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Original article

Risk of dementia in survivors of active tuberculosis in Korea: A nationwide cohort study

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ABSTRACT

Background: Concern has been growing regarding post-tuberculosis (TB) morbidities, including neurologic and vascular comorbidities. However, the association between post-TB status and the risk of dementia has been evaluated in only few studies. Therefore, in the present study, the risk of dementia was investigated in a nationwide population-based cohort.

Methods: Using the Korean National Health Insurance Service (KNHIS) database, this study included TB survivors (n = 50,182) and matched controls (n = 50,182) for age, sex, and year of index date. The risk of dementia was estimated using Cox proportional hazards regression, and stratified analyses for related factors were performed.

Results: During a mean 3.5 years of follow-up, the incidence of dementia was 9.32 for Alzheimer disease and 1.17 for vascular dementia per 1000 person-years for TB survivors and 7.21 and 0.67, respectively, for matched controls. The overall risk of Alzheimer disease was 1.11 (95% confidence interval (CI) 1.03–1.20)-fold higher in TB survivors than in matched controls. For vascular dementia, 1.48 (95% CI 1.16–1.89)-fold higher risk was found in TB survivors than in matched controls. The strength of the association between TB and dementia was higher in CNS TB (aHR 1.76, 95% CI 1.18–2.64) than non-CNS TB (aHR 1.11, 95% CI 1.05–1.19) compared to controls, especially for patients with vascular dementia (3.33, 95% CI 1.06–10.49).

Conclusion: TB survivors had a significantly higher risk of dementia than the general population.

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Introduction

Despite recent advances in the treatment of tuberculosis (TB) and substantial efforts to reduce its burden, TB remains an important global public health concern. Worldwide, approximately 10 million individuals were estimated to be infected with *M. tuberculosis*, and 1.5 million died of the disease in 2020 [1,2]. In addition, TB-related healthcare resource use and medical costs are substantial in many countries [1].

Recently, the effects of TB were shown to not end after treatment completion but are prolonged for an extended period, causing chronic inflammatory response. In recent studies, the long-term mortality of TB survivors was substantially higher than in the general population [3–5]. In addition, concern is growing regarding the disease burden associated with new comorbidities in TB survivors. In terms of post-TB morbidity, various chronic diseases including respiratory diseases [6], cardiovascular diseases [7,8], and lung cancer [9] have been observed, indicating future health implications for TB survivors [10].

Dementia is a prevalent neurodegenerative disorder represented by amyloid- β deposition in the brain. Public health concern has emerged due to the steady increase in the prevalence of dementia and the continuing lack of a cure [11]. In this regard, exploring the possible risk of dementia to establish preventive strategies has become an area of interest; however, the etiology of dementia remains unclear. In the last decade, evidence indicating the possible role of systemic inflammation in the pathogenesis of dementia has been reported [12,13]. In line with this concern, inflammation persisting after TB treatment might have a critical role in the subsequent development of dementia. However, this issue has been evaluated in only a few studies [14].

Therefore, in the present study, using a nationwide population-based cohort study in Korea, the risk of dementia in TB survivors was compared with that in subjects who did not experience TB.

Methods

Data source

The Korean National Health Insurance Service (KNHIS) database contains qualification database on demographic factors (e.g., age, sex, place of residence, and income level) and links to a death registry database to manage qualification of the enrollees. Claims data were also gathered for information on the use of medical facilities and records of prescriptions with International Classification of Diseases 10th revision (ICD-10) diagnosis codes identified in the medical bills submitted by healthcare providers and medical care institutions for reimbursement [15].

The KNHIS database also includes a health check-up database. The KNHIS provides biennial national cardiovascular health screening for all beneficiaries ≥ 40 years of age. During biennial health screenings, KNHIS study subjects undergo self-administered questionnaires for lifestyle factors (e.g., alcohol consumption, smoking, and physical activity), medical and family history, anthropometric measurements (blood pressure, body weight, and height), and laboratory tests (blood glucose, lipid profile, and serum creatinine). Detailed information of the KNHIS database was described elsewhere [16,17].

Standard protocol approvals, registrations, and patient consents

The requirement for participant's consent was waived since we used retrospective de-identified data collected in the KNHIS database. The Institutional Review Board (IRB) of Hanyang University Hospital approved this study (IRB No. HYUH-2021-12-007).

Study population

In the KNHIS database, patients who were diagnosed with TB were identified based on the diagnosis codes for TB registered in the claims database and inclusion in an additional insurance coverage with special copayment reduction. In Korea, all cases of TB are confirmed based on sputum smears and radiologic examination. Reporting diagnosed TB cases to the Centers for Disease Control, Ministry of Health and Welfare is mandatory; therefore, physicians disclose patient's personal information, examination results, treatments, and treatment outcomes [18]. The KNHIS claim database contains complete information regarding insured medical services and unique insurance codes for active TB [19–22].

Active TB was defined based on the following criteria [20–22]: ≥ 2 outpatient or hospitalization claims with the ICD-10 code of active TB (A15–A19, U88.0–U88.1), special insurance codes for TB (V206, V246, and V000), and ≥ 2 anti-TB medications (isoniazid, rifampicin, ethambutol, pyrazinamide, prothionamide, para-aminosalicylate, and cycloserine) in the claims database for > 90 days. From January 1, 2010, to December 31, 2017, after excluding patients diagnosed with multidrug-resistant TB ($n = 1088$) or who did not complete anti-TB treatment ($n = 24,862$), 205,506 TB survivors were identified.

Among the survivors, a total of 110,212 who did not participate in the national health screening program within 2 years before TB diagnosis were excluded. Patients who did not have available information from health screening data ($n = 854$) or who died within 1 year after TB diagnosis ($n = 1456$) were also excluded. For controls, 1,021,856 individuals were selected from the KNHIS for research purposes were matched in an approximate 1:5 ratio to 205,056 TB survivors based on age and sex. Individuals who did not undergo national health screening in the same year as subjects diagnosed with TB ($n = 602,976$), had missing any health screening information ($n = 6195$), who died within 1 year after enrollment ($n = 2185$) were excluded. The first date of claims for TB diagnosis was considered the index date for TB survivors. The index date of controls corresponded to that of the matched TB cases.

Among 92,984 cases and 410,550 matched controls with health screening data, individuals < 50 years of age ($n = 32,260$ for TB cases and $n = 162,046$ for controls) or were previously diagnosed with dementia (F00, G30, and F01) prior to TB diagnosis or index date ($n = 2098$ for TB cases and $n = 6003$ for controls), or had incident dementia within 1 year from TB diagnosis or index date ($n = 1070$ for TB cases and $n = 1782$ for controls) were excluded. After that, each control was selected for each 57,556 TB cases. Matching was performed based on the year of index date of TB cases based on age, sex, and year of health screening date. Finally, a total of 50,182 cases and 50,182 matched controls was analyzed (Fig. 1).

Study outcome and follow-up

The primary endpoint of this study was newly diagnosed dementia, defined as ≥ 2 outpatient or hospitalization records with ICD-10 codes for dementia (F00, G30, and F01), F00 or G30 as the primary diagnosis for Alzheimer's disease (AD), or F01 for vascular dementia (VD). The study cohort was followed from 1 year after the index date to the date of dementia incidence, death, or the end of the study period (December 31, 2020), whichever came first.

Covariates

Information on participants' lifestyle was obtained from the health screening program self-questionnaire. Smoking status was classified into never, former, and current smoker. Daily alcohol consumption was classified as none (0 g/day), mild (< 30 g/day), and heavy (≥ 30 g/day). Regular physical activity was defined as engaging in > 30 min of

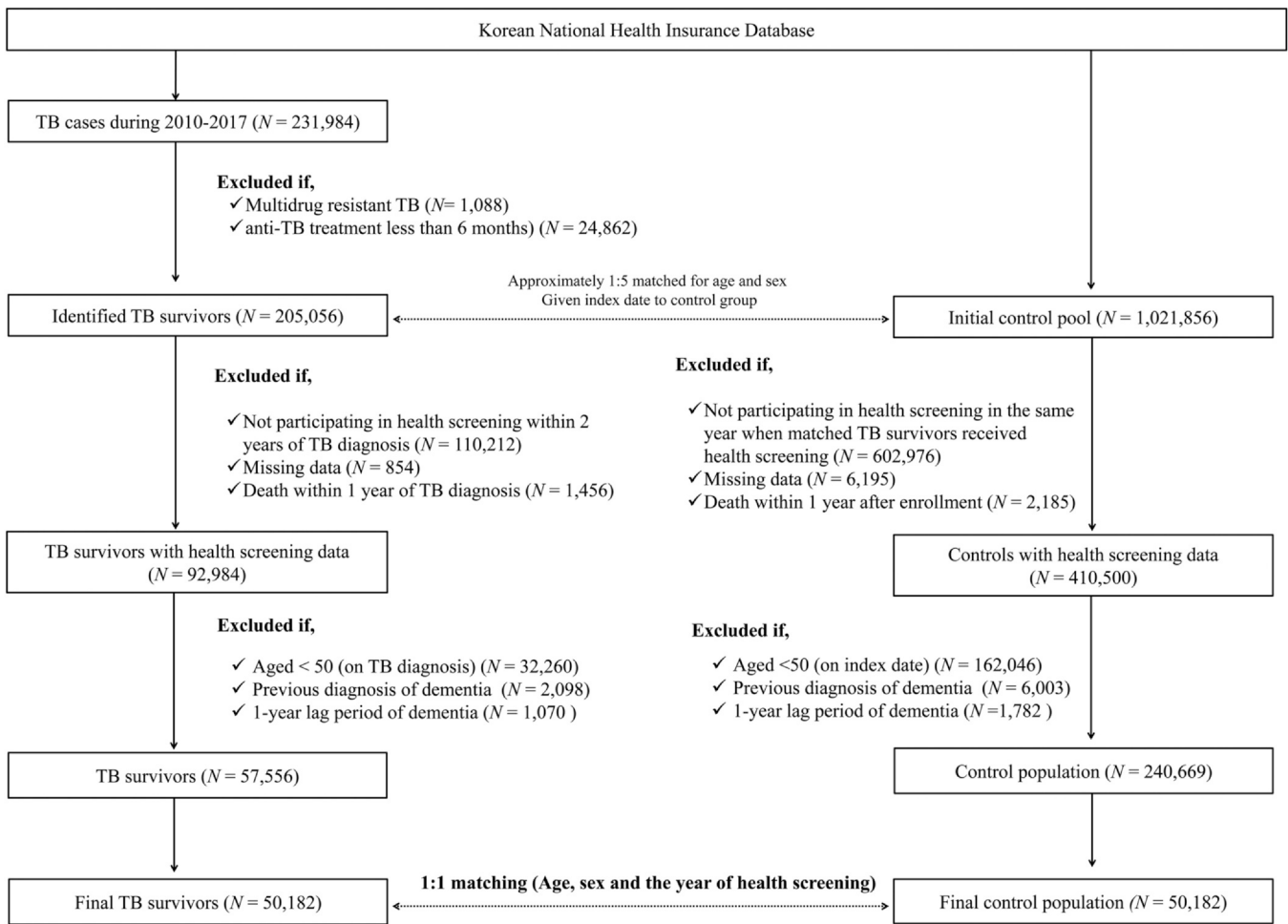


Fig. 1. Flow diagram of study participants.

moderate physical activity at least 5 times per week or > 20 min of strenuous physical activity at least 3 times per week. Body mass index (BMI) was calculated as the subject's weight in kilograms divided by the square of the subject's height in meters, and the resulting BMI values were classified into four categories according to the Asia-Pacific criteria of the World Health Organization [23]: underweight (< 18.5 kg/m²), normal (18.5–23 kg/m²), overweight (23–25 kg/m²), and obese (≥ 25 kg/m²). The Charlson Comorbidity Index (CCI) was also calculated to assess comorbidity level [24]. Comorbidities were defined by medical claims according to the ICD-10 codes (for hypertension, I10–I13 or I15; for diabetes, E11–E14; for dyslipidemia, E78; for traumatic brain injury, S00–S09) [25–27].

Statistical analysis

Descriptive statistics are presented as number (percentage) for categorical variables and mean ± standard deviation (SD) for continuous variables. The two groups were compared using the χ^2 test or Fisher's exact test for categorical variables as appropriate and Student's *t*-test for continuous variables. The association between TB survivors and the incidence of dementia was estimated using Cox proportional hazards regression with crude and multivariable-adjusted models. In model 1, sex, age, BMI, smoking status, alcohol consumption, regular exercise activity, income level, and residency were adjusted; CCI score was further adjusted in model 2 (main model). In model 3, we further adjusted for diabetes, hypertension, dyslipidemia, and traumatic brain injury. Hazard ratio (HR) and 95% confidence interval (CI) were calculated. TB survivors were further

categorized as central nerve system [CNS] TB infection (A17.0, A17.1, A17.80, A17.81, A17.88), or non-CNS TB infection, and the risk of dementia for each category was explored.

Stratified analyses were performed based on sex, age, BMI, smoking status, alcohol consumption, and CCI score. Forest plots for the HR and 95% CI by subgroup were established. All statistical analyses were performed using SAS statistical package version 9.4 (SAS Institute Inc., Cary, NC, USA), and a P-value < 0.05 was considered statistically significant.

Results

Table 1 shows that matching variables including age and sex were equally distributed between TB survivors and matched controls. Approximately 42% of subjects were female, and 66% were > 60 years of age. Significantly more TB survivors had low BMI (P < 0.001), but their monthly income was higher than controls (P < 0.001). The presence of comorbidities except hypertension was higher in TB survivors than in matched controls (P < 0.001 for all). TB survivors were more likely to have CCI ≥ 3 (48.7% vs. 25.9%) than controls. The mean duration of follow-up after the index date was 3.5 years (SD 2.2 years) for TB survivors and 3.6 years (SD 2.2 years) for matched controls, respectively (Fig. 1).

Risk of dementia in TB survivors

During follow-up, the incidence rate of dementia was 14.2 per 1000 person-years for TB survivors and 11.0 for matched controls

Table 1
Baseline characteristics of study participants.

	TB survivors (N = 50,182)	Matched controls† (N = 50,182)	p-value*
Age (years) (N, %) [†]			
50–59	17,038 (34.0)	17,038 (34.0)	1.00
60–69	15,888 (31.7)	15,888 (31.7)	
70–79	14,573 (29.0)	14,573 (29.0)	
≥ 80	2683 (5.4)	2683 (5.4)	
Sex (N, %) [†]			
Male	29,020 (57.8)	29,020 (57.8)	1.00
Female	21,162 (42.2)	21,162 (42.2)	
Body mass index (kg/m ²) (N, %)			
< 18.5	4538 (9.0)	1141 (2.3)	< 0.001
18.5–23	24,724 (49.3)	16,879 (33.6)	
23–25	10,900 (21.7)	13,889 (27.7)	
≥ 25	10,020 (20.0)	18,273 (36.4)	
Income (N, %)			
Low	40,250 (80.2)	40,953 (81.6)	< 0.001
High	9932 (19.8)	9229 (18.4)	
Regular exercise (N, %)			
No	40,668 (81.0)	38,545 (76.8)	< 0.001
Yes	9514 (19.0)	11,637 (23.2)	
Smoking (pack-years) (N, %)			
Non-smokers	29,317 (58.4)	30,869 (61.5)	< 0.001
Ex-smokers	9350 (18.6)	11,091 (22.1)	
Current smokers	11,515 (23.0)	8222 (16.4)	
Alcohol drinking (pack- years) (N, %)			
Non-drinkers	32,447 (64.7)	31,510 (62.8)	< 0.001
Mild drinkers	13,161 (26.2)	15,639 (31.2)	
Heavy drinkers	4574 (9.1)	3033 (6.0)	
Comorbidities (N, %)			
Hypertension, yes	21,917 (43.7)	23,120 (46.1)	< 0.001
Diabetes mellitus, yes	14,596 (29.1)	11,019 (22.0)	< 0.001
Dyslipidemia, yes	20,482 (40.8)	18,632 (37.1)	< 0.001
Chronic pulmonary obstructive disease, yes	14,989 (29.9)	4871 (9.7)	< 0.001
Asthma, yes	14,268 (28.4)	6189 (12.3)	< 0.001
Congestive heart failure, yes	2212 (4.4)	1198 (2.4)	< 0.001
Stroke, yes	626 (1.3)	340 (0.7)	< 0.001
Malignancy, yes	3704 (7.4)	1909 (3.8)	< 0.001
Traumatic brain injury	2651 (5.3)	2118 (4.2)	< 0.001
Charlson comorbidity index			
0–2	25,722 (51.3)	37,167 (74.1)	< 0.001
≥ 3	24,460 (48.7)	13,015 (25.9)	
Residency			
Urban	21,473 (42.8)	21,418 (42.7)	0.726
Rural	28,709 (57.2)	28,764 (57.3)	

Data are presented as number (percentages) for categorical variables and mean ± standard deviation for numerical variables.

N, number; PTB, pulmonary tuberculosis

* χ^2 test or Fisher exact test for categorical variables, as appropriate

† Matched for age, sex, and the year of index date

(Table 2). Regarding dementia subtypes, the incidence rate was 9.32 for AD and 1.17 for VD per 1000 person-years for TB survivors and 7.21 for AD and 0.67 for VD for controls. The cumulative incidence curves for TB survivors and matched controls are shown in Fig. 2. In the main model (Model 2), TB survivors had a higher risk of dementia (adjusted HR, aHR 1.12, 95% CI 1.05–1.19), AD (aHR 1.11, 95% CI 1.03–1.20) and VD (aHR 1.48, 95% CI 1.16–1.89) than controls. Further adjustment of comorbidities did not change the results (Table 2).

Risk of dementia in CNS TB survivors

As shown in Table 3, the incidence rate of dementia was highest among CNS TB survivors at 77% (95% CI 1.18–2.66), followed by non-CNS TB survivors at 11% (95% CI 1.05–1.19), and lowest among controls. The risk of AD was non-significantly higher in CNS TB survivors compared to controls (aHR 1.54, 95% CI 0.89–2.66), while non-

CNS TB survivors showed a 11% (95% CI 1.03–1.20) increased risk of AD compared to controls. CNS TB survivors had a particularly higher risk of VD (aHR 3.33, 95% CI 1.06–10.49) compared to controls, which was higher compared to that was found in non-CNS TB survivors (aHR 1.47, 95% CI 1.15–1.87). Further adjustment of comorbidities did not affect the results.

Risk of dementia based on stratified analysis

In various stratified analyses, a higher risk of dementia in TB survivors than in matched controls was consistently found in most subgroups (Fig. 2 and Supplementary Table S1). Regardless of dementia subtype, similar results were observed (Fig. 3 and Supplementary Table S2 for AD; Fig. 3 and Supplementary Table S3 for VD).

Discussion

In the present large population-based cohort study, the risk of dementia was evaluated in TB survivors and compared with that of age- and sex-matched controls. The results showed that TB survivors had 12% increased risk of dementia compared with age- and sex-matched controls. The risk of dementia was particularly higher in VD patients (48% increased risk) than in AD patients (11% increased risk). When analyzed by types of TB, compared to controls, CNS-TB survivors had a particularly higher risk of VD, while the increased risk of AD was not significant. A higher risk of dementia in TB survivors compared with matched controls was consistent in most subgroup analyses for AD and VD.

In previous studies, the risk of dementia in TB survivors has rarely been reported.

In a retrospective cohort study in Taiwan, patients with TB reportedly had a significantly higher risk of developing dementia than the general population [14]. However, potential confounding factors for smoking, alcohol consumption, and physical activity were not considered, and detailed information on daily lives of participants was unavailable. In addition, the types of dementia (e.g., AD and VD) were not considered. Thus, the major strength of the present study is consideration of potential confounding factors as well as types of dementia in the analyses. Even after adjustment for these confounders, the results clearly showed post-TB status to be consistently associated with a higher risk of both types of dementia. Systemic inflammation is thought to participate in a positive feedback loop of amyloid- β deposition, a key metabolism in AD development. For example, chronic inflammatory conditions, such as rheumatoid arthritis [28] and periodontitis [29], are associated with increased risk of AD. Thus, the association between chronic inflammation and AD development might also be applicable to TB survivors. TB patients have higher amounts of proinflammatory cytokines (TNF- α , IL-6, IFN- γ , and IL-1 β) [30,31], which can increase peripheral amyloid- β level. In addition, high serum levels of the acute-phase proteins and IL-6 were suggested to be predictive of cognitive decline [32], and the increase in plasma levels of inflammatory proteins might be indicative of clinical AD onset [33]. IL-6 reduces microglia activity at low levels, which are active in the presence of amyloid- β at the early stage of developing AD, and released an anti-inflammatory cytokine, IL-10, that hinders the release of pro-inflammatory cytokines [34,35]. In the Framingham study, critical proinflammatory cytokines, TNF- α and IL-1 β , involved in the pathogenesis of TB were shown to be associated with subsequent risk of AD in older adults [36]. Another potential mechanism is shared genetic susceptibility. For example, TB and AD share the apolipoprotein (APOE) ϵ 4 allele, which is a risk factor for both diseases [37]. The presence of a positive association of the noncoding or microRNAs (miRNA-135, miRNA-193b, and miRNA-384) that control APOE in both TB and AD also support this concept [38].

Table 2
Adjusted hazard ratio (95% confidence interval) for the newly development of dementia for pulmonary TB survivors.

