnostic Criterion for Alzheimer's Disease," *Alzheimer's & Dementia* 7, no. 4 (2011): 474–485.e474, <https://doi.org/10.1016/j.jalz.2011.04.007>.
53. C. R. Jack Jr., "Alliance for Aging Research AD Biomarkers Work Group: Structural MRI," supplement *Neurobiology of Aging* 32, no. S1 (2011): S48–S57, <https://doi.org/10.1016/j.neurobiolaging.2011.09.011>.
54. M. Bobinski, M. J. de Leon, A. Convit, et al., "MRI of Entorhinal Cortex in Mild Alzheimer's Disease," *Lancet* 353, no. 9146 (1999): 38–40, [https://doi.org/10.1016/s0140-6736\(05\)74869-8](https://doi.org/10.1016/s0140-6736(05)74869-8).
55. L. deToledo-Morrell, T. Stoub, M. Bulgakova, et al., "MRI-Derived Entorhinal Volume Is a Good Predictor of Conversion From MCI to AD," *Neurobiology of Aging* 25, no. 9 (2004): 1197–1203, <https://doi.org/10.1016/j.neurobiolaging.2003.12.007>.
56. J. Acosta-Cabrero, G. B. Williams, G. Pengas, and P. J. Nestor, "Absolute Diffusivities Define the Landscape of White Matter

Degeneration in Alzheimer's Disease," *Brain* 133, no. 2 (2010): 529–539, <https://doi.org/10.1093/brain/awp257>.

57. F. Agosta, M. Pievani, S. Sala, et al., "White Matter Damage in Alzheimer Disease and Its Relationship to Gray Matter Atrophy," *Radiology* 258, no. 3 (2011): 853–863, <https://doi.org/10.1148/radiol.10101284>.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: sen270019-sup-0001-suppl-data.docx.