RESEARCH ARTICLE

Exploring the link between comorbidities and Alzheimer's dementia in the Australian Imaging, Biomarker & Lifestyle (AIBL) study

Catherine Quynh Nhu Nguyen[1] | Liwei Ma[1] | Yi Ling Clare Low[1] | Edwin C. K. Tan[2] | Christopher Fowler[1] | Colin L. Masters[1] | Liang Jin[1] | Yijun Pan[1,3,4] (iD) | the AIBL research group

[1]The Florey Institute, The University of Melbourne, Parkville, Victoria, Australia

[2]School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

[3]Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia

[4]Department of Organ Anatomy, Graduate School of Medicine, Tohoku University, Sendai, Miyagi, Japan

Correspondence
Liang Jin and Yijun Pan, The Florey Institute, The University of Melbourne, Parkville, Victoria 3010, Australia.
Email: liang.jin@unimelb.edu.au and yijun.pan@unimelb.edu.au

Abstract

INTRODUCTION: Mounting evidence suggests that certain comorbidities may influence the clinical evolution of Alzheimer's dementia (AD).

METHODS: We conducted logistic regression analyses on the medical history and cognitive health diagnoses of participants in the Australian Imaging, Biomarker & Lifestyle study ($n = 2443$) to investigate cross-sectional associations between various comorbidities and mild cognitive impairment (MCI)/AD.

RESULTS: A mixture of associations were observed. Higher comorbidity of anxiety and other neurological disorders was associated with higher odds of AD, while arthritis, cancer, gastric complaints, high cholesterol, joint replacement, visual defect, kidney and liver disease were associated with lower odds of AD.

DISCUSSION: This study underscores the links between specific comorbidities and MCI/AD. Further research is needed to elucidate the longitudinal comorbidity-MCI/AD associations and underlying mechanisms of these associations.

KEYWORDS
Alzheimer's dementia, cognitive impairment, comorbidity, cross-sectional, mild cognitive impairment

Highlights

- Comorbidities that significantly increased AD odds included anxiety and other neurological disorders.
- Arthritis, cancer, gastric complaints, high cholesterol, joint replacement, visual defect, kidney and liver disease were associated with lower odds of AD.

- Alcohol consumption had the most significant confounding effect in the study.
- Visual-AD association was modified by age, sex, and *APOE ε*4 allele status.
- Anxiety-AD and depression-AD associations were modified by sex.

1 | BACKGROUND

Alzheimer's dementia (AD) is a neurodegenerative disease and the most common cause of dementia, accounting for 60-80% of all cases.[1] AD progresses from preclinical, prodromal (mild cognitive impairment [MCI]), to dementia stages.[1,2] In the preclinical stage, early pathological changes are generally not recognizable, and functional impairments in daily activities are not observed. Prodromal AD (MCI) is a transitional stage; a previous study showed that the conversion rate of AD from MCI ranged from 10-34% over 1 year and 11-38% over 5 years.[3] In the dementia stage, considerable neuropathological changes occur in the brain and cognitive function deteriorates leading to diminished communication skills and impaired daily living.[1,4–6]

The apolipoprotein E (*APOE*) gene has been identified as a major player influencing the onset of AD, with the *ε*4 allele increasing AD risk by up to 15-fold and the *ε*2 allele reducing the risk by nearly half.[7–10] In addition, various diseases (e.g., hypercholesterolemia, depression, cancer, diabetes, stroke, and other cardiovascular diseases) have been suggested to be comorbid with AD.[11,12] These comorbidities can potentially be modifiers to the clinical evolution of MCI/AD, attributed to pathological mechanisms potentially shared between them and MCI/AD, such as the presence of the *APOE ε*4 allele and accumulation of amyloid-beta (Aβ).[11,12] However, the lack of consistent study design and methodology has often led to inconclusive results and a mixture of positive, negative, and neutral associations between comorbidities and MCI/AD.[11,12] For example, while diabetes mellitus has been shown in some studies to increase AD risk to the point of dubbing AD "type 3 diabetes," other studies observed no significant change in risk, which could be due to different design factors such as the population, sampling methods, and the different types of diabetes investigated.[13–15]

The Australian Imaging, Biomarker and Lifestyle (AIBL) study was launched in 2006, which aims to investigate the natural history of Alzheimer's disease, from preclinical onset to development of dementia. The current study utilized lifestyle, clinical and cognitive data collected at the AIBL study baseline for cross-sectional analyses to determine the comorbidities that are associated with increased/decreased incidence of MCI/AD within older Australians. Unravelling these associations may make it possible to identify modifying factors to the clinical evolution of MCI/AD and assist with assessing cognitive impairment.

2 | METHODS

2.1 | Human ethics and data collection

The AIBL study was approved by the institutional ethics committees of St. Vincent's Health and the University of Melbourne. All AIBL participants have provided written informed consent before any assessments and the study abided by the Helsinki Declaration of 1975. All secondary data used in the present study has been de-identified. The data were collected from 2831 older Australians, and the cohort is gender balanced. The data were collected over a maximum of 10 time points spanned up to 18 months apart at the study centers in Perth or Melbourne. The data includes information on participant demographics, medical history, lifestyle factors (e.g., alcohol, smoking), *APOE* genotypes, and cognitive health diagnosis. Cognitive health was evaluated by a set panel of neuropsychological tests conducted by geriatricians and neuropsychologists. Medical history and lifestyle information were collected via a comprehensive questionnaire. All participant data were stored in the AIBL database. For the secondary data analysis, permission was granted to collect the dataset directly from the AIBL scientific committee.

2.2 | Exposure and outcome

The comorbidities measured as exposures include (in descending order of prevalence) visual defects, arthritis, hypertension, high cholesterol, gastric complaints, cancer, depression, falls, anxiety, joint replacement, (para)thyroid disease, diabetes, atrial fibrillation, kidney disease, neurological disorders, angina, heart attack, transient ischemic heart attack, liver disease, and stroke. To ensure we had a reasonable sample size for analysis, only the 20 most prevalent comorbidities in AIBL participants were assessed. The exposure status was determined at baseline based on medical history and self-report.[16] Explanatory notes for some comorbidities are provided in the Supplementary Materials (Definitions and criteria of comorbidities in AIBL study).

Participants were categorized as cognitively unimpaired (CU), MCI, AD, or other dementia (OD) as per previously described.[16] OD participants were excluded from further analysis since OD was not an outcome of interest or relevance.

2.3 | Covariates

Age, sex, smoking status, highest level of education completed, alcohol consumption frequency, and *APOE* genotype were measured for sub-analysis. These covariates were chosen due to other studies identifying them as possible risk factors for AD.[7,17–22] Age was categorized as <60 years, 60–69 years, 70–79 years, 80–89 years, and ≥90 years. Sex was categorized as "female" and "male." Smoking status was categorized as "current," "former," and "never smoking." Education level was grouped as "0–8 years," "9–12 years," "13–15 years," and "15+ years." Alcohol consumption frequency was categorized as "daily or almost daily," "weekly," "monthly or occasional," and "never." *APOE* genotype was categorized as "ε4 allele carrier" and "ε4 allele non-carrier." Information on these covariates was obtained from lifestyle questionnaires or self-report at baseline.