		Number	Event	Follow-up (PY)	IR*	Crude HR (95% CI)	Model 1† aHR (95% CI)	Model 2‡ aHR (95% CI)	Model 3§ aHR (95% CI)
All dementia	Controls	50,182	1992	181,000.41	11.01	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	TB survivors	50,182	2473	173,692.49	14.24	1.30 (1.22, 1.38)	1.27 (1.20, 1.35)	1.12 (1.05, 1.19)	1.13 (1.06, 1.20)
Alzheimer dementia	Controls	50,182	1305	181,000.41	7.21	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	TB survivors	50,182	1619	173,692.49	9.32	1.30 (1.21, 1.40)	1.26 (1.17, 1.36)	1.11 (1.03, 1.20)	1.12 (1.04, 1.21)
Vascular dementia	Controls	50,182	121	181,000.41	0.67	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	TB survivors	50,182	203	173,692.49	1.17	1.76 (1.40, 2.20)	1.84 (1.46, 2.32)	1.48 (1.16, 1.89)	1.52 (1.19, 1.93)

N, number; HR (95% CI) hazard ratio (95% confidence interval); IR, incidence rate; PY, person-years

* per 1000-PY

† Model 1: adjusted for age, sex, BMI, smoking, drinking status, regular exercise, income level, and place of residency.

‡ Model 2: adjusted for age, sex, BMI, smoking, drinking status, regular exercise, income level, place of residency and Charlson comorbidity index.

§ Model 3: adjusted for age, sex, BMI, smoking, drinking status, regular exercise, income level, place of residency, Charlson comorbidity index, the presence of hypertension, diabetes, dyslipidemia and previous history of traumatic brain injury.

Small vessel disease in the brain is a common condition in older adults and has been implicated in cognitive decline, dementia, and stroke, causing up to 45% of dementia cases and accounting for up to 25% of stroke [39,40]. Regarding atherosclerosis, systemic inflammation has been suggested to play a role in the development of cerebral vessel diseases, resulting in cognitive dysfunction [41,42]. For example, elevated serum inflammatory marker (C-reactive protein) or IL-6 was associated with cognitive dysfunction or neurodegenerative diseases [32,43,44]. In a population-based prospective cohort study, increase of inflammatory protein was suggested to indicate predisposition to VD [33].

In this study, the relative risk of dementia compared to controls was higher in CNS TB survivors than non-CNS TB survivors, and was particularly prominent for VD. The results in this study are in line with the inflammation hypothesis linking infection and VD; direct invasion of microorganisms in the CNS causes higher inflammatory cytokine levels in the brain, predisposing it to cerebral vascular change and VD [33]. In addition, hospitalization following a severe infection was related to an increased risk of dementia, with the greatest risk of VD in cases of CNS infection [45]. Similarly, TB survivors were shown in several studies to have an increased risk of ischemic stroke, in which systemic inflammation was suggested to play a major role in the development of this disease entity [8,46].

The notable contribution of TB to increased risk of dementia can provide several important clinical implications. The results of the present study indicate the importance of close monitoring of cognitive functions in post-TB survivors, especially those with risk factors for dementia. Because the relative risk of VD is higher than that of AD, health care providers should focus on screening and managing cardiovascular risk factors in TB survivors rather than simply

monitoring for TB recurrence. Particularly for patients surviving after CNS TB, we there is need to careful follow-up to determine whether CNS infection-related cognitive deficiency persists. Managing their risk factors for cerebrovascular disease and applying proper screening for cerebral arteriosclerosis are recommended. Accompanying this effort, the development of biomarkers predicting AD, and VD is needed for this population. Regarding public health, the positive association between post-TB status and dementia could encourage health policy makers to develop strategies that prevent TB from progressing to dementia.

The present study had several limitations. First, baseline cognitive function and several risk factors for dementia, such as environmental factors, educational status, and factors related to genetic predisposition, were not included. Second, the follow-up period was relatively short considering the time for dementia occurrence. Longer follow-up duration would have provided more comprehensive insight into the development of dementia in TB survivors. However, TB infection can possibly activate or accelerate disease onset or progression of dementia in patients highly susceptible to dementia. Third, information on cardiovascular medications was not available, which can lead to lack of control for the residual confounding factors related to predisposing cardiovascular risk factors. However, to minimize these effects, we included the presence of three major cardiovascular diseases (diabetes, hypertension, and dyslipidemia) in our analyses. Fourth, the severity of TB (e.g., cavity, bilateral lesion in chest radiography, or acid-fast bacillus smear positivity) was not taken into account in the study. Future studies incorporating those factors will be needed to find the association between TB infection and the risk of dementia in detail. At last, bias existed due to the retrospective study design despite model adjustment for potential confounders.

