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FEATURED ARTICLE

Association of life-course traumatic brain injury with dementia risk: A nationwide twin study

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Abstract

Introduction: The impact of life-course traumatic brain injury (TBI) on dementia is unclear.

Methods: Within the Swedish Twin Registry (STR), 35,312 dementia-free twins were followed for up to 18 years. TBI history was identified via medical records. Data were analyzed using generalized estimating equation (GEE) and conditional logistic regression.

Results: In multi-adjusted GEE models, the odds ratio (OR, 95% confidence interval [CI]) of dementia was 1.27 (1.03–1.57) for TBI at any age, 1.55 (1.04–2.31) for TBI at 50 to 59 years, and 1.67 (1.12–2.49) for TBI at 60 to 69 years. Cardiometabolic diseases (CMDs) increased dementia risk associated with TBI at age 50 to 69 years. The ORs in GEE and conditional logistic regression did not differ significantly ($P = .37$).

Discussion: TBI, especially between ages 50 and 69 years, is associated with an increased risk of dementia, and this is exacerbated among people with CMDs. Genetic and early-life environmental factors may not account for the TBI–dementia association.

KEYWORDS
cardiometabolic diseases, dementia, life-course traumatic brain injury, population-based twin study

1 | INTRODUCTION

Dementia is a burdensome disease for patients, caregivers, and society as a whole. An estimated 50 million people worldwide were living with dementia in 2018, and this number is projected to more than triple over the next 30 years.[1] The identification of modifiable risk factors has been prioritized as a strategy to prevent or delay the development of dementia.

Traumatic brain injury (TBI)—a non-degenerative, non-congenital insult to the brain from an external mechanical force—can cause temporary or permanent cognitive impairment.[2–4] Several studies have explored the association between TBI and cognitive function or dementia, but with conflicting findings.[5–8] Overall, TBI has been reported to confer a 1.6- to 3.7-fold increased risk of dementia,[5,7] though some studies have found no such association.[6,8] Furthermore, TBI may impact cognitive function to a different degree depending on the age of onset. Previous research has suggested that slow cognitive decline may occur after a TBI at any age,[9] though this decline appears to be more severe among individuals who experience a TBI at an older versus younger age.[10,11] This may be related to brain plasticity. Older individuals may have less ability to compensate for TBI-related brain damage during the initial recovery period or may experience greater brain degeneration after the initial recovery period due to reduced plasticity of the aging brain.[9] Therefore, when exploring the relationship between TBI and dementia, the timing of TBI over the life course deserves more attention. Despite this, most studies assessing the association between TBI and dementia have focused instead on people with a history of TBI in certain age groups (e.g., over 55 years or 18 to 65 years),[5,7] and no studies, to our knowledge, have used a life-course approach to examine the impact of TBI in different periods of life on dementia.

Accumulating evidence has shown that cardiometabolic diseases (CMDs) are associated with dementia risk,[12] and TBI is related to CMDs.[13,14] Thus, it is plausible that CMDs could play a moderating role in the association between TBI and dementia, but to date this issue remains unclear. Moreover, mounting evidence has suggested that both dementia and outcomes after TBI may be affected by genetic and early-life environmental factors.[15–18] It is unknown whether and to what extent these factors contribute to the TBI–dementia association. A twin study design provides us with the possibility of evaluating these unmeasured factors because twins generally share a common early-life environment and genetic background.

In this study, using data from a large cohort of nationwide Swedish twins, we aimed to (1) examine the association between life-course TBI and dementia, exploring the role of CMDs in this association, and (2) assess whether genetic and early-life environmental factors contribute to the TBI–dementia association using co-twin matched analysis.

RESEARCH IN CONTEXT

1. **Systematic review**: PubMed and Web of Science databases were searched, and titles and abstracts were screened. Traumatic brain injury (TBI) may impact cognitive function to a different degree depending on the age of onset. However, no studies have explored the association between TBI occurring during the lifespan and dementia. In our study, we used a life-course approach to examine the impact of TBI on dementia at different periods of life.
2. **Interpretation**: In this population-based study, we found that TBI, especially occurring between ages 50 and 69 years, is associated with an increased risk of dementia, and this risk is exacerbated among individuals with cardiometabolic diseases. Genetic and early-life environmental factors may not account for the TBI–dementia association.
3. **Future directions**: Future studies need to examine the role of severity and location of TBI on dementia and explore the biological pathways linking TBI and dementia.

HIGHLIGHTS

- Traumatic brain injury (TBI), especially occurring between ages 50 and 69 years, is associated with an increased risk of dementia.
- Cardiometabolic diseases (CMDs) increase dementia risk associated with TBI at the age of 50 to 69 years.
- Genetic and early-life environmental factors may not account for the TBI–dementia association.
- It is important to avoid brain damage, especially among people with CMDs, to prevent the development of dementia.

2 | METHODS

2.1 | Study population

Participants were derived from the nationwide Swedish Twin Registry (STR), which was initiated in the 1960s.[19] From 1998 to 2002, all living twins from the STR who were born in 1958 or earlier were invited to participate in the Screening Across the Lifespan Twin (SALT) study, a full-scale screening via a computer-based telephone interview. Of the 44,919 twin individuals in the SALT study, we excluded 152 with prevalent dementia, 36 who developed early-onset dementia prior to age 60, 565 who died before age 60, and 8854 who were <50 years old at baseline and therefore had a low possibility of developing the outcome during the follow-up. Therefore, a total of 35,312 individuals were included in the current study and followed-up until 2016 (Figure 1).

2.2 | Data collection

Information on demographics (age, education, and marital status), lifestyle (smoking status, alcohol consumption, and physical activity),

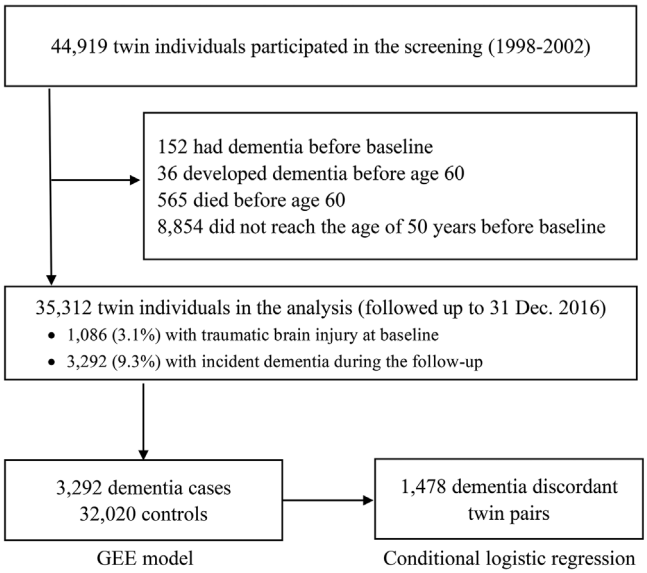

FIGURE 1 Flowchart of the study population. GEE, generalized estimating equation

zygosity, and anthropometrics (height and weight) was collected through the baseline SALT survey. Information on sex was collected from the STR based on self-report. Education level was dichotomized as <8 or ≥8 years based on the maximum number of years of formal schooling.[20] Zygosity was divided into monozygotic, dizygotic, or undetermined zygosity. Marital status was categorized as married/cohabitating versus single (including divorced and widowed). Smoking status was dichotomized as never versus former/current smoking. Alcohol consumption was categorized as no/mild drinking versus heavy drinking. Physical activity was ascertained using a question from the SALT interview about annual exercise patterns and dichotomized as active (including the responses "more than average," "much more than average," and "maximum") and inactive (including the responses "almost never," "much less than average," "less than average," and "average").[21] Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2) and grouped into <20.0 (underweight), 20.0 to 24.9 (normal weight), 25.0 to 29.9 (overweight), and ≥30 (obese).[22]

Information on medical history was obtained via linkage with the Sweden National Patient Registry (NPR), which covers all inpatient diagnoses since the 1960s and outpatient care since 2001.[23] Each medical record in the NPR included up to eight discharge diagnoses according to International Classification of Disease (ICD) codes. The seventh revision (ICD-7) was used until 1968, the eighth revision (ICD-8) was used from 1969 to 1986, the ninth revision (ICD-9) was used from 1987 to 1996, and the tenth revision (ICD-10) has been used from 1997 to the end of available follow-up in 2016. Survival status was identified through the Swedish Cause of Death Register.[24]

Baseline type 2 diabetes (T2D), heart disease, stroke, and hypertension (ICD-7 codes 444–447; ICD-8 codes 400–404; ICD-9 codes 401–405; and ICD-10 codes I10–I15) were ascertained based on medical history. Information on baseline dyslipidemia was obtained based on self-report in the SALT survey. Participants were asked if they have had high cholesterol or had taken treatment for lipid disorders. The presence of dyslipidemia was defined as having a medical history of high cholesterol or taking medication for lipid disorders.

Informed consent was obtained from all participants. The study was approved by the Regional Ethics Board at Karolinska Institutet, Stockholm, Sweden and the Institutional Review Board of the University of Southern California, USA.

2.3 | Ascertainment of TBI

At baseline, information on participants' previous TBI diagnoses and their corresponding recorded dates was obtained from the NPR. The ICD codes for TBI included the following: ICD-7 codes N800–N801, N803, and N850–N856; ICD-8 codes N800–N801, N803–N804, and N850–N854; ICD-9 codes 800–801, 803–804, and 850–854; and ICD-10 codes S01.0–S01.9, S02.0, S02.1, S02.3, S02.7–S02.9, S04.0, S06.0–S06.9, S07.0, S07.1, S07.8, S07.9, S09.7–S09.9, T90.1, T90.2, T90.4, T90.5, T90.8, and T90.9.

Life-course TBI was divided into five groups according to the age at which TBI first occurred: ≤39, 40 to 49, 50 to 59, 60 to 69, and ≥70 years. Participants' total number of TBI occurrences was summed and further divided into three categories: TBI-free, one TBI, and two or more TBIs. Building on the current literature,[5,7] in exploratory analyses we further divided TBI into different severity groups ("mild" vs. "moderate-to-severe") and excluded participants with undetermined TBI severity.

2.4 | Assessment of dementia

Information on all-cause dementia diagnoses—including Alzheimer's disease (AD; ICD-8 code 290; ICD-9 codes 290.0–290.1 and 331.0; ICD-10 codes F00.0 and G30), vascular dementia (VaD; ICD-9 code 290.4; ICD-10 code F01), and other or unspecified types of dementia (ICD-9 codes 290.8–290.9 and 331.2; ICD-10 codes F02, F03, F05, G31.0, and G31.8) was determined based on information in the NPR and the Cause of Death Register. All dementia diagnoses were determined based on neurological examinations at neurology clinics. The age at onset of dementia was estimated based on the earliest recorded date of the dementia diagnosis.

2.5 | Assessment of CMDs

Based on previous literature, CMDs were defined as T2D, heart disease, and stroke.[12,25] NPR data was used to ascertain baseline T2D (ICD-7 code 260; ICD-8 and -9 code 250; and ICD-10 codes E10–E14), heart disease (ICD-7 codes 420 and 434; ICD-8 codes 410–414 and 427; ICD-9 codes 410–414 and 428; ICD-10 codes I20–I25 and I50),

and stroke (ICD-7 codes 330–334; ICD-8 codes 430–438; ICD-9 codes 430–437; ICD-10 codes I60–I68 and G47). Age of CMD onset was defined based on the earliest date of T2D, heart disease, or stroke diagnosis.

2.6 | Statistical analysis

The differences in baseline characteristics between the TBI-free group and TBI group were analyzed using the χ^2 tests for categorical variables and *t*-tests for continuous variables.

Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between TBI and dementia were estimated from generalized estimating equation (GEE) models and conditional logistic regression models. Among all twin individuals (n = 35,312, including 3292 incident dementia cases and 32,020 controls), GEE models were applied to examine the association between TBI and dementia in the unmatched case-control analysis.[24] Next, conditional logistic regression models were used to assess the TBI–dementia association in co-twin matched dementia-discordant twin pairs. In these twin pairs, one twin developed dementia and the other did not, and unmeasured factors (such as genetic and early-life environmental factors) could be controlled for, allowing us to explore the contribution of genetic and early-life environmental factors to the TBI–dementia association. The basic model was adjusted for age, sex, and education. The multivariable model was further adjusted for marital status, smoking status, alcohol consumption, physical activity, BMI, T2D, heart disease, stroke, hypertension, and dyslipidemia.

Logistic regression was used to test the difference in ORs from the GEE model and the conditional logistic regression model by examining the difference in the proportion of TBI between unmatched and matched control participants.[21,24,26] A statistically significant OR from the logistic regression indicates that genetic and early-life environmental factors may play a role in the TBI–dementia association; otherwise, the influence of these shared factors on the observed relationship is likely small or null.

In sensitivity analyses, we excluded individuals who developed dementia within 5 years of TBI to minimize the impact of potential preclinical dementia that could bias the association between TBI and dementia. TBI has been associated with an elevated risk of death,[27] so we further adjusted for death during the follow-up.

The synergetic effect of TBI (yes vs. no) and CMDs (yes vs. no) on the risk of dementia was assessed by creating a dummy variable with four groups: (1) TBI- and CMD-free (reference group), (2) presence of TBI but no CMDs, (3) presence of CMDs but no TBI, and (4) coexistence of TBI and CMDs. The additive interaction between TBI and CMDs on dementia risk was tested by estimating the relative excess risk due to interaction (RERI), the attributable proportion (AP), and the synergy index (S). Additionally, we examined the multiplicative interaction between TBI and CMDs on dementia risk by incorporating the two variables and an interaction term in the same model.

Missing values for education (n = 1429), marital status (n = 890), smoking status (n = 1378), alcohol consumption (n = 1472), physical activity (n = 6643), and BMI (n = 2141) were imputed by Rubin's rule for pooling estimates to obtain valid statistical inferences. Statistical analyses were performed by SPSS 25.0 (IBM Corp.) and SAS 9.4 (SAS Institute). Two-sided *P*-values <.05 were considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the study population

Among 35,312 participants in the study (mean age = 62.8 ± 9.7 years, 54.0% female), 1086 (3.1%) had a history of TBI at baseline. Of them, 285 (26.3%) had TBI at or before 39 years of age, 253 (23.3%) between ages 40 and 49 years, 259 (23.8%) between ages 50 and 59 years, 161 (14.8%) between ages 60 and 69 years, and 128 (11.8%) at the age of 70 years or older.

Compared to TBI-free individuals, those who experienced TBI at any age were more likely to be male; single; heavy drinkers; and have T2D, heart disease, stroke, or hypertension (Table 1). There were no significant differences between TBI-free individuals and those with a history of TBI in terms of age, education, smoking status, physical activity, BMI, age of CMD onset, and dyslipidemia.

3.2 | Association of TBI with dementia in unmatched case-control analyses

During the 18-year follow-up period, 3292 (9.3%) participants developed dementia, including 1096 (33.3%) with AD, 692 (21.0%) with VaD, and 1504 (45.7%) with other or unspecified types of dementia. Of the 1086 participants with a history of TBI, 128 developed dementia. The mean time interval between TBI occurrence and dementia diagnosis was 20.3 ± 9.7 years. In the multi-adjusted GEE model, compared to the TBI-free participants, the OR (95% CI) of dementia was 1.27 (1.03–1.57) for individuals with a history of TBI at any age, 0.86 (0.43–1.72) for TBI at age ≤39 years, 1.34 (0.81–2.21) for TBI between ages 40 and 49 years, 1.55 (1.04–2.31) for TBI between ages 50 and 59 years, 1.67 (1.12–2.49) for TBI between ages 60 and 69 years, and 0.92 (0.59–1.42) for TBI at age ≥70 years. Regarding dementia subtypes, TBI at any age was not significantly associated with AD (OR 1.23, 95% CI 0.88–1.74) or VaD (OR 1.10, 95% CI 0.73–1.66). However, TBI at the age of 60 to 69 years (OR 1.84, 95% CI 1.01–3.35) was significantly associated with AD (Table 2).

Compared to TBI-free participants, those who experienced one TBI had an increased risk of dementia (OR 1.27, 95% CI 1.01–1.61). No statistically significant risk of dementia was observed for participants who experienced two or more TBIs in their lifetime (OR 1.27, 95% CI 0.79–2.04; Table S1 in supporting information). However, these individuals had an increased risk of mortality (OR 1.58, 95% CI 1.11–2.25).

TABLE 1 Baseline characteristics of the study population by traumatic brain injury (TBI) status (N = 35,312)

Characteristics	TBI-free (n = 34,226)	TBI (n = 1086)	*P* value
Age (years)	62.8 ± 9.7	63.3 ± 10.6	.064
Female	18606 (54.4)	446 (41.1)	<.001
Education			.252
<8 years	13,200 (40.1)	383 (38.3)	
≥8 years	19,684 (59.9)	616 (61.7)	
Marital status			<.001
Married/cohabiting	23,862 (71.5)	646 (62.9)	
Single	9533 (28.5)	381 (37.1)	
Zygosity			.039
Monozygotic	6791 (19.8)	199 (18.3)	
Dizygotic	22,884 (66.9)	715 (65.9)	
Undetermined	4551 (13.3)	172 (15.8)	
Smoking status			.073
Never smoked	16,526 (50.2)	473 (47.3)	
Former/current smoker	16,408 (49.8)	527 (52.7)	
Alcohol consumption			<.001
No/mild drinking	30,697 (93.4)	841 (84.8)	
Heavy drinking	2151 (6.6)	151 (15.2)	
Physical active	13,974 (50.2)	413 (49.2)	.573
BMI			.827
<20.0 (underweight)	1598 (5.0)	54 (5.5)	
20.0–24.9 (normal weight)	15,366 (47.7)	461 (46.8)	
25.0–29.9 (overweight)	12,487 (38.8)	389 (39.5)	
≥30 (obese)	2735 (8.5)	81(8.2)	
CMDs	5727 (16.7)	274 (25.2)	<.001
Type 2 diabetes	2093 (6.1)	83 (7.6)	.039
Heart disease	3399 (9.9)	159 (14.6)	<.001
Stroke	1384 (4.0)	103 (9.5)	<.001
Age of CMD onset (years)	60.3 ± 13.3	60.0 ± 14.0	.748
Hypertension	1658 (4.8)	73 (6.7)	.005
Dyslipidemia	4279 (12.5)	129 (11.9)	.540

Abbreviations: BMI, body mass index; CMDs, cardiometabolic diseases; SD, standard deviation.
Data were presented as means ± standard deviations or number (%).

3.3 | Joint effect of TBI and CMDs on dementia risk

In joint effect analysis, we excluded participants who had TBI at ≤49 or ≥70 years of age (n = 666), as TBI during these age ranges was not significantly associated with dementia in the previous analyses. This left 34,646 participants who were TBI-free or who had TBI between ages 50 and 69 years. The multi-adjusted OR (95% CI) of dementia was 1.00 (0.90–1.11) for participants with CMDs but no TBI, 1.28 (0.88–1.84) for participants with TBI but no CMDs, and 2.47 (1.57–3.87) for those with both TBI and CMDs (reference: TBI- and CMD-free). There was a significant additive interaction (RERI 1.19, 95% CI 0.04–2.33, *P* = .04; AP 0.48, 95% CI 0.19–0.77, *P* < .01; Figure 2 and Table S2 in supporting information) and multiplicative interaction (OR 1.93, 95% CI 1.08–3.48; *P* = .03) between TBI at the age of 50 to 69 years and CMDs on dementia risk.

3.4 | Association between TBI and dementia in co-twin matched case-control analysis

In conditional logistic regression conducted among 1478 dementia-discordant twin pairs, the TBI–dementia association remained significant (OR 1.58, 95% CI 1.02–2.44; Table 3). There was no statistically

TABLE 2 Odds ratios (ORs) and 95% confidence intervals (CIs) of dementia in relation to traumatic brain injury (TBI) (N = 35,312)

		All-cause dementia (n = 3292)		Alzheimer's disease (n = 1096)		Vascular dementia (n = 692)	
	No. of subjects	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]
TBI-free	34226	Reference	Reference	Reference	Reference	Reference	Reference
TBI	1086	1.25 (1.01–1.54)	1.27 (1.03–1.57)	1.16 (0.83–1.63)	1.23 (0.88–1.74)	1.16 (0.77–1.74)	1.10 (0.73–1.66)
Age of first TBI							
≤39 years	285	0.84 (0.42–1.68)	0.86 (0.43–1.72)	1.25 (0.54–2.89)	1.33 (0.57–3.11)	0.42 (0.06–2.94)	0.40 (0.06–2.75)
40–49 years	253	1.29 (0.78–2.12)	1.34 (0.81-2.21)	1.05 (0.44–2.48)	1.12 (0.47–2.66)	1.70 (0.70–4.13)	1.65 (0.67–4.04)
50–59 years	259	1.53 (1.03–2.28)	1.55 (1.04–2.31)	1.62 (0.86–3.04)	1.71 (0.91–3.19)	1.71 (0.80–3.65)	1.64 (0.76–3.54)
60–69 years	161	1.68 (1.13–2.51)	1.67 (1.12–2.49)	1.81 (0.99–3.30)	1.84 (1.01–3.35)	1.00 (0.40–2.50)	1.02 (0.41–2.56)
≥70 years	128	0.89 (0.58–1.37)	0.92 (0.59–1.42)	0.44 (0.18–1.08)	0.47 (0.19–1.18)	0.97 (0.46–2.08)	0.88 (0.41–1.89)

[a]Generalized estimating equation model adjusted for age, sex, and education.
[b]Generalized estimating equation model adjusted for age, sex, education, marital status, smoking status, alcohol consumption, physical activity, body mass index, type 2 diabetes, heart disease, stroke, hypertension, and dyslipidemia.

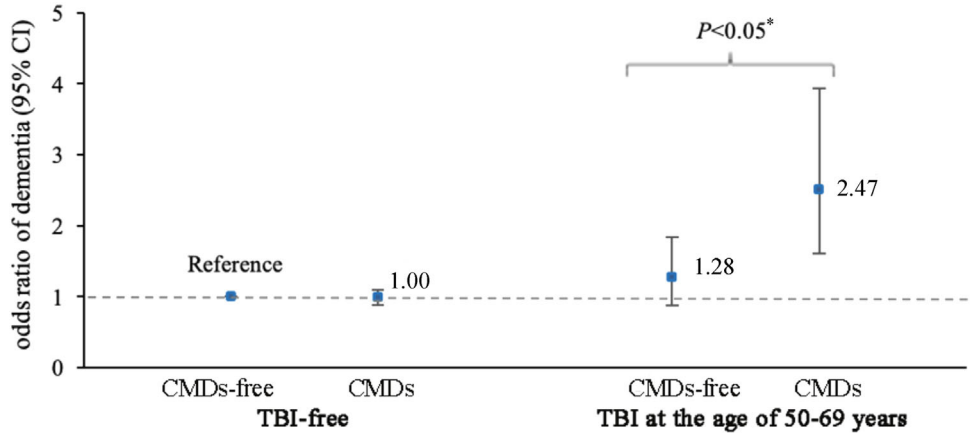

FIGURE 2 Joint effect of traumatic brain injury (TBI) at the age of 50 to 69 years and cardiometabolic diseases (CMDs) on dementia (reference: TBI- and CMD-free). Note: Multi-adjusted odds ratios (95% confidence intervals [CIs]) of dementia in relation to joint exposure of TBI at the age of 50 to 69 years and CMDs from generalized estimating equation models (adjusted for age, sex, education, marital status, smoking status, alcohol consumption, physical activity, body mass index, hypertension, and dyslipidemia). *P-value of <.05 refers to the difference in the risk of dementia between participants with and without CMDs among participants who experienced TBI at the age of 50 to 69 years

significant difference between the ORs from the GEE model and the conditional logistic model (OR 0.86, 95% CI 0.62–1.20; $P = .37$).

3.5 | Supplementary analyses

Similar results to those from the initial analyses were obtained when we performed sensitivity analyses after: (1) excluding participants diagnosed with dementia within 5 years after TBI (Table S3 in supporting information); (2) excluding participants aged <55 years at baseline (Table S4 in supporting information); (3) additionally adjusting for death during the follow-up, as TBI was significantly related to mortality (OR 1.26, 95% CI 1.07–1.48; Table S5 in supporting information); (4) additionally including TBI cases that occurred during the follow-up but before dementia diagnosis (n = 2441; Table S6 in supporting information); and (5) excluding participants with stroke that occurred before or within 1 month after TBI (OR 1.32, [95% CI 1.06–1.64] for TBI). Additionally, after classifying TBI according to severity, the multi-adjusted OR (95% CI) of dementia was 1.29 (1.01–1.66) for participants with mild TBI and 1.33 (0.79–2.23) for participants with moderate-to-severity TBI (Table S7 in supporting information).

4 | DISCUSSION

In this nationwide population-based study of Swedish twins, we found that (1) TBI, especially occurring between the ages of 50 and 69 years, was associated with almost 30% increased risk of dementia; (2) the risk of dementia associated with TBI at age 50 to 69 years became stronger

TABLE 3 Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between traumatic brain injury (TBI) and dementia in co-twin matched case-control analysis in dementia-discordant twin pairs (N = 1478)

	Co-twin with dementia	
Co-twin control	TBI-free	TBI
TBI-free	1385	53
TBI	34	6
Basic-adjusted OR (95% CI)[a]	1.58 (1.03–2.44)	
Multi-adjusted OR (95% CI)[b]	1.58 (1.02–2.44)	

[a]Conditional logistic regression model adjusted for sex and education.
[b]Conditional logistic regression model adjusted for sex, education, marital status, smoking status, alcohol consumption, physical activity, body mass index, type 2 diabetes, heart disease, stroke, hypertension, and dyslipidemia.

among people with CMDs; and (3) genetic and early-life environmental factors are unlikely to account for the TBI–dementia association.

Several studies have indicated that TBI is associated with an increased risk of dementia or AD.[5,28–29] Among these, one further identified that TBI patients aged ≥55 and ≥65 years were particularly vulnerable to dementia.[5] However, that study assessed the association between TBI and dementia among participants aged ≥55 years. In the current investigation, we found that TBI occurring between ages 50 and 69 years was associated with increased dementia risk, although TBI at ≤49 or ≥70 years was not associated with dementia. This may be due to greater brain plasticity in individuals who experienced TBI ≤49 years of age,[5] and greater post-TBI mortality among individuals who experienced TBI ≥70 years of age.[6,27,30] In addition, we found that TBI occurring between ages 60 and 69 years was related to AD but not VaD, suggesting that neurodegeneration may play a role in the TBI–dementia association. To our knowledge, our study is among the first to use a life-course approach to investigate the association between TBI and dementia.

Though we hypothesized that dementia risk may be even higher among people who experienced multiple TBIs in their lifetime, there was no significant association between a history of two or more TBIs and dementia. Given that only 220 study participants had two or more TBIs, this could be due to limited statistical power. Another possibility is that the increased mortality among these participants could have led to selective survival.

Previous studies have associated CMDs with an increased risk of dementia.[31] In the present study, we explored the effect modification of CMDs on the TBI–dementia association. We found a significant synergetic effect between CMDs and TBI occurring between ages 50 and 69 years, which suggests that individuals with CMDs who experience TBI at this stage of the life course represent an especially high-risk group for dementia. Our findings highlight the need to monitor TBI patients with CMDs for early detection of dementia.

Emerging evidence has suggested that genetic and early-environmental factors are related to the development of TBI and neurodegenerative disease.[15–16,32] However, to our knowledge, no studies have specifically assessed the role of these unmeasured factors in the TBI–dementia association. In our co-twin matched case-control analysis, we found that the TBI–dementia association was not much altered compared to the results from unmatched control analysis, suggesting that genetic and early-life environmental factors are unlikely to contribute to the association between TBI and dementia.

Several biological mechanisms have been proposed to explain the TBI–dementia association. A head injury can lead to the activation of microglia and the release of oxygen radicals, which might disrupt the blood-brain barrier, expose the brain to neurotoxins or inflammatory agents, induce chronic neuronal degeneration, and eventually increase individuals' susceptibility to neurodegenerative diseases such as AD.[33–36] Additionally, human and animal studies have shown that TBI can induce the accumulation of abnormal proteins associated with neurodegeneration in neuronal cell bodies and injured axons.[36–38] These abnormal proteins—including tau, amyloid beta, and alpha-synuclein—may trigger progressive neurodegenerative cascades, ultimately leading to progression to dementia.[5,39] Another mechanism for the link between TBI and dementia could be reduced cognitive reserve in people with TBI. Some preclinical brain pathologies that were previously insufficient to cause cognitive symptoms could begin to do so after a TBI that impairs the brain's compensatory ability.[40,41]

This study has several strengths. First, the access to information on lifelong TBI history in the STR allowed for the exploration of the association between TBI over the life course and dementia. Second, the twin study design provided us an opportunity to further explore the role of unmeasured confounders such as genetic and early-life environmental factors in the observed TBI–dementia association. However, some limitations need to be acknowledged. First, clinical diagnoses were obtained from the NPR, which included records from people who sought treatment in inpatient or outpatient clinics. Therefore, some participants with mild forms of medical conditions, including mild forms of TBI, might have been missed. However, these misclassifications are more likely to be non-differential, leading to an underestimation of the reported associations. Therefore, caution is needed when comparing our findings to those from other population-based cohort studies with regular follow-up examinations. Second, we did not have information on the location of TBI in the brain, which may moderate the impact of TBI on dementia. Third, despite controlling for a range of confounders in our analyses, residual confounding from unmeasured factors—including apolipoprotein E ε4 genotype, the use of intensive care unit care and neurosurgical interventions post-TBI, and subsequent epilepsy after TBI—could not be ruled out. Finally, dementia and its subtypes were diagnosed clinically without neuroimaging and pathological confirmation. Without this pathological confirmation, the clinical diagnosis of AD could instead represent other types of neurodegenerative disease, such as chronic traumatic encephalopathy.

In conclusion, our study provides further evidence that TBI, especially occurring between ages 50 and 69 years, is associated with a 30% increased risk of dementia, and this risk is exacerbated among individuals with CMDs. Moreover, genetic and early-life environmental factors are unlikely to account for the TBI–dementia association. Our

findings highlight the importance of avoiding brain damage, especially among people with CMDs, to prevent the development of dementia.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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