2.4 | Data analysis

The AIBL dataset was exported and viewed via Microsoft Excel (Version 16.8), and the exposure and outcome data were statistically analyzed via Stata/BE 17.0 (StataCorp LLC, College Station, TX)[23] to determine the strength of cross-sectional association between each comorbidity and MCI/AD. These associations were represented as odds ratios (ORs), comparing the odds of developing MCI/AD in the target cohort (exposed to the comorbidity) to the reference cohort (unexposed to the comorbidity). In addition, the statistical differences in demographic data between the cognitive health groups (CU, MCI, or AD) were assessed using an analysis of variance (ANOVA) test for quantitative variables (age in years) and a chi-squared test for qualitative variables (sex, *APOE* genotype, education level, smoking status, and alcohol consumption). Univariable and multivariable logistic regression models (LRMs) were used to calculate the unadjusted and adjusted ORs (with corresponding 95% confidence intervals [CI] and *p* values), respectively. By using multivariable LRMs, selected comorbidities were also analyzed for their association with MCI/AD across covariates by stratifying ORs by the groups of each covariate. The change in magnitude of the stratified ORs and the likelihood ratio test (LRT) were used to determine whether these covariates had any significant modifying effect on these associations. For the LRT, a *p* value of .05 was the chosen threshold for significance. Adjusted ORs were also calculated to assess any confounding effect. The complete-case analysis method was used when incorporating exposure and covariate data into the analyses, by omitting participants that lacked the exposure or covariate data in the specific analysis.

3 | RESULTS

3.1 | Participant description

A total of 2831 participants from AIBL dataset were initially evaluated, and data from 388 participants were excluded from secondary

RESEARCH IN CONTEXT

1. **Systematic review**: Increased or decreased risk of Alzheimer's dementia (AD) has been observed in individuals with comorbidities. These associations have frequently been investigated in separate cohorts, often focusing on a single comorbidity or a group of diseases such as cancer. To our knowledge, this is the first epidemiological study to comprehensively assess cross-sectional associations between 20 comorbidities and mild cognitive impairment (MCI)/AD using a single dataset.

2. **Interpretation**: We found that higher comorbidity of anxiety and other neurological disorders was associated with higher odds of AD, while arthritis, cancer, gastric complaints, high cholesterol, joint replacement, visual defect, kidney and liver disease were associated with lower odds of AD.

3. **Future direction**: Longitudinal research is essential to elucidate the significant associations identified in this study and to determine whether the results can be generalized to the population beyond the AIBL cohort.

analysis in the present study due to missing cognitive health diagnoses (*n* = 353) or being OD (*n* = 35). Ultimately, 2443 participants were eligible for further analyses (1493 CU, 456 MCI, and 494 AD) (Figure 1A). The proportion of each cognitive health group for AIBL participants is presented in Figure 1B.

A summary of demographic covariates for each cognitive health group is summarized in Table 1. There were no missing data for sex, but up to 27.8% missing data for other covariates. The mean age of CU, MCI, and AD participants was approximately 76 years. The sex distribution was generally comparable in each group. About one-quarter of CU participants were *APOE* ε4 allele carriers, in contrast to half of MCI participants and two-thirds of AD participants. More than half of MCI and AD participants completed <12 years of education (i.e. high school and/or primary school), in contrast to about two-fifths of CU participants. More than half of participants in each group had never smoked, and less than 4% of each group were current smokers; additionally, about two-fifths of CU, MCI, and AD participants were former smokers. Almost half of MCI and CU participants reported drinking every day or almost every day, whereas only about two-fifths of AD participants reported drinking at this frequency.

The number of participants affected by each comorbidity in the three cognitive health groups is summarized in the Table S1. The comorbidity with the highest number of MCI (*n* = 266) and AD (*n* = 284) cases was visual defects. The comorbidity with the lowest number of MCI and AD cases was stroke (*n* = 10) and liver disease (*n* = 9), respectively.
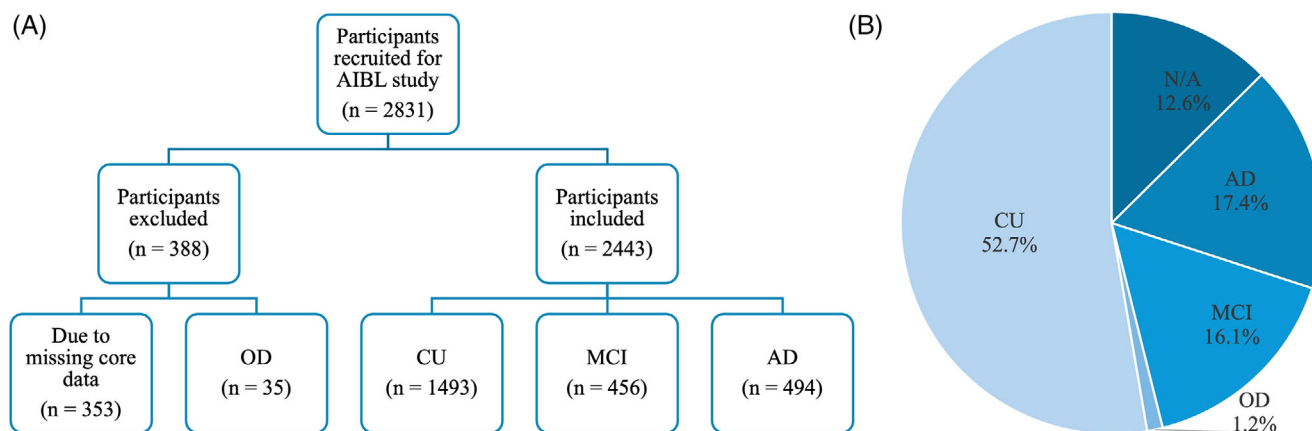
(A)

(B)

FIGURE 1 (A) Flowchart demonstrating the selection process of AIBL participants for quantitative analysis. (B) Pie chart representing the proportion of each cognitive health group in the AIBL cohort.

TABLE 1 Statistical summary of covariates.

Covariate	CU (n = 1493)	MCI (n = 446)	AD (n = 494)	p-Value
Age in years, mean (SD)	76.2 (7.0)	75.9 (8.4)	76.4 (9.7)	<.001
Sex, number (%)				.011
Female	853 (57.1)	224 (49.1)	274 (55.5)	
Male	640 (42.9)	232 (50.9)	220 (44.5)	
*APOE ε*4 allele carrier, number (%)				<.001
Yes	409 (28.1)	206 (53.8)	270 (64.8)	
No	1045 (71.9)	177 (46.2)	147 (35.2)	
Highest education level, number (%)				<.001
0–8	100 (6.8)	52 (12.6)	74 (16.9)	
9–12	521 (35.2)	197 (47.7)	186 (42.6)	
13–15	313 (21.2)	72 (17.4)	83 (19.0)	
15+	545 (36.8)	92 (22.3)	94 (21.5)	
Smoking status, number (%)				.369
Current	38 (3.2)	12 (3.6)	5 (1.3)	
Former	458 (38.0)	129 (38.5)	149 (39.6)	
Never	709 (58.8)	194 (57.9)	222 (59.1)	
Alcohol consumption, number (%)				<.001
Most or every day	556 (47.6)	132 (47.7)	119 (37.3)	
Weekly	288 (24.7)	49 (17.7)	55 (17.2)	
Monthly or occasional	141 (12.1)	35 (12.6)	42 (13.2)	
Never	182 (15.6)	61 (22.0)	103 (32.3)	

Note: Missing data: Age = 18 (0.74%), *APOE* genotype = 189 (7.7%); education level = 114 (4.7%), smoking status = 526 (21.6%); alcohol consumption = 680 (27.8%).

3.2 | Unadjusted ORs

The unadjusted associations between the comorbidities and MCI/AD are summarized in Tables S2 and S3. Approximately half of the ORs for AD were >1, indicating an increase in odds of developing AD for those with the comorbidity compared to those without. A similar trend was observed for MCI, although these results were subject to greater uncertainty as the corresponding confidence intervals crossed null value (*p* > .05).

TABLE 2 Multivariable logistic regression of the relationship between comorbidities and MCI, stratified by covariates.

Covariate	Comorbidity-MCI association, OR [95% CI]					
	Arthritis	Cancer	Gastric complaints	Heart attack	Thyroid disease	Visual defects
Age						
<60 years	n/a[a]	n/a[a]	0.36 [0.05, 2.37]	n/a[a]	n/a[a]	0.48 [0.07, 3.61]
60–69 years	1.03 [0.56, 1.92]	1.43 [0.71, 2.91]	0.67 [0.33, 1.45]	0.54 [0.07, 4.35]	0.49 [0.17, 1.44]	0.93 [0.45, 1.95]
70–79 years	0.53 [0.37, 0.74]	0.70 [0.46, 1.06]	0.56 [0.39, 0.82]	1.78 [0.93, 3.41]	0.59 [0.34, 1.00]	0.50 [0.33, 0.76]
80–89 years	0.60 [0.38, 0.95]	0.54 [0.33, 0.87]	0.59 [0.38, 0.91]	1.91 [1.06, 3.43]	0.50 [0.26, 0.96]	0.24 [0.14, 0.43]
≥90 years	1.05 [0.25, 4.46]	0.56 [0.15, 2.00]	0.38 [0.09, 1.53]	n/a[a]	0.52 [0.10, 2.65]	0.27 [0.05, 1.49]
Sex						
Female	0.71 [0.51, 0.99]	0.86 [0.58, 1.27]	0.53 [0.38, 0.75]	1.26 [0.62, 2.56]	0.59 [0.32, 0.91]	0.42 [0.28, 0.64]
Male	0.63 [0.45, 0.89]	0.57 [0.39, 0.84]	0.67 [0.46, 0.96]	1.50 [0.90, 2.50]	0.51 [0.24, 1.10]	0.55 [0.37, 0.83]
Smoking status						
Never	0.63 [0.45, 0.89]	0.61 [0.41, 0.92]	0.56 [0.39, 0.82]	1.45 [0.83, 2.55]	0.60 [0.36, 1.00]	0.53 [0.34, 0.83]
Former	0.50 [0.33, 0.75]	0.71 [0.45, 1.11]	0.45 [0.29, 0.69]	1.47 [0.74, 2.95]	0.54 [0.29, 1.00]	0.38 [0.23, 0.62]
Current	0.61 [0.16, 2.34]	1.21 [0.26, 5.54]	2.60 [0.67, 10.23]	n/a[a]	n/a[a]	1.88 [0.20, 17.49]
Highest education level						
0–8 years	0.30 [0.14, 0.64]	0.74 [0.30, 1.82]	0.34 [0.15, 0.75]	0.77 [0.23, 2.55]	0.92 [0.37, 2.31]	0.32 [0.14, 0.76]
9–12 years	0.56 [0.39, 0.80]	0.74 [0.48, 1.13]	0.50 [0.34, 0.74]	1.81 [0.99, 3.29]	0.38 [0.20, 0.69]	0.48 [0.31, 0.74]
13–15 years	0.71 [0.41, 1.23]	0.69 [0.36, 1.33]	0.72 [0.40, 1.29]	1.40 [0.54, 3.64]	0.39 [0.15, 1.02]	0.92 [0.42, 1.99]
15+ years	0.80 [0.49, 1.29]	0.98 [0.59, 1.62]	0.77 [0.47, 1.28]	0.62 [0.19, 2.08]	0.85 [0.42, 1.72]	0.57 [0.29, 1.10]
Alcohol consumption						[b]
Never	0.64 [0.35, 1.19]	1.10 [0.58, 2.06]	0.53 [0.29, 0.98]	0.53 [0.15, 1.88]	1.05 [0.48, 2.30]	0.57 [0.25, 1.31]
Monthly or occasional	0.37 [0.18, 0.79]	0.68 [0.30, 1.58]	0.59 [0.27, 1.31]	1.57 [0.47, 5.28]	0.29 [0.08, 1.01]	0.37 [0.13, 1.03]
Weekly	0.55 [0.30, 1.01]	0.57 [0.27, 1.23]	0.78 [0.41, 1.51]	1.84 [0.69, 4.87]	0.50 [0.19, 1.33]	1.57 [0.53, 4.63]
Every or most days	0.61 [0.42, 0.90]	0.58 [0.37, 0.92]	0.44 [0.29, 0.67]	1.40 [0.71, 2.76]	0.78 [0.45, 1.37]	0.35 [0.22, 0.56]
APOE ε4 allele carrier						
No	0.66 [0.46, 0.95]	0.80 [0.53, 1.22]	0.66 [0.45, 0.97]	1.54 [0.82, 2.87]	0.39 [0.20, 0.75]	0.39 [0.25, 0.61]
Yes	0.82 [0.56, 1.22]	0.61 [0.38, 0.95]	0.55 [0.37, 0.83]	1.56 [0.79, 3.08]	0.66 [0.38, 1.14]	0.57 [0.36, 0.91]

[a]ORs cannot be calculated when there are zero individuals in either the exposed or unexposed group.
[b]The LRT gave a *p* value < .05.

3.3 | Stratified ORs

The associations between comorbidities and MCI/AD when stratified by covariates are summarized in Tables 2 and 3, respectively. Overall, the stratified ORs for each comorbidity were in the same direction as the unadjusted OR, and only the magnitude of association changed, albeit often minimally. Most of the LRTs (Table S4) were not statistically significant (*p* > .05), providing weak evidence against the null hypothesis that these covariates do not modify the association between many comorbidities and MCI/AD. However, caution should be taken when using the LRT for determining effect modification significance, as studies are often too underpowered to detect interaction and may give a high *p* value even when modification is present.

When stratified by age, older participants with comorbidities were often found to have lower odds of MCI/AD than those without. Two exceptions were the associations between depression, high cholesterol, and AD, for which the ORs increased almost three-fold and

five-fold, respectively, when comparing the youngest age group with the oldest age group. It should be noted that there were small numbers of participants in the groups for ages <60 and ≥90, which often led to underpowered sub-analyses (as reflected by the wide confidence intervals) or no possible analyses at all, and thus potentially unreliable results. If these groups are disregarded, the modifying effect from age is negligible. In addition, there was strong evidence against the null hypothesis that the association between visual defects and AD is not modified by age (LRT *p* = .038), suggesting that age could be a potential effect modifier for this association.

When stratified by sex, the odds of MCI/AD were higher for males with gastric complaints or visual defects. Cancer had significantly different strengths of associations with MCI when stratified, while anxiety, depression, neurological disorders, stroke, and visual defects had significantly different strengths of associations with AD. Moreover, there was strong evidence against the null hypothesis that the association between anxiety, depression, or visual defects and AD is not

TABLE 3 Multivariable logistic regression of the relationship between comorbidities and AD, stratified by covariates.

Covariate	Comorbidity-AD association, OR [95% CI]												
	Anxiety	Arthritis	Cancer	Depression	Falls	Gastric complaints	High cholesterol	Joint replacement	Kidney disease	Liver disease	Neurological disorders	Stroke	Visual defects
Age (years)													
<60	3.33 [0.56, 19.95]	1.33 [0.07, 24.32]	0.61 [0.05, 7.88]	1.07 [0.20, 5.77]	1.33 [0.07, 24.32]	0.40 [0.06, 2.70]	0.46 [0.07, 3.14]	n/a[a]	n/a[a]	n/a[a]	n/a[a]	n/a[a]	[b] 0.73 [0.08, 6.31]
60–69	3.15 [1.71, 5.78]	0.60 [0.33, 1.09]	0.74 [0.34, 1.60]	2.71 [1.51, 4.88]	1.25 [0.54, 2.92]	0.67 [0.35, 1.30]	0.59 [0.28, 1.25]	1.02 [0.42, 2.45]	0.44 [0.10, 1.95]	0.37 [0.05, 2.89]	5.68 [2.33, 13.84]	n/a[a]	0.91 [0.46, 1.81]
70–79	2.18 [1.47, 3.23]	0.56 [0.39, 0.81]	0.61 [0.38, 0.97]	1.90 [1.27, 2.83]	1.74 [1.14, 2.66]	0.51 [0.34, 0.76]	0.75 [0.48, 1.16]	0.52 [0.29, 0.95]	0.29 [0.10, 0.80]	0.34 [0.10, 1.10]	1.13 [0.56, 2.28]	3.37 [1.40, 8.11]	0.49 [0.32, 0.77]
80–89	1.38 [0.89, 2.16]	0.40 [0.26, 0.60]	0.42 [0.27, 0.68]	1.53 [0.98, 2.37]	1.28 [0.85, 1.93]	0.49 [0.32, 0.75]	0.95 [0.52, 1.74]	0.45 [0.27, 0.76]	0.41 [0.20, 0.86]	0.36 [0.12, 1.03]	2.45 [1.36, 4.41]	2.02 [1.04, 3.93]	0.26 [0.15, 0.45]
≥90	2.50 [0.85, 7.31]	0.30 [0.11, 0.82]	0.88 [0.34, 2.27]	2.93 [0.97, 8.83]	0.55 [0.22, 1.37]	0.65 [0.25, 1.73]	2.19 [0.47, 10.34]	0.76 [0.23, 2.49]	0.78 [0.18, 3.38]	n/a[a]	0.81 [0.19, 3.43]	1.20 [0.37, 3.87]	0.18 [0.04, 0.76]
Sex	[b]			[b]									[b]
Female	1.57 [1.13, 2.18]	0.54 [0.39, 0.73]	0.60 [0.40, 0.90]	1.56 [1.13, 2.17]	1.64 [1.19, 2.26]	0.51 [0.37, 0.71]	0.84 [0.56, 1.28]	0.54 [0.34, 0.84]	0.41 [0.21, 0.82]	0.37 [0.16, 0.87]	1.79 [1.09, 2.92]	3.76 [1.93, 7.32]	0.35 [0.24, 0.51]
Male	3.07 [2.10, 4.49]	0.52 [0.37, 0.73]	0.57 [0.39, 0.85]	2.73 [1.87, 3.98]	1.50 [0.99, 2.28]	0.63 [0.43, 0.92]	0.64 [0.41, 0.98]	0.77 [0.48, 1.24]	0.42 [0.20, 0.90]	0.34 [0.10, 1.12]	2.38 [1.36, 4.18]	2.21 [1.15, 4.25]	0.69 [0.45, 1.05]
Smoking status													
Never	1.64 [1.16, 2.31]	0.49 [0.36, 0.67]	0.53 [0.36, 0.78]	1.95 [1.40, 2.72]	1.29 [0.90, 1.84]	0.57 [0.40, 0.80]	0.54 [0.35, 0.83]	0.51 [0.32, 0.80]	0.34 [0.16, 0.71]	0.49 [0.23, 1.05]	2.72 [1.68, 4.42]	1.74 [0.86, 3.53]	0.39 [0.26, 0.57]
Former	1.67 [1.10, 2.51]	0.39 [0.26, 0.58]	0.54 [0.34, 0.85]	1.57 [1.03, 2.40]	1.30 [0.86, 1.96]	0.45 [0.30, 0.67]	0.59 [0.36, 0.98]	0.68 [0.40, 1.17]	0.42 [0.19, 0.90]	0.13 [0.02, 0.99]	1.04 [0.52, 2.08]	2.77 [1.40, 5.47]	0.44 [0.27, 0.72]
Current	2.20 [0.19, 25.52]	2.18 [0.20, 22.95]	1.07 [0.10, 11.65]	1.48 [0.13, 16.39]	0.93 [0.09, 10.04]	0.72 [0.07, 7.68]	1.54 [0.09, 26.82]	1.78 [0.16, 20.10]	2.83 [0.24, 34.14]	n/a[a]	5.83 [0.40, 84.60]	n/a[a]	n/a[a]

(Continues)

TABLE 3 (Continued)

	Comorbidity-AD association, OR [95% CI]												
Covariate	Anxiety	Arthritis	Cancer	Depression	Falls	Gastric complaints	High cholesterol	Joint replacement	Kidney disease	Liver disease	Neurological disorders	Stroke	Visual defects
Highest education level (years)													
0–8	1.10 [0.57, 2.13]	0.45 [0.23, 0.88]	0.79 [0.37, 1.70]	2.26 [1.16, 4.38]	1.85 [0.96, 3.58]	0.46 [0.24, 0.87]	0.49 [0.20, 1.16]	0.36 [0.16, 0.81]	0.60 [0.23, 1.54]	n/a[a]	1.93 [0.69, 5.36]	1.80 [0.58, 5.60]	0.39 [0.18, 0.85]
9–12	2.00 [1.34, 2.98]	0.48 [0.33, 0.71]	0.82 [0.53, 1.27]	1.68 [1.12, 2.52]	1.28 [0.84, 1.97]	0.53 [0.35, 0.79]	0.67 [0.41, 1.09]	0.65 [0.39, 1.11]	0.30 [0.13, 0.72]	0.39 [0.14, 1.12]	1.63 [0.86, 3.10]	3.15 [1.55, 6.36]	0.71 [0.44, 1.15]
13–15	2.23 [1.29, 3.87]	0.47 [0.28, 0.79]	0.67 [0.36, 1.25]	1.79 [1.04, 3.10]	2.05 [1.17, 3.60]	0.50 [0.28, 0.90]	0.76 [0.40, 1.44]	0.69 [0.32, 1.47]	0.38 [0.09, 1.63]	0.20 [0.03, 1.48]	2.21 [0.93, 5.22]	3.61 [0.94, 13.80]	0.40 [0.22, 0.74]
15+	2.31 [1.36, 3.91]	0.51 [0.31, 0.83]	0.36 [0.19, 0.68]	1.93 [1.14, 3.25]	1.31 [0.77, 2.24]	0.73 [0.44, 1.21]	0.81 [0.43, 1.53]	0.80 [0.42, 1.53]	0.37 [0.11, 1.22]	0.63 [0.19, 2.12]	3.96 [1.97, 7.94]	2.14 [0.77, 5.99]	0.44 [0.24, 0.81]
Alcohol consumption													
Never	1.45 [0.86, 2.44]	0.44 [0.27, 0.73]	0.61 [0.34, 1.08]	1.66 [0.98, 2.80]	1.96 [1.19, 3.23]	0.64 [0.39, 1.05]	0.50 [0.25, 1.00]	0.48 [0.24, 0.97]	n/a[a]	0.28 [0.06, 1.28]	2.34 [1.10, 4.98]	n/a[a]	0.38 [0.20, 0.74]
Monthly or occasional	1.40 [0.65, 2.99]	0.54 [0.26, 1.09]	0.40 [0.16, 0.96]	1.97 [0.90, 4.29]	0.58 [0.25, 1.30]	0.35 [0.16, 0.79]	1.13 [0.52, 2.46]	1.24 [0.48, 3.17]	0.12 [0.02, 0.95]	0.32 [0.04, 2.55]	0.65 [0.18, 2.34]	3.58 [0.85, 14.98]	0.56 [0.20, 1.60]
Weekly	2.29 [1.24, 4.21]	0.67 [0.37, 1.20]	0.44 [0.20, 0.98]	1.74 [0.94, 3.23]	1.37 [0.72, 2.57]	0.66 [0.35, 1.26]	0.65 [0.31, 1.37]	1.05 [0.50, 2.23]	0.70 [0.31, 1.58]	0.61 [0.14, 2.72]	2.64 [1.04, 6.67]	5.93 [1.86, 18.92]	0.63 [0.29, 1.36]
Every or most days	1.81 [1.17, 2.80]	0.40 [0.27, 0.60]	0.64 [0.40, 1.02]	1.56 [1.01, 2.41]	1.09 [0.68, 1.74]	0.40 [0.26, 0.64]	0.49 [0.28, 0.86]	0.46 [0.25, 0.84]	0.60 [0.25, 1.44]	0.24 [0.06, 0.99]	2.36 [1.23, 4.53]	2.03 [0.98, 4.23]	0.42 [0.26, 0.69]
APOE ε4 allele carrier													[b]
No	1.88 [1.23, 2.90]	0.47 [0.32, 0.70]	0.69 [0.43, 1.10]	2.27 [1.50, 3.44]	1.81 [1.19, 2.75]	0.47 [0.30, 0.74]	0.61 [0.32, 1.14]	0.67 [0.38, 1.16]	0.36 [0.15, 0.91]	0.27 [0.06, 1.11]	1.80 [0.94, 3.45]	2.38 [1.12, 5.07]	0.28 [0.18, 0.43]
Yes	1.98 [1.34, 2.88]	0.63 [0.44, 0.89]	0.57 [0.38, 0.87]	1.67 [1.15, 2.43]	1.74 [1.19, 2.56]	0.59 [0.41, 0.86]	0.76 [0.48, 1.21]	0.62 [0.38, 1.03]	0.45 [0.21, 0.95]	0.36 [0.14, 0.95]	2.70 [1.61, 4.53]	4.88 [2.25, 10.58]	0.66 [0.43, 1.01]

[a]ORs cannot be calculated when there are zero individuals in either the exposed or unexposed group.
[b]The LRT gave a p value <.05.

modified by sex (LRT $p = .009$, $p = .027$, $p = .018$), suggesting that sex could be a potential effect modifier for these associations.

No consistent trend was observed for smoking status across all three groups. It should be noted that the participant pool for current smokers ($n = 55$) was significantly smaller than that of former smokers ($n = 736$) and non-smokers (never group, $n = 1125$), rendering the sub-analysis underpowered and not meaningful enough. Disregarding current smokers, a more consistent trend emerges in both groups: non-smokers exhibit higher ORs for MCI than former smokers for several comorbidities, while odds for AD are higher for former smokers than non-smokers for several comorbidities. The overall change is minimal.

When stratified by education level, the odds for AD tended to increase with decreasing education level for participants with some comorbidities (e.g., depression), while the opposite trend was observed for other comorbidities (e.g., anxiety). The associations between comorbidities and MCI also showed inconsistent trends. The strength of some comorbidity-MCI associations was stronger among participants in the 15+ age group than for those in the 13–15 age group. In the remaining education groups, it was observed that the odds increased with increasing education levels. It is important to note that some sub-analyses may not be sufficiently meaningful due to the small number of participants, for example, those with up to 8 years of education ($n = 226$).

Regarding the frequency of alcohol consumption, the associations between comorbidities and MCI/AD showed inconsistent trends. The higher odds of MCI were observed in non-drinkers (never group) with a history of cancer or thyroid disease compared to the other alcohol consumption groups. Additionally, a trend toward increasing ORs for associations between other comorbidities and MCI was observed with higher consumption frequency (weekly or every/most day groups). The higher odds of AD were observed in non-drinkers with a history of falls. Moreover, a trend toward increasing ORs for associations between other comorbidities and AD was observed with a moderate to high or highest consumption frequency (from monthly to every/most day groups). However, the modifying effect of alcohol consumption was minimal for all associations.

For the presence of the *APOE* $\varepsilon4$ allele, higher odds of MCI were observed in $\varepsilon4$ allele carriers with arthritis, heart attack, thyroid disease, or visual defects compared to non-carriers. Except for depression, falls, and joint replacement, $\varepsilon4$ allele carriers with the other comorbidities were more likely to have AD compared to non-carriers. Although significantly different strengths of associations were observed between the two groups for a few comorbidities, such as stroke, visual defects, with AD, the *APOE* $\varepsilon4$ allele had a minimal modifying effect overall. Moreover, there was strong evidence against the null hypothesis that the association between visual defects and AD was not modified by the presence of the *APOE* $\varepsilon4$ allele (LRT $p = .007$), suggesting that *APOE* $\varepsilon4$ allele could be a potential effect modifier for this association.

3.4 | Adjusted ORs

The ORs after adjustment for all covariates for each comorbidity associated with MCI/AD are summarized in Table 4. When compared with the unadjusted ORs (see Tables S2 and S3), the confounding effect was considered significant if the difference between the unadjusted and adjusted ORs was >10%.[24]

For comorbidity-MCI associations, the OR for heart attack decreased significantly from 1.51 to 1.00, while the OR for thyroid disease increased significantly from 0.54 to 0.68 after adjusting for all covariates. Concerning comorbidity-AD associations, the ORs were significantly changed for all comorbidities except liver disease. In addition, the OR for neurological disorders increased from 2.01 to 2.54, while there was a significant attenuation for the other diseases. These observations suggest potential confounding effects in the target associations.

As shown in Table 4, higher comorbidity of arthritis, cancer, gastric complaints, and visual defect was associated with lower odds of MCI, and the p values provide strong evidence against the null hypothesis that there is no association between these comorbidities and MCI ($p < .05$). In addition, a higher comorbidity of anxiety and other neurological disorders was associated with increased odds of AD, while arthritis, cancer, gastric complaints, high cholesterol, joint replacement, visual defect, kidney and liver disease were associated with decreased odds of AD, and the p values also provide strong evidence against the null hypothesis ($p < .05$).

The ORs after adjustment for each covariate are summarized in Table S5. After individual adjustment for age, an attenuating effect was observed for the ORs of the association between falls, joint replacement, or stroke and AD. A minimal confounding effect of sex was observed for all associations. After individual adjustment for smoking status, an attenuating effect was observed for the ORs of the association between six comorbidities (anxiety, arthritis, falls, high cholesterol, or stroke) and AD; minimal confounding effects were observed for the remaining diseases. For all associations except neurological diseases (odds increased from 2.01 to 2.28), a minimal confounding effect of education level was observed. After individual adjustment for alcohol consumption, an attenuating effect was observed for the ORs of the association between six comorbidities (anxiety, arthritis, depression, falls, gastric complaints, high cholesterol, or stroke) and AD; minimal confounding effects were observed for the remaining diseases. After adjustment for *APOE* $\varepsilon4$ status, a significant confounding effect was only observed for only three associations—between falls, neurological disorders, or stroke and AD. Additionally, the OR of the association between stroke and AD increased significantly after adjustment for *APOE* $\varepsilon4$ status, from 2.87 to 3.36. Of all the associations analyzed, only the cancer-MCI/AD associations had no individual confounding effect by any of the covariates.

TABLE 4 Multivariable logistic regression of the relationship between comorbidities and MCI/AD, adjusted for covariates.

Model	Comorbidity–MCI association, OR [95% CI] (p value)					
	Arthritis	Cancer	Gastric complaints	Heart attack	Thyroid disease	Visual defects
Adjusted for all covariates[b]	0.61	0.67	0.59	1.00	0.68	0.49
	[0.43, 0.86]	[0.46, 0.98]	[0.42, 0.83]	[0.55, 1.79]	[0.42, 1.10]	[0.32, 0.75]
	(.005)[a]	(.040)[a]	(.003)[a]	(.989)	(.113)	(.001)[a]

Model	Comorbidity–AD association, OR [95% CI] (p value)												
	Anxiety	Arthritis	Cancer	Depression	Falls	Gastric complaints	High cholesterol	Joint replacement	Kidney disease	Liver disease	Neurological disorders[a]	Stroke	Visual defects
Adjusted for all covariates[b]	1.45	0.39	0.49	1.38	1.04	0.52	0.51	0.50	0.32	0.37	2.54	1.86	0.38
	[1.02, 2.05]	[0.28, 0.55]	[0.33, 0.72]	[0.97, 1.97]	[0.73, 1.50]	[0.39, 0.71]	[0.32, 0.81]	[0.31, 0.80]	[0.15, 0.65]	[0.14, 0.96]	[1.54, 4.21]	[0.99, 3.49]	[0.25, 0.57]
	(.039)[a]	(<.001)[a]	(<.001)[a]	(.072)	(.813)	(<.001)[a]	(.004)[a]	(.004)[a]	(.002)[a]	(.041)[a]	(<.001)[a]	(.054)	(<.001)[a]

[a] These associations indicate significant confounding effects.
[b] Covariates adjusted = age, sex, smoking status, the highest level of education completed, alcohol consumption frequency, and APOE genotype.

4 | DISCUSSION

This study provides an overview of how various diseases are linked to MCI/AD. The quantitative analysis reveals a range of diseases cross-sectionally associated with AD to varying degrees. For diseases associated with lower odds of AD, future research could explore whether the disease pathogenesis may interfere with the clinical evolution of AD. Conversely, for diseases associated with higher odds of AD, it may be beneficial for people living with these medical conditions to undergo monitoring for MCI and AD onset.

Six comorbidities were found to be most negatively associated with AD (OR ≤ 0.5 and p < .05). Among these, the results for arthritis, cancer, and joint replacement in the present study are consistent with previous studies[25–28]; while the associations between visual impairment, kidney or liver disease and AD yielded conflicting results compared to previous studies.[29–32] We found that higher visual defects were associated with 50%–60% lower odds of MCI/AD after adjustment for potential covariates, which is consistent with a study conducted by Ou et al.[33] The authors found that participants who suffered from open-angle glaucoma had a 9% lower risk of incident AD after controlling for confounders (HR 0.91; 95% CI: 0.88%0.93). However, most previous studies found a significant positive association between visual impairment and dementia.[34–37] Further research is required to investigate this conflicting results. For diseases with low survival rates such as kidney and liver diseases, the decreased odds may result from mortality selection—this is when a subset of the population with the exposure dies before they can develop the outcome or be measured.[38] As the exposed participants who survived long enough to be measured are more likely to be healthier and outcome-free, this can downplay any positive associations between the exposure and outcome.

The comorbidities with a significant increase in odds were anxiety and neurological disorders. These findings are consistent with previous studies[39–41] and are supported by studies that have observed overlap in pathologies between these comorbidities and AD.[42,43] Comorbidities such as depression, falls, and stroke were observed to be insignificantly associated with AD. Mixed associations have been found for some of these comorbidities in the literature, demonstrating that the inconsistencies in these studies are due to different populations, methodologies, and the complexity of certain comorbidities (such as the different subtypes and treatment effects).[44–46]

Although the ORs of the comorbidity-AD associations changed to some extent after stratifying the covariates, only sex and the *APOE* sub-analyses showed relatively consistent patterns between groups. Several studies have identified *APOE ε4* as a risk factor, reflected in the higher ORs for AD in *APOE ε4* allele carriers compared to non-carriers in the *APOE* sub-analysis.[47] However, the higher ORs for males compared to females contradict studies that have observed a higher AD prevalence and risk in females.[48,49] It remains controversial whether females really have a higher risk of AD than males or whether the higher incidence arises from other factors, such as the longer life expectancy of females.[50]

Significant confounding effects of covariates were observed for some comorbidities (Table S3). Alcohol consumption frequency

emerged as the most significant confounder, impacting almost half of the analyzed associations (six comorbidity-AD associations). In addition to its association with higher odds of AD,[51] frequent alcohol consumption is linked to various adverse health outcomes, including cardiovascular diseases[52,53] and mental disorders,[54,55] which may confound the comorbidity-AD associations. Smoking appeared to positively confound the association between anxiety, arthritis, falls, high cholesterol, or stroke and AD. In addition to the positive link between smoking and AD,[56] older smokers have been observed to experience increased frailty compared to non-smokers, potentially resulting in more falls.[57] Furthermore, smoking is a known risk factor for cardiovascular diseases such as stroke and heart attack.[58–60] The *APOE ε4* allele saw confounding effects on some associations, which can be attributed to the fact that the gene is also a risk factor for several comorbidities. For example, the *APOE ε4* allele is associated with increased gait variability, which can lead to increased falls,[61] and it is also associated with an increased ischemic stroke risk.[62]

Limitations acknowledged within the current study include the cross-sectional study design. Since data for exposure and outcome were measured only once at the AIBL study baseline, deriving actual causal relationships is challenging, and reverse causality may occur. Furthermore, cognitive decline during the study follow-up was not considered for the current cross-sectional analyses. Therefore, future longitudinal analyses are required to validate the current findings in AIBL. Additionally, some potential sources of bias in the present study should be considered. The history of comorbidities selected at baseline may be subject to recall bias from self-reporting. Similarly, information on smoking and alcohol consumption could be biased by self-reporting due to social stigma, potentially underestimating the true effect of these covariates on the association between comorbidity and AD. This could be a reason contributing to the imbalanced sample size in some covariate categories (e.g., a low number of current smokers and lower stratified ORs compared to former smokers and non-smokers).