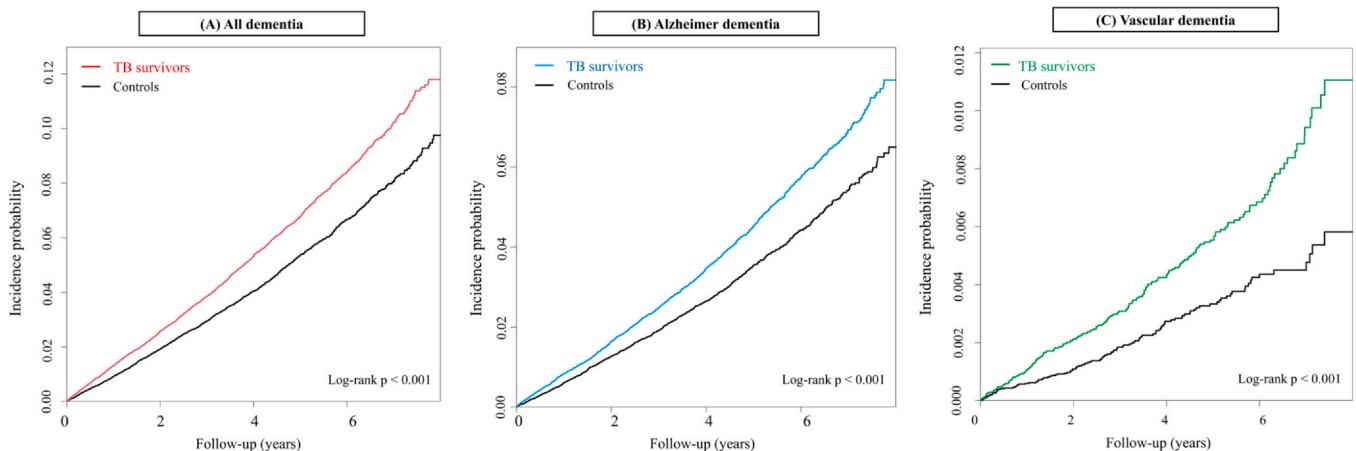


Fig. 2. Kaplan-Meier curves for risk of overall dementia (A), Alzheimer's disease (AD) (B) and vascular dementia (VD) (C) in patients with tuberculosis (TB) and matched controls.

Table 3
Adjusted hazard ratio (95% confidence interval) for the newly development of dementia for active TB survivors specified for CNS TB.

		Number	Event	Follow-up (PY)	IR*	Crude HR (95% CI)	Model 1† aHR (95% CI)	Model 2‡ aHR (95% CI)	Model 3§ aHR (95% CI)
All dementia	Controls	50,182	1992	181,000.41	11.01	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	Non-CNS TB	49796	2449	172,244.56	14.22	1.30 (1.22, 1.38)	1.27 (1.19, 1.35)	1.11 (1.05, 1.19)	1.12 (1.05, 1.20)
	CNS TB	386	24	1447.93	16.58	1.49 (1.00, 2.23)	1.98 (1.32, 2.96)	1.76 (1.18, 2.64)	1.78 (1.19, 2.66)
Alzheimer dementia	Controls	50,182	1305	181,000.41	7.21	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	Non-CNS TB	49796	2449	172,244.56	9.32	1.30 (1.21, 1.40)	1.26 (1.16, 1.35)	1.11 (1.03, 1.20)	1.12(1.04, 1.21)
	CNS TB	386	24	1447.93	8.98	1.23 (0.71, 2.13)	1.72 (0.99, 2.96)	1.54 (0.89, 2.66)	1.55 (0.90, 2.68)
Vascular dementia	Controls	50,182	121	181,000.41	0.67	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	Non-CNS TB	49796	2449	172,244.56	1.16	1.74 (1.39, 2.19)	1.82 (1.45, 2.30)	1.47 (1.15, 1.87)	1.50 (1.18, 1.91)
	CNS TB	386	24	1447.93	2.07	3.06 (0.97, 9.60)	4.02 (1.28, 12.65)	3.33 (1.06, 10.49)	3.42 (1.09, 10.76)

N, number; HR (95% CI) hazard ratio (95% confidence interval); IR, incidence rate; PY, person-years; CNS, central nerve system
CNS TB: A17.0, A17.1, A17.80, A17.81, A17.88 for brain and spine TB infection

* per 1000-PY

† Model 1: adjusted for age, sex, BMI, smoking, drinking status, regular exercise, income level, and place of residency

‡ Model 2: adjusted for age, sex, BMI, smoking, drinking status, regular exercise, income level, place of residency and Charlson comorbidity index

§ Model 3: adjusted for age, sex, BMI, smoking, drinking status, regular exercise, income level, place of residency, Charlson comorbidity index, the presence of hypertension, type 2 diabetes, dyslipidemia and previous history of traumatic brain injury

Figure Legends

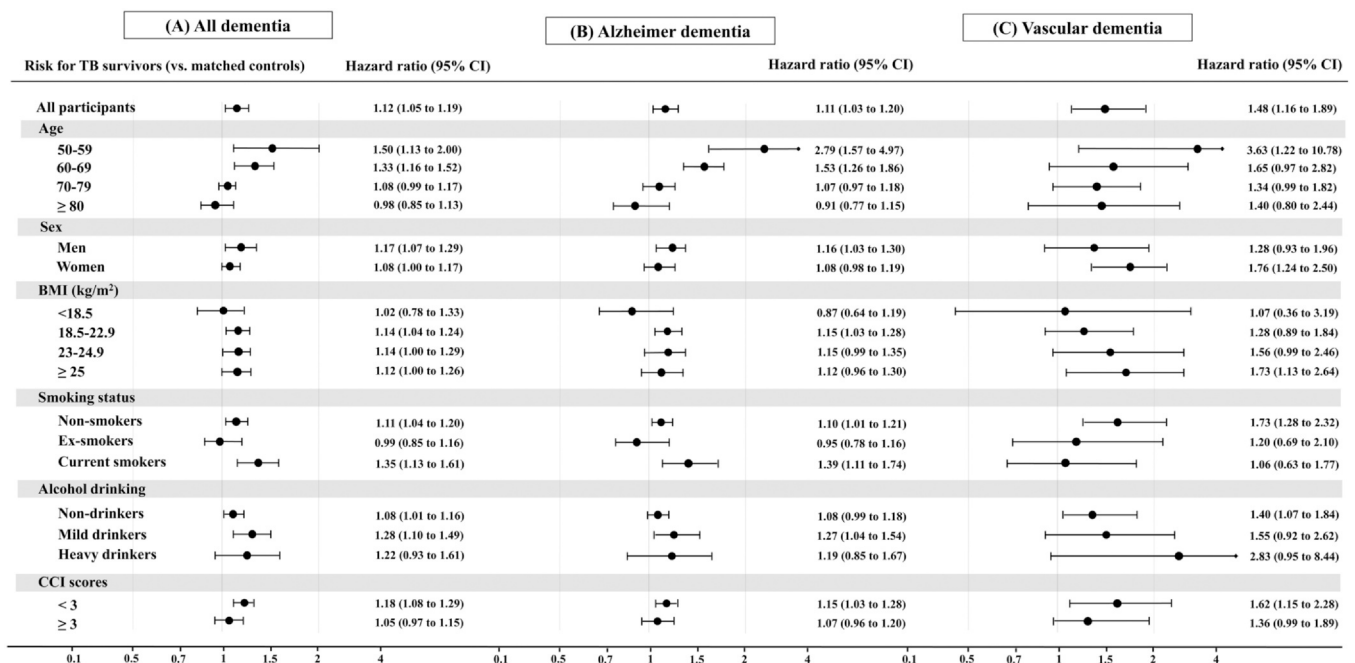


Fig. 3. Forest plots showing the hazard ratios (HRs) and 95% confidence intervals (CIs).

The associations between demographics and vascular risk factors and overall dementia (A), Alzheimer's disease (AD) (B), and vascular dementia (VD) (C) in patients with tuberculosis (TB) and matched controls. All models were adjusted for sex, age, BMI, smoking status, alcohol consumption, regular exercise activity, income level, residency, and Charlson Comorbidity Index (CCI).

Conclusion

In the present study, TB survivors had increased risk of both AD and VD compared with controls from a representative general population.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.jiph.2023.12.006](https://doi.org/10.1016/j.jiph.2023.12.006).

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