Risk of Dementia in Patients with Toxoplasmosis- A Nationwide, Population-based Cohort Study in Taiwan

Hung-Yi Yang (✉ euphoria.yang@gmail.com)

Tri-Service General Hospital

Wu-Chien Chien

National Defense Medical Center

Chi-Hsiang Chung

National Defense Medical Center

Ruei-Yu Su

Tri-Service General Hospital

Chung-Yu Lai

National Defense Medical Center

Chuan-Chi Yang

Taoyuan Armed Forces General Hospital

Nian-Sheng Tzeng

Tri-Service General Hospital

Research Article

Keywords: toxoplasmosis, sulfadiazine, clindamycin, tissue cysts, infected meat

Posted Date: May 5th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-480048/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background

Toxoplasma gondii (*T. gondii*) has infected about 25–30% of individuals worldwide, and it was difficult to detect its latent status. We aimed to evaluate the association between toxoplasmosis, the risk of dementia, and the effects of antibiotics in Taiwan.

Material and methods

This nationwide, population-based, retrospective cohort study was conducted by using the two million Longitudinal Health Insurance Database retrieved from Taiwan's National Health Insurance Research Database. The Fine and Gray's competing risk analysis was used for the development of dementia in the toxoplasmosis cohort relative to the non-toxoplasmosis cohort. A sensitivity analysis was also conducted. The effects of the antibiotics (sulfadiazine or clindamycin) on the risk of dementia were also analyzed.

Results

We enrolled a total of 800 subjects, and identified 200 patients with toxoplasmosis and 600 sex- and age-matched controls without toxoplasmosis infections in a ratio of 1:3, selected between 2000 and 2015. The crude hazard ratio (HR) of the risk in the development of dementia was 2.570 (95% confidence interval [CI] = 1.511–4.347, $p < 0.001$). After adjusting for sex, age, monthly insurance premiums, urbanization level, geographic region, and comorbidities, the adjusted HR was 2.878 (95% CI = 1.709–4.968, $p < 0.001$). The sensitivity analysis revealed that toxoplasmosis was associated with the risk of Alzheimer and other degenerative dementia even after excluding the diagnosis of these two types of dementia in the first and first five years. The usage of the sulfadiazine or clindamycin in the treatment of toxoplasmosis was associated with a decreased risk of dementia.

Conclusion

This finding supports the evidence that toxoplasmosis is associated with dementia and the antibiotics treatment against toxoplasmosis is associated with a reduced risk of dementia. Further studies are necessary to explore the underlying mechanisms of these associations.

Introduction

Toxoplasmosis, caused by *Toxoplasma gondii* (*T. gondii*), which has infected about 25–30% individuals worldwide [1]. Individuals can become infected due to the ingestion of tissue cysts, infected meat, or food contaminated with sporulated oocysts [1]. After ingestion, the bradyzoites and sporozoites released from the cysts and oocysts would change the form to tachyzoites [2], which could spread into the blood stream and lymphatic system and cause distant organ invasion. The tachyzoites could then induce acute inflammation in the organs which might cause myocarditis, hepatitis, pneumonitis or retinochoroiditis [2]. They can also cross the blood-brain barrier and invade the brain cells during the first week of infection [1]. In addition, it would become a chronic infection by the latent toxoplasmic cysts and remain in the tissues or central nervous system (CNS) [1]. Elevated risk of cerebral toxoplasmosis was noted in the elderly due to the possibility of the increase of immunosuppression [3]. In Taiwan,

the Center for Disease Control listed the antibiotics, sulfadiazine, and clindamycin, as the treatment for toxoplasmosis [4].

Dementia is a common neurodegenerative disease including symptoms of the worsening of cognition, emotional change, difficulties with language expression, and even motivation decrease [5]. The most common cause is Alzheimer dementia (AD), and other causes including Lewy Body disease, frontotemporal lobe degeneration or vascular disease are also common [6]. The pathophysiology of AD is of major concern and is related to the amyloid β ($A\beta$) protein and the intracellular neurofibrillary tangles [7]. However, the inflammatory process could also be associated with some neurodegenerative disorders like AD, Parkinson disease (PD), Huntington disease (HD), amyotrophic lateral sclerosis (ALS), or multiple sclerosis (MS). Chronic inflammations could be induced by some infectious agents including viruses (herpes simplex virus), