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The association between vertebrobasilar insufficiency and the risk of dementia: a nationwide register-based retrospective cohort study in Taiwan

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ABSTRACT

Objectives Neurodegenerative disorders are reportedly characterised by decreased regional cerebral blood flow. However, the association between vertebrobasilar insufficiency (VBI) and dementia remains unclear. In this nationwide, population-based, retrospective cohort study, we explored the potential association between VBI and dementia.

Design Nationwide population-based cohort study.

Setting Patients with VBI were newly diagnosed between 2000 and 2005 from the Taiwan National Health Insurance Research Database.

Participants We included 3642 subjects as the VBI group. The control cohort included 14 568 randomly selected age-matched and sex-matched VBI-free individuals.

Outcome measures All subjects were followed until the diagnosis of dementia, death or the end of 2010. Patients with VBI, dementia (viz, vascular and non-vascular, including Alzheimer's) subtypes and other confounding factors were identified according to the International Classification of Diseases Clinical Modification Codes. Cox proportional hazards regression analysis was employed to examine adjusted HRs after adjusting for confounding factors.

Results Patients with VBI had a 1.807-fold (95% CI 1.643 to 1.988, p<0.001) higher risk to develop all-cause dementia than individuals without VBI. The risk was significantly higher in the VBI group than in the non-VBI group regardless of age (<65 years: HR: 2.997, 95% CI 1.451 to 6.454, p<0.001; ≥65 years: HR: 1.752, 95% CI 1.584 to 1.937, p<0.001). The VBI group had a higher risk of all-cause dementia than the non-VBI group regardless of sex and follow-up time intervals (<1 year, 1–2 years and ≥2 years).

Conclusion Patients with VBI appear to have an increased risk of developing dementia. Further research is needed to investigate the underlying pathophysiology.

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Strengths and limitations of this study

► The major strength of this study is the use of nationwide population-based data, with a large sample size providing sufficient statistical power to explore the relationship between vertebrobasilar insufficiency (VBI) and dementia.

► The longitudinal observational design of this study, with a lengthy follow-up, enabled us to assess the temporal relationship between VBI and dementia.

► The National Health Insurance Database dataset of this study is derived from an administrative coding database, lacking details of clinical symptoms and signs of dementia, such as the predominant symptoms, mental or mood status, imaging data and other laboratory results.

INTRODUCTION

Vertebrobasilar insufficiency (VBI) mainly affects elderly people and involves reduced blood flow in the posterior part of the brain. The vertebrobasilar (VB) flow system is also called the posterior circulation, comprising the vertebral arteries, basilar artery, and posterior cerebral arteries and their branches, supplying the brainstem, thalamus, hippocampus, cerebellum, and regions of the occipital and temporal lobes.[1] VBI typically arises because of the formation of atherosclerotic plaques, resulting in insufficient blood flow through the posterior circulation and is essentially thought to be a transient ischaemic attack (TIA) in the posterior circulation.[2] VBI can present with transient and recurrent impairments, including dizziness, instability in standing and walking, double vision, hearing loss, speech disorders, nausea or vomiting.[3 4] Previous studies have indicated that recurrent VBI may increase the future risk of posterior circulation stroke.[5 6] Furthermore, some patients with VBI may suffer from progressive deterioration of memory and higher cortical functions, as well as dementia.[7 8]

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases,

characterised by slowly progressive deterioration of memory and cognitive function, and decreased regional cerebral blood flow.[9 10] Dementia can be classified as non-vascular dementia (non-VD) (including AD), accounting for 80%–90% of all cases of dementia, and vascular dementia (VD), accounting for the remainder.[11] The risk factors of dementia increase with age and include a variety of other conditions, such as diabetes, hypertension, dyslipidaemia, ischaemic heart disease, alcoholism, heart failure, depression, head injury, stroke and Parkinson's disease.[12–15] Furthermore, vascular-associated cognitive decline has been reported to be more common than previously thought.[16] Investigating links between these risk factors and dementia may therefore provide appropriate preventative strategies, and reduce the risk and socioeconomic burden of dementia.

Patients with carotid stenosis (anterior circulation) are more susceptible to cognitive and memory impairment.[17 18] However, the association between VBI (posterior circulation) and cognitive impairment has been poorly studied. Patients with VBI perform below average on a number of cognitive tests with age-corrected scores[19] and have significantly lower Benton Facial Recognition Test scores than age-matched controls, which could indicate early changes in visuospatial cognitive skills.[20] Moreover, 3 months of treatment with a cerebral vasodilator resulted in cognitive improvements in patients with VBI.[21] These studies suggest that certain cognitive impairments exist in patients with VBI.

Taken together, the association between VBI and dementia remains to be determined, and the temporal relationship between VBI and dementia is still unknown. Therefore, we designed a nationwide, population-based cohort study aimed at exploring the possible temporal association between VBI and dementia.

METHODS
Ethics statement
This study was approved by the joint institutional review board of Tri-Service General Hospital (approval TSGHIRB No. 2-104-05-045). Confidentiality was assured following the data regulations of the Health and Welfare Data Science Center, Ministry of Health and Welfare, Executive Yuan, Taiwan, which releases patients' data to investigators only for research to protect patients' privacy. The study group and a control cohort were selected from the Longitudinal Health Insurance Database (LHID). Because data in the LHID is de-identified, the requirement for obtaining informed consent from the study participants was waived by the joint institutional review board. All the study methods were according to the guidelines approved by the joint institutional review board and forenamed governmental regulations.

Data source
This study was conducted using claims data from the National Health Insurance Research Database (NHIRD),

which is maintained by the National Health Research Institute (NHRI) in Taiwan. The National Health Insurance (NHI) programme of Taiwan is a universal insurance programme established in 1995, and it is a mandatory single-payer healthcare system, covering the healthcare costs of more than 99% of Taiwan's residents (approximately 23 million). In this study, we used the LHID in Taiwan (2000–2005), which is a subset of the NHIRD. The LHID contains data of 1 million people, randomly sampled from the NHIRD, and has been demonstrated to be representative the entire population of Taiwan. The LHID contains the demographic data, dates of clinical visits, drug prescriptions and disease diagnosis codes in the format of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The NHRI reported no statistically significant differences in the sex and age distribution between the LHID subset and the total NHIRD. The NHI has a rigorous monitoring system, whereby it audits healthcare records to validate medical claims for diagnosis and treatment, to ensure that claims for reimbursement are based on valid diagnoses.

Study design and sampled participants
This population-based cohort study aimed to investigate the association of VBI and the risk of dementia by comparing two groups: the VBI group and the non-VBI group. We identified patients who were 20 years of age and older, with newly diagnosed VBI (ICD-9-CM 433.0, 433.2, 433.3, 435.0, 435.1, 435.3) based on outpatient care data in the NHIRD between 1 January 2000 and 31 December 2005, as the VBI group. The date of diagnosis of VBI was considered as the index date. All diagnoses of VBI were made on the basis of the clinical symptoms and signs with a focus on the cardiovascular and neurological systems and/or supporting imaging studies (Doppler ultrasonography, magnetic resonance angiography or CT angiography) from outpatient departments of participating hospitals and clinics.[22] For each patient with VBI, four insured subjects were selected randomly from subjects without a diagnosis of VBI in the LHID, as the non-VBI group, and were frequency-matched by sex, age and comorbidities that are known to be dementia risk factors and that were established before the index date. Selection according to comorbidities was based on outpatient data of the following ICD codes: hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), ischaemic heart disease (ICD-9-CM codes 410–414), hyperlipidaemia (ICD-9-CM code 272), tobacco use disorder (ICD-9-CM code 305.1), alcoholism (ICD-9-CM codes 291, 303.9, 334.4, 980.0), obesity (ICD-9-CM codes 278, 649.1, 783.1), atrial fibrillation (ICD-9-CM code 427.3), Parkinson's disease (ICD-9-CM code 332.0), cerebral vascular accident (ICD-9-CM codes 430–432, 433–437), major depression (ICD-9-CM code 296), chronic kidney disease (ICD-9-CM code 585) and carotid artery insufficiency (ICD-9-CM code 433.1, 435.8). Each patient in both groups was then followed up from the
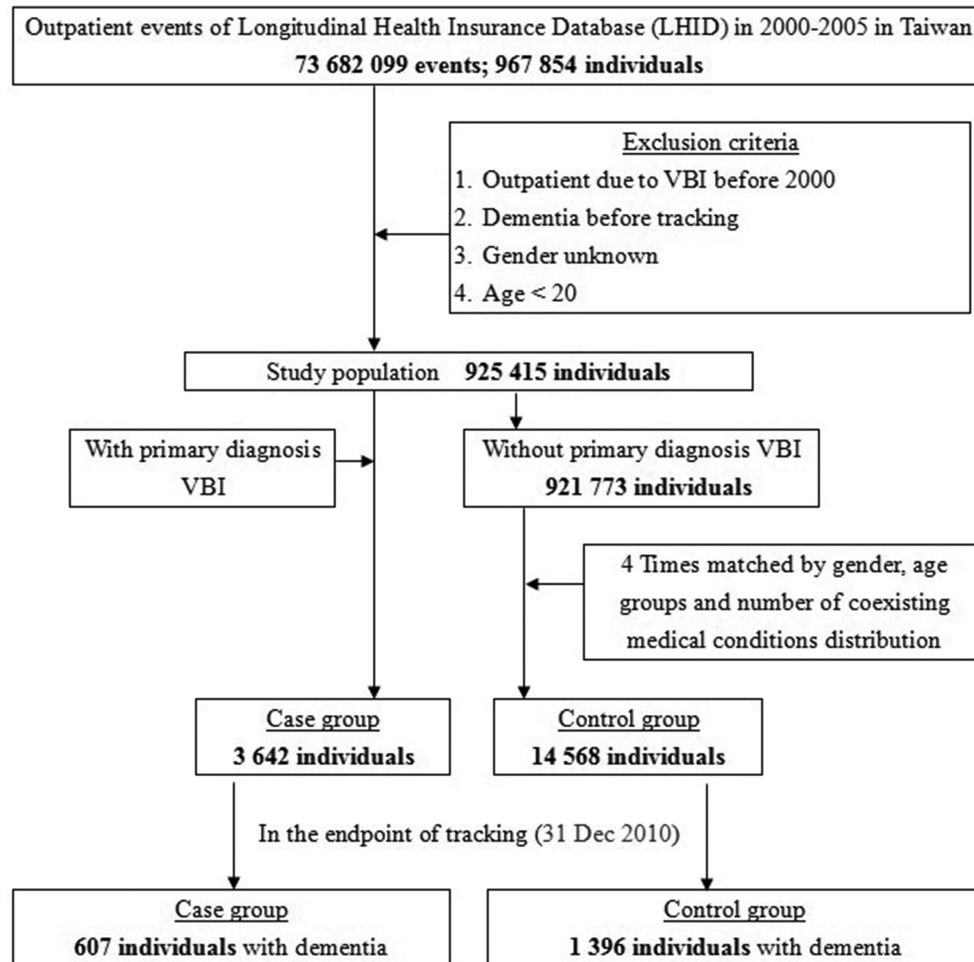
Figure 1 Flowchart of study sample selection from the National Health Insurance Research Database in Taiwan.

index date until the occurrence of dementia. For those who did not have dementia, the last day of follow-up was defined as the date of insurance withdrawal or the last day of the study period (31 December 2010) (figure 1).

Outcome measures and definitions of dementia subtypes by ICD classification

The primary outcome was classified as all-cause dementia (ICD-9-CM 290–294 and 331.0). The diagnosis of dementia was made based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,[23] after assessing the patients' medical history, daily activities, physical and social function, behaviour and cognitive function, blood tests and brain imaging. We also examined different subtypes of dementia. VD was identified in the claims data using the ICD-9-CM code 290.4; all of the remaining patients with dementia were classified as non-VD, and patients with AD were differentiated from those with non-VD using ICD-9-CM code 331.0.

Statistical analyses

All analyses were performed using SPSS V.22 software (SPSS). Continuous variables were presented as mean±SD and categorical variables as frequencies and percentages. Differences between the study and control groups

in terms of demographic characteristics (age and sex) and comorbidities (hypertension, diabetes, ischaemic heart disease, hyperlipidaemia, smoking, alcoholism, obesity, atrial fibrillation, Parkinson's disease, cerebrovascular accident, major depression, chronic kidney disease and carotid artery insufficiency) were examined by χ^2 or Fisher's exact test. Multivariate Cox proportional hazards regression analysis was used to determine the risk of dementia, and the results were presented as HRs with 95% CIs. To investigate the interaction of covariates with the association between VBI and dementia, we also calculated adjusted HRs, stratified by age (<65 years, ≥65 years), sex and follow-up time. A two-tailed p value <0.05 was considered to indicate statistical significance. Although dementia mostly affects older people, those aged ≥65 years, it can occur in people aged <65 years, known as young-onset dementia.[24] Therefore, we performed analysis of age as a two-level ordinal variable (with cut-offs at 65 years). To explore whether VBI is a time-dependent risk factor for dementia in this study, we also investigated the association between follow-up time after diagnosis of VBI and the risk of dementia. Since patients with VBI may be more likely to die from stroke or other related medical conditions, we further

Table 1 Baseline demographic status and comorbidity compared between comparison and VBI group

Variable	VBI group n=3642 (%)	Comparison group n=14568 (%)	p Value
Age, years (SD)*	67.37 (13.82)	65.41 (15.99)	0.733
<65	1362 (37.40)	5.448 (37.40)	
≥65	2280 (62.60)	9120 (62.60)	
Sex			0.999
Female	1794 (49.26)	7176 (49.26)	
Male	1848 (50.74)	7392 (50.74)	
Comorbidity			
Hypertension	671 (18.42)	2443 (16.77)	0.153
DM	304 (8.35)	1105 (7.59)	0.298
IHD	204 (5.60)	803 (5.51)	0.742
Hyperlipidaemia	31 (0.85)	94 (0.65)	0.109
TUD	1 (0.03)	8 (0.05)	0.436
Alcoholism	0 (0)	1 (0.01)	0.800
Obesity	0 (0)	0 (0)	–
AF	27 (0.74)	126 (0.86)	0.276
PD	28 (0.77)	87 (0.60)	0.146
CVA	106 (2.91)	471 (3.23)	0.178
Depression	7 (0.19)	16 (0.11)	0.298
CKD	0 (0)	0 (0)	–
CAI	7 (0.19)	36 (0.25)	0.072

*t-test.

AF, atrial fibrillation; CAI, carotid artery insufficiency; CKD, chronic kidney disease; CVA, cerebral vascular accident; DM, diabetes mellitus; IHD, ischaemic heart disease; PD, Parkinson's disease; TUD, tobacco use disorder; VBI, vertebrobasilar insufficiency.

assessed adjusted HRs of death and utilised competing risk models as well as Cox models.

RESULTS

For the period 2000–2005, this study identified 3642 patients newly diagnosed with VBI and 14568 subjects without VBI. There were no significant differences between the VBI group and non-VBI group in the distribution of sex, age and comorbidities (table 1).

During an average follow-up of 4.23±1.57 years, a total of 607 patients with VBI (16.7%) of the VBI group and 1396 non-VBI individuals (9.6%) of the non-VBI group developed dementia. Patients with VBI had a 1.807-fold (95% CI 1.643 to 1.988, p<0.001) higher risk of developing all-cause dementia than individuals without VBI (table 2).

To explore whether VBI is an age-dependent risk factor for all-cause dementia, patients were divided into two groups according to age, namely <65 and ≥65 years. In comparison with age-matched/sex-matched controls, the VBI group had a higher risk of all-cause dementia than the non-VBI group, regardless of age (<65 years: HR: 2.997, 95% CI 1.451 to 6.454, p<0.001; ≥65 years: HR: 1.752, 95% CI 1.584 to 1.937, p<0.001). We also examined whether VBI is a sex-dependent risk factor for development of dementia. Cox regression analysis revealed that

the VBI group had a higher risk of all-cause dementia, regardless of sex (men: HR: 1.732, 95% CI 1.514 to 1.981, p<0.001; women: HR: 1.888, 95% CI 1.649 to 2.160, p<0.001) (table 2). Since age has a potential impact on dementia occurrence, we also examined the associations between VBI and the risk of dementia after controlling for age as a continuous variable. The results were similar, as shown in online supplementary table S1.

We next analysed the incidence of dementia using multivariate Cox proportional hazards regression analysis, based on follow-up time intervals. Our data showed that patients with VBI were likely to develop subsequent dementia after diagnosis regardless of follow-up time intervals (<1 year, 1–2 years and ≥2 years) (table 3). Kaplan-Meier analysis showed that, compared with the matched controls, patients with VBI had a significantly higher incidence of all-cause dementia (log-rank test p<0.001) (figure 2). We further examined the associations between VBI and the risk of different subtypes of dementia, as shown in online supplementary tables S2 and S3.

After considering the competing risk of death, the results were similar. Patients with VBI had a 1.725-fold (95% CI 1.452 to 1.996, p<0.001) higher risk of developing all-cause dementia than individuals without VBI (see online supplementary figure S1). The risk was most

Table 2 Incidence of dementia and hazard ratios (multivariate Cox proportional hazards regression analysis) for the study cohort according to stratification by age and sex

Variable	VBI group			Non-VBI group			Crude HR (95% CI)	Adjusted HR (95% CI)
	Event	PYs	Rate	Event	PYs	Rate		
All dementia	607	14 802	41.01	1396	62 194	22.45	2.285 (2.179 to 2.397)***	1.807 (1.643 to 1.988)***
Age (years)								
<65	72	6388	11.27	97	25 961	3.74	3.012 (1.745 to 5.642)***	2.997 (1.451 to 6.454)***
≧ 65	535	8415	63.58	1299	36 234	35.85	2.250 (2.140 to 2.366)***	1.752 (1.584 to 1.937)***
Sex								
Male	300	7058	42.51	721	29 709	24.27	2.337 (2.092 to 2.393)***	1.732 (1.514 to 1.981)***
Female	307	7745	39.64	675	32 485	20.78	2.336 (2.183 to 2.498)***	1.888 (1.649 to 2.160)***

Model adjusted for age, sex, hypertension, diabetes mellitus, ischaemic heart disease, hyperlipidaemia, tobacco use disorder, alcoholism, obesity, atrial fibrillation, Parkinson's disease, cerebral vascular accident, depression, chronic kidney disease and carotid artery insufficiency; all variables in the model were significant in univariate analysis. Interaction: VBI × age groups: p=0.025*, VBI × sex: p=0.679.
*p<0.05.
***p<0.001.
PYs, person-years; Rate, incidence per 10 000 person-years; VBI, vertebrobasilar insufficiency.
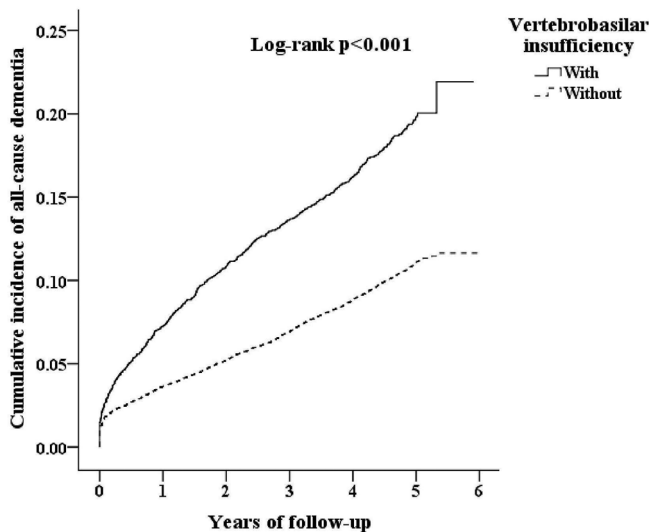

Figure 2 Cumulative incidence curves of all-cause dementia for the individual with and without vertebrobasilar insufficiency.

prominent in both the <65 year group (HR: 2.845, 95% CI 1.376 to 5.897, p<0.01) and the ≥65 year group (HR: 1.672, 95% CI 1.434 to 1.963, p<0.001) in the VBI group,

as compared with the non-VBI group (see online supplementary table S4). The VBI group had a higher risk of all-cause dementia than the non-VBI group regardless of sex and follow-up time intervals (<1 year, 1–2 years and ≥2 years) (see online supplementary table S5).

DISCUSSION

To the best of our knowledge, this is the first longitudinal study using a nationwide, population-based database to demonstrate the increased risk of all-cause dementia in patients with VBI. Our findings showed that patients with VBI had a 1.807-fold higher risk of developing all-cause dementia in comparison with a matched non-VBI cohort. The risk of developing subsequent dementia was higher in the VBI group, regardless of age, when compared with the non-VBI group. Furthermore, the impact of VBI on dementia risk was independent of sex and various follow-up intervals.

The present results support those of previous studies reporting an association between VBI and cognitive impairment.[19 20] Similarly, patients with AD have been found to show reduced cerebral blood flow in the

Table 3 Incidence of dementia and HRs (multivariate Cox proportional hazards regression analysis) for the study cohort according to various follow-up periods

Follow-up	VBI group			Non-VBI group			Crude HR (95% CI)	Adjusted HR (95% CI)
	Event	PYs	Rate	Event	PYs	Rate		
<1 year	248	118	2100.27	508	296	1713.44	1.958 (1.814 to 2.112)***	1.326 (1.139 to 1.544)***
≥1, <2 years	112	287	390.76	206	871	236.60	2.251 (2.006 to 2.527)***	1.753 (1.392 to 2.209)***
≥2 years	247	14 398	17.16	682	61 027	11.18	2.108 (1.960 to 2.267)***	1.537 (1.329 to 1.778)***

Model adjusted for age, sex, hypertension, diabetes mellitus, ischaemic heart disease, hyperlipidaemia, tobacco use disorder, alcoholism, obesity, atrial fibrillation, Parkinson's disease, cerebral vascular accident, depression, chronic kidney disease and carotid artery insufficiency; all variables in the model were significant in univariate analysis. Interaction: VBI × follow-up groups: p=0.726.
PYs, person-years; Rate, incidence per 10 000 person-years; VBI, vertebrobasilar insufficiency.
***p<0.001.

posterior circulation,[25] and patients with lower regional cerebral blood flow in the vertebrobasilar system have been found to show verbal memory impairment, language disturbances and apathy.[26] Cervicocerebral stenosis has also been shown to be associated with cognitive dysfunction, and revascularisation of the anterior and posterior circulation using stents has been reported to improve cognition.[27–29] Collectively, these studies, along with our own, reinforce the association between decreased regional cerebral blood flow, especially in the posterior circulation, and cognitive decline. Our study further considers the potential medical and psychological confounding factors and comorbidities, using a large nationwide sample size and a longitudinal design, providing results that are more generalisable to the general population.

AD is considered to be the most common cause of dementia, followed by VD.[11 16] We demonstrated that, in addition to AD, patients with VBI also exhibit a higher risk of VD than a control cohort. This is in agreement with a previous study that identified cerebrovascular insufficiency as an important risk factor for incident dementia.[30] Furthermore, poor cognitive performance has been reported to be strongly associated with stroke risk factors and cerebral microvascular disease.[31 32] The vascular risk factors for VBI, for example, hypertension, hyperlipidaemia, diabetes and obesity, are also reported to be independent mid-life risk factors for clinical AD.[33 34] Therefore, in this study, after considering the possible vascular risk factors or comorbidities of dementia, our multivariate Cox analyses demonstrated that VBI remains an independent predictor of subsequent dementia risk.

Dementia is generally acknowledged to be an ageing-related disorder, and its incidence is known to increase with age in the general population.[35] Ageing is also thought to be associated with subcortical microangiopathy, and elderly people may have impaired cerebral blood flow to the brain's posterior regions.[10] We demonstrated that VBI is more likely to result in dementia regardless of age. Previous studies have reported a slightly greater probability of development of dementia among women.[36] However, we found that the higher risk of dementia in the VBI group was not influenced by the patient's sex after adjusting for multivariate effects. This result partly supports a previous report that demonstrated that the severity of cognitive impairment was independent of sex in patients with stroke in the posterior cerebral artery territory.[37] In addition, in our results, the higher risk of dementia in the VBI group was not influenced by varying follow-up time intervals. Collectively, we suggest that these findings indicate that VBI is an independent potential risk factor for dementia regardless of age, sex and follow-up time.

