



# Association of scrub typhus with incidence of dementia : A nationwide population-based cohort study in Korea

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## Introduction

Scrub typhus is an infectious disease that is transmitted by human bites from mites infected with *Orientia tsutsugamushi*.

This bacterium infects host vascular endothelial cells and is released from infected cells, **causing systemic vasculitis that can invade the central nervous system.**

Dementia is a degenerative disorder that affects the brain, which is an important issue in an aging society.

Considering the characteristics of scrub typhus infection that occurring frequently in old age and involving the inflammation of systemic blood vessels that can invade the CNS, **it may be associated with the occurrence of dementia.**

This study aimed to investigate this hypothesis using **large population-based cohort data from the Health Insurance Review and Assessment Service (HIRA) in South Korea.**

## Material & Methods

**Data source**  
HIRA dataset contains basic information on patient's sociodemographic characteristics and prescriptions, diagnosis and diagnostic procedures and treatments prescribed by coded information in South Korea since January 2007

**Study population**  
**Scrub typhus group** : From January 2009 to December 2018, among people aged 60 to 89, those diagnosed with scrub typhus  
**Control group** : stratified according to age and sex at a ratio of 1:5 to the case group in the same study population

**Washout period for all** : from January 2007 to December 2008  
**The index date** : after 90 days of scrub typhus diagnosis date

**Outcomes**  
**Primary outcome** : the event and timing of **newly diagnosed dementia**  
**Secondary outcome** : classified patients by **dementia subgroup into Alzheimer's disease (AD), vascular dementia, and other.**

**Covariates**  
Age, Sex, central degenerative diseases, HTN, DM, MDD

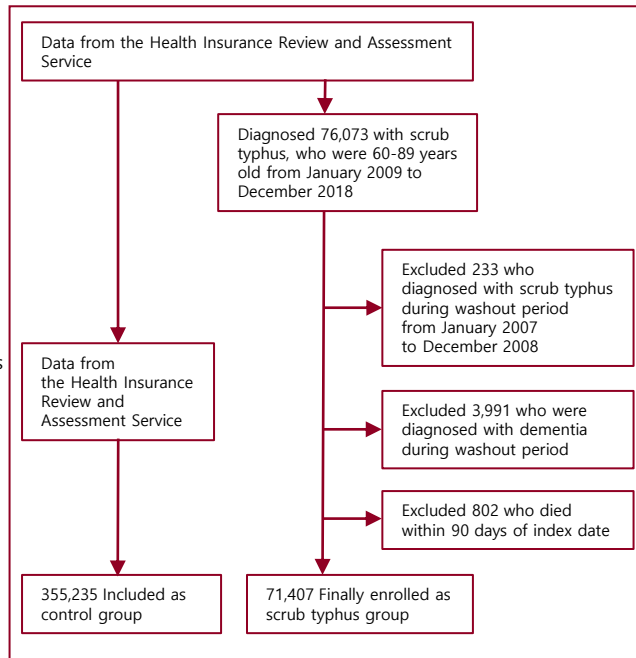
**Statistical analysis**  
intergroup comparisons : Fisher's exact test, Student's t-test and the chi-squared test  
Hazards of dementia incidence : Cox proportional hazards analysis  
Cumulative incidence curves : Kaplan-Meier curves

**A total of 71,047 subjects** were included in the **scrub typhus group**. The **control group** was randomly selected at a ratio of 1:5 with sex and age matching; thus, **355,235 subjects** were included.

Of the total 426,282 participants, 93,767 (22.0%) were diagnosed with dementia during the observation period between the index date and December 31, 2020.

**In the scrub typhus group, 17,206 (24.2%) people were diagnosed with dementia, a significantly higher incidence comparing to the control group (n=76,561 [21.6%]; p<0.001).**

### Flow char of the study population



Cox proportional hazards analysis revealed that **dementia incidence was higher among individuals with a past history of scrub typhus than in the controls.**

**Crude HR was 1.19 (95% CI, 1.12-1.35, p<0.001) and the adjusted HR (aHR) was 1.12 (95% CI, 1.10-1.15, p<0.001).**

## Results

### Participants' characteristics

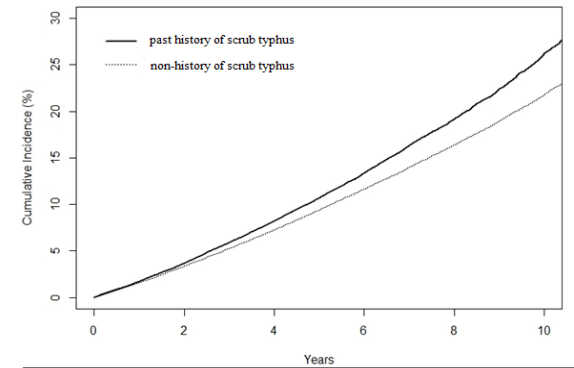
	Total (n=426,282)	Past history of scr		p-value
		ub typhus (n=71,047)	ub typhus (n=355,235)	
Age, years	70.6 ± 7.0	70.6 ± 7.0	70.6 ± 7.0	>0.999
60-69	200,580 (47.1)	33,430 (47.1)	167,150 (47.1)	>0.999
70-89	225,702 (52.9)	37,617 (52.9)	188,085 (52.9)	
Sex				
Male	159,126 (37.3)	26,521 (37.3)	132,605 (37.3)	>0.999
Female	267,156 (62.7)	44,526 (62.7)	222,630 (62.7)	
Comorbidity				
Stroke	78,950 (18.5)	13,804 (19.4)	65,146 (18.3)	<0.001
Central degenerative disease	33,365 (7.8)	6,876 (9.7)	26,489 (7.5)	<0.001
DM	219,539 (51.5)	40,010 (56.3)	179,529 (50.5)	<0.001
HTN	286,721 (67.3)	47,067 (66.2)	239,654 (67.5)	<0.001
MDD	108,171 (25.4)	20,291 (28.6)	87,880 (24.7)	<0.001
Dementia subtype				
All	93,767 (22.0%)	17,206 (24.2%)	76,561 (21.6%)	
Alzheimer	66,602 (15.6%)	12,614 (17.8)	53,988 (15.2)	<0.001
Vascular	9,294 (2.2)	1,475 (2.1)	7,819 (2.2)	
Others	17,871 (4.2%)	3,117 (4.4%)	14,754 (4.2%)	
Follow-up duration, years	5.6 ± 2.9	5.7 ± 2.9	5.6 ± 2.9	<0.001

The Kaplan-Meier curves for the cumulative incidence of dementia shows dementia incidence in both groups increased over time, and **the incidence of dementia was higher in the scrub typhus group than in the non-history of scrub typhus group.** As time goes, the gap in the incidence rate also increased

When classified into subgroups, **the risk of AD was higher in the scrub typhus group (aHR, 1.15; 95% CI, 1.13-1.18, p<0.001).**

However, there was no statistically significant differences regarding the vascular dementia risk (aHR, 0.98; 95% CI, 0.83-1.16, p=0.820) and other types of dementia (aHR, 1.05; 95%CI, 1.10-1.10, p=0.023).

### Cumulative incidence of dementia during follow-up



At risk per year	0	2	4	6	8	10
Past history of scrub typhus	71,047	63,337	45,885	32,847	18,831	7,742
Non history of scrub typhus	355,235	311,334	223,015	158,548	90,721	36,991

### Multivariate Cox proportional hazard analysis of dementia by subtype

	crude HR	p-value	adjusted HR	p-value
Dementia				
All	1.19 (1.16-1.21)	<0.001	1.12 (1.10-1.15)	<0.001
Alzheimer's disease	1.22 (1.19-1.25)	<0.001	1.15 (1.13-1.18)	<0.001
Vascular	1.01 (0.86-1.20)	0.871	0.98 (0.83-1.16)	0.820
Others	1.11 (1.07-1.16)	<0.001	1.05 (1.00-1.10)	0.023

## Conclusion

In conclusion, our findings suggest **that a history of scrub typhus infection in old age is significantly associated with increased dementia risk, especially AD.**

Additionally, **prevention and appropriate treatment of scrub typhus should be emphasized as a preventive measure for dementia.**