In addition, although various covariates were adjusted for, other potential confounders such as socioeconomic status and marital status were not analyzed due to their absence from the AIBL study questionnaire or insufficient data availability. Exclusion of participants who did not complete the baseline lifestyle survey, questionnaires, or cognitive assessments (missing data) could reduce statistical power, introduce bias in parameter estimation, or diminish sample representativeness, potentially leading to invalid conclusions.[63] Additionally, there is a possibility of misdiagnosis with MCI/AD or misclassification as CU at baseline, which could result in under- or over-estimation of associations. However, the occurrence of misdiagnosis in the AIBL study is low, with less than 5% of CU participants previously diagnosed as MCI and less than 1% of MCI participants previously misdiagnosed as AD. Thus, incorrect diagnoses are unlikely to significantly impact the results. Moreover, the study participants are based in Melbourne and Perth, limiting the generalizability of findings to older populations worldwide. Nonetheless, some findings align with studies in other countries, reducing the likelihood of significant discrepancies. Last, several analyses were underpowered due to small sample sizes in some groups, particularly affecting stratified analyses and introducing uncertainty regarding the modifying strength of covariates.

This study benefits from two major strengths. First, the design of the AIBL study allowed analyses of multiple exposures, covariates, and outcomes. This means that a range of comorbidities and their associations with MCI/AD could be measured alongside various confounders or effect modifiers. To our knowledge, this is the first study to assess 20 comorbidity associations with MCI/AD using a single dataset. Secondly, the availability of covariate data in the AIBL study allowed adjustments for confounding and exploration of effect modification in these comorbidity associations with MCI/AD.

Future studies should longitudinally investigate the relationship between certain diseases and MCI/AD to verify the mechanisms underlying these relationships to determine if there is causation. They should focus on how these associations between comorbidities and MCI/AD vary within each covariate. By including a larger sample size, stratified analyses can reach sufficient power to obtain more confident results. In addition, the brain $A\beta$ levels of more AIBL participants are now assessed using PET imaging; these data will allow more precise analysis investigating the relationship between comorbidities and brain $A\beta$ levels.

CONFLICT OF INTEREST STATEMENT

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

CONSENT STATEMENT

All human subjects provided informed consent.

ORCID

Yijun Pan https://orcid.org/0000-0002-1442-3333

REFERENCES

1. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2022;18:700-789.
2. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. *Molecules*. 2020;25:5789.
3. Ward A, Tardiff S, Dye C, Arrighi HM. Rate of conversion from prodromal Alzheimer's disease to Alzheimer's dementia: a systematic review of the literature. *Dement Geriatr Cogn Disord Extra*. 2013;3:320-332.
4. Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med*. 2010;362:329-344.
5. Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement*. 2016;12:292-323.

6. Apostolova LG. Alzheimer disease. *Contin Lifelong Learn Neurol*. 2016;22:419.

7. Daviglus ML, Bell CC, Berrettini W, et al. NIH state-of-the-science conference statement: preventing Alzheimer's disease and cognitive decline. *NIH Consens State Sci Statements*. 2010;27:1-30.

8. Doraiswamy PM, Leon J, Cummings JL, Marin D, Neumann PJ. Prevalence and impact of medical comorbidity in Alzheimer's disease. *J Gerontol A*. 2002;57:M173-M177.

9. Rajamaki B, Hartikainen S, Tolppanen A-M. The effect of comorbidities on survival in persons with Alzheimer's disease: a matched cohort study. *BMC Geriatr*. 2021;21:173.

10. Wang JH, Wu YJ, Tee BL, Lo RY. Medical comorbidity in Alzheimer's disease: a nested case-control study. *J Alzheimers Dis*. 2018;63:773-781.

11. Valentine D, Teerlink CC, Farnham JM, et al. Comorbidity and cancer disease rates among those at high-risk for Alzheimer's disease: a population database analysis. *Int J Environ Res Public Health*. 2022;19:16419.

12. Haaksma ML, Vilela LR, Marengoni A, et al. Comorbidity and progression of late onset Alzheimer's disease: a systematic review. *PLOS ONE*. 2017;12:e0177044.

13. McIntosh EC, Nation DA, Initiative ftAsDN. Importance of treatment status in links between type 2 diabetes and Alzheimer's disease. *Diabetes Care*. 2019;42:972-979.

14. Steen E, Terry BM, Rivera EJ, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease – is this type 3 diabetes? *J Alzheimer's Dis*. 2005;7:63-80.

15. Smolina K, Wotton CJ, Goldacre MJ. Risk of dementia in patients hospitalised with type 1 and type 2 diabetes in England, 1998-2011: a retrospective national record linkage cohort study. *Diabetologia*. 2015;58:942-950.

16. Fowler C, Rainey-Smith SR, Bird S, Bomke J, Bourgeat P, Brown BM, et al. Fifteen years of the Australian imaging, biomarkers and lifestyle (AIBL) study: progress and observations from 2,359 older adults spanning the spectrum from cognitive normality to Alzheimer's disease. *J Alzheimers Dis Rep*. 2021;5:443-468.

17. Zhou S, Zhou R, Zhong T, Li R, Tan J, Zhou H. Association of smoking and alcohol drinking with dementia risk among elderly men in China. *Curr Alzheimer Res*. 2014;11:899-907.

18. Laws KR, Irvine K, Gale TM. Sex differences in cognitive impairment in Alzheimer's disease. *World J Psychiatry*. 2016;6:54-65.

19. Michaelson DM. APOE ε4: the most prevalent yet understudied risk factor for Alzheimer's disease. *Alzheimers Dement*. 2014;10:861-868.

20. Liu C-C, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol*. 2013;9:106-118.

21. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci USA*. 1993;90:1977-1981.

22. Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS. Modifiable pathways in Alzheimer's disease: mendelian randomisation analysis. *BMJ*. 2017;359:j5375.

23. StataCorp. *Stata Statistical Software: Release 17*. StataCorp LLC; 2021.

24. Budtz–Jørgensen E, Keiding N, Grandjean P, Weihe P. Confounder selection in environmental epidemiology: assessment of health effects of prenatal mercury exposure. *Ann Epidemiol*. 2007;17:27-35.

25. Korner A, Lopez AG, Lauritzen L, Andersen PK, Kessing LV. Acute and transient psychosis in old age and the subsequent risk of dementia: a nationwide register-based study. *Geriatr Gerontol Int*. 2009;9:62-68.

26. Ma L, Low YLC, Zhuo Y, et al. Exploring the association between cancer and cognitive impairment in the Australian imaging biomarkers and lifestyle (AIBL) study. *Sci Rep*. 2024;14:4364.

27. Driver JA, Beiser A, Au R, et al. Inverse association between cancer and Alzheimer's disease: results from the Framingham heart study. *BMJ*. 2012;344:e1442.

28. Reich KM, Gill SS, Eckenhoff R, et al. Association between surgery and rate of incident dementia in older adults: a population-based retrospective cohort study. *J Am Geriatr Soc*. 2024;1:12.

29. Zhang C-Y, He F-F, Su H, Zhang C, Meng X-F. Association between chronic kidney disease and Alzheimer's disease: an update. *Metab Brain Dis*. 2020;35:883-894.

30. Nho K, Kueider-Paisley A, Ahmad S, et al. Association of altered liver enzymes with Alzheimer disease diagnosis, cognition, neuroimaging measures, and cerebrospinal fluid biomarkers. *JAMA Netw Open*. 2019;2:e197978-e.

31. Javaid FZ, Brenton J, Guo L, Cordeiro MF. Visual and ocular manifestations of Alzheimer's disease and their use as biomarkers for diagnosis and progression. *Front Neurol*. 2016;7:55.

32. Rogers MA, Langa KM. Untreated poor vision: a contributing factor to late-life dementia. *Am J Epidemiol*. 2010;171:728-735.

33. Ou Y, Grossman DS, Lee PP, Glaucoma SloanFA. Alzheimer disease and other dementia: a longitudinal analysis. *Ophthalmic Epidemiol*. 2012;19:285-292.

34. Paik JS, Ha M, Jung YH, et al. Low vision and the risk of dementia: a nationwide population-based cohort study. *Sci Rep*. 2020;10:9109.

35. Kuzma E, Littlejohns TJ, Khawaja AP, Llewellyn DJ, Ukoumunne OC, Thiem U. Visual impairment, eye diseases, and dementia risk: a systematic review and meta-analysis. *J Alzheimers Dis*. 2021;83:1073-1087.

36. Tran EM, Stefanick ML, Henderson VW, et al. Association of visual impairment with risk of incident dementia in a women's health initiative population. *JAMA Ophthalmol*. 2020;138:624-633.

37. Lee GI, Chi SA, Kim K, et al. Visual impairment increases the risk of dementia, especially in young males in a 12-year longitudinal follow-up study of a national cohort. *Sci Rep*. 2021;11:11393.

38. Domingue BW, Belsky DW, Harrati A, Conley D, Weir DR, Boardman JD. Mortality selection in a genetic sample and implications for association studies. *Int J Epidemiol*. 2017;46:1285-1294.

39. Dobrosavljevic M, Zhang L, Garcia-Argibay M, et al. Attention-deficit/hyperactivity disorder as a risk factor for dementia and mild cognitive impairment: a population-based register study. *Eur Psychiatry*. 2021;65:1-19.

40. Lavretsky H, Siddarth P, Kepe V, Ercoli LM, Miller KJ, Burggren AC, et al. Depression and anxiety symptoms are associated with cerebral FDDNP-PET binding in middle-aged and older nondemented adults. *Am J Geriatr Psychiatry*. 2009;17:493-502.

41. Devanand DP, Lee S, Huey ED, Goldberg TE. Associations between neuropsychiatric symptoms and neuropathological diagnoses of Alzheimer disease and related dementias. *JAMA Psychiatry*. 2022;79:359-367.

42. Sun L, Li W, Qiu Q, et al. Anxiety adds the risk of cognitive progression and is associated with axon/synapse degeneration among cognitively unimpaired older adults. *EBioMedicine*. 2023;94:104703.

43. Cui P, Ma X, Li H, Lang W, Hao J. Shared biological pathways between Alzheimer's disease and ischemic stroke. *Front Neurosci*. 2018;12:605.

44. Andersen K, Lolk A, Kragh-Sorensen P, Petersen NE, Green A. Depression and the risk of Alzheimer disease. *Epidemiology*. 2005;16:233-238.

45. Ramakers IH, Visser PJ, Aalten P, Kester A, Jolles J, Verhey FR. Affective symptoms as predictors of Alzheimer's disease in subjects with mild cognitive impairment: a 10-year follow-up study. *Psychol Med*. 2010;40:1193-1201.

46. Kuzma E, Lourida I, Moore SF, Levine DA, Ukoumunne OC, Llewellyn DJ. Stroke and dementia risk: a systematic review and meta-analysis. *Alzheimers Dement*. 2018;14:1416-1426.

47. Saddiki H, Fayosse A, Cognat E, et al. Age and the association between apolipoprotein E genotype and Alzheimer disease: a cerebrospinal fluid biomarker-based case-control study. *PLoS Med*. 2020;17:e1003289.

48. Rajan KB, Weuve J, Barnes LL, McAninch EA, Wilson RS, Evans DA. Population estimate of people with clinical Alzheimer's disease

and mild cognitive impairment in the United States (2020-2060). *Alzheimers Dement*. 2021;17:1966-1975.

49. Hendriks S, Peetoom K, Bakker C, et al. Global prevalence of young-onset dementia: a systematic review and meta-analysis. *JAMA Neurol*. 2021;78:1080-1090.

50. Shaw C, Hayes-Larson E, Glymour MM, et al. Evaluation of selective survival and sex/gender differences in dementia incidence using a simulation model. *JAMA Netw Open*. 2021;4:e211001.

51. Heymann D, Stern Y, Cosentino S, Tatarina-Nulman O, Dorrejo JN, Gu Y. The association between alcohol use and the progression of Alzheimer's disease. *Curr Alzheimer Res*. 2016;13:1356-1362.

52. Larsson SC, Wallin A, Wolk A, Markus HS. Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. *BMC Med*. 2016;14:1-11.

53. Hu C, Huang C, Li J, Liu F, Huang K, Liu Z, et al. Causal associations of alcohol consumption with cardiovascular diseases and all-cause mortality among Chinese males. *Am J Clin Nutr*. 2022;116:771-779.

54. Boden JM, Fergusson DM. Alcohol and depression. *Addiction*. 2011;106:906-914.

55. Shivani R, Goldsmith RJ, Anthenelli RM. Alcoholism and psychiatric disorders: diagnostic challenges. *Alcohol Res Health*. 2002;26:90-98.

56. Durazzo TC, Mattsson N, Weiner MW. Smoking and increased Alzheimer's disease risk: a review of potential mechanisms. *Alzheimers Dement*. 2014;10:S122-S145.

57. Kojima G, Iliffe S, Jivraj S, Liljas A, Walters K. Does current smoking predict future frailty? The English longitudinal study of ageing. *Age Ageing*. 2017;47:126-131.

58. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. *Expert Rev Cardiovasc Ther*. 2010;8:917-932.

59. Edwards R. The problem of tobacco smoking. *BMJ*. 2004;328:217-219.

60. Chen Z, Boreham J. Smoking and cardiovascular disease. *Semin Vasc Med*. 2002;02:243-252.

61. Sakurai R, Montero-Odasso M. Apolipoprotein E4 allele and gait performance in mild cognitive impairment: results from the gait and brain study. *J Gerontol A*. 2017;72:1676-1682.

62. Kumar A, Misra S, Kumar P, Faruq M, Sagar R, Yadav AK, et al. Relationship of apolipoprotein (APOE) ε4 gene polymorphism with the risk of ischemic stroke: a hospital based case-control study. *Meta Gene*. 2017;12:154-158.

63. Kang H. The prevention and handling of the missing data. *Korean J Anesthesiol*. 2013;64:402-406.

SUPPORTING INFORMATION

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