Several mechanisms may underlie the pathological association between VBI and dementia. First, amnesia and memory impairment are thought to be later complications of VBI, and previous studies have indicated that this is due to hypoperfusion of the terminal branches of the vertebrobasilar system, which supply areas of the brain,

such as the thalamus, hippocampus, occipital lobe and cerebellum, which are involved in important cognitive functions, particularly memory, visual-spatial functioning and visuomotor adaptations.[8 38 39] Papez circuit hypoperfusion or disruption at the mammillo-thalamic tract and possibly thalamo-medial-temporal disconnection have also been proposed to be responsible for memory impairment.[26] Second, deposition of amyloid, which is a protein normally found in the brain, has been known to play a role in AD pathogenesis. Cerebral amyloid angiopathy has also been considered to be associated with vascular cognitive impairment and may exist as a feature of AD.[40] Moreover, increasing evidence from experimental animal models has suggested an association between the vascular effects of amyloidopathy and cognitive impairment.[41] Finally, advanced neuroimaging studies have reported that patients with carotid stenosis have extensive structural and functional disruptions in brain networks that correlate with neurocognitive decline, even at a subclinical stage.[42 43] These findings suggest that carotid stenosis may not only affect focal neural circuits but also disrupt remote interhemispheric connections that are related to cognition and memory. Since these studies support the relationship between neuropsychological performance and functional and structural disruptions in carotid stenosis (anterior circulation), it may reasonably be hypothesised that such brain structural and functional changes in relation to cognitive and memory changes may also exist in patients with VBI (with an affected posterior circulation). Further studies are warranted to assess this hypothesis.

The major strength of the present study is the use of a large sample size (NHIRD), which provided sufficient statistical power to explore the relationship between VBI and dementia. However, the present study also had certain limitations. First, the diagnosis of VBI and dementia was based on diagnostic codes entered into the health insurance system database by the physicians; therefore, additional clinical information about VBI or dementia (imaging data, laboratory and cognitive test data, or prognoses of both diseases) was not available. Thus, we could not determine whether the degree of VBI was associated with dementia severity and other dementia characteristics. Furthermore, the inter-rater variability of the investigators may also exist in this study. In the future, protocols for training the site personnel to make a more correct diagnosis of VBI and dementia, and to decrease the inter-rater variability, are needed. Second, in this study, the NHIRD dataset was derived from an administrative coding database lacking details of clinical symptoms and signs of dementia, such as the predominant symptoms, mental or mood status, imaging data and other laboratory results. Thus, the precise diagnosis of other subtypes of the dementia was not available in this study, and the results regarding the subtypes of the dementia (see online supplementary tables 2–5) should be interpreted with caution. Third, as a retrospective longitudinal study, we had no access to information about some adaptable or

personal potential confounders, such as education, lifestyle (smoking or alcohol consumption), physical activity, body mass index, social engagement, family histories or medications, which were not available in the NHIRD and which may potentially confound our results. Fourth, in this study, the comorbidities were matched when choosing controls for dementia cases. Although this matching strategy may have advantages in eliminating the potential influence of confounders, it may be vulnerable to overmatching, especially when the matching variable has some relationship with the outcome. For example, some of the comorbidities might also involve the pathways linking VBI to dementia, which may mask the association between the exposure and outcome. Finally, in this study, we used a longitudinal observational design, with a long follow-up period, which enabled us to assess the temporal relationship between VBI and dementia; however, our findings demonstrated only an association, but not necessarily a causal relationship. Further study is warranted to examine the potential causal relationship between VBI and dementia. Collectively, because of the underlying methodological limitations in this study mentioned above, the present findings in this study should be interpreted and generalised with caution.

In conclusion, in this large-scale, nationwide, population-based longitudinal study, we provided evidence supporting a temporal association between VBI and the risk of dementia regardless of the subjects' age, sex and follow-up intervals. Although the exact mechanism underlying this association is unknown, these findings may provide further insight into a possible shared pathophysiology between VBI and dementia. Additional studies are warranted to elucidate the mechanism and causality of this relationship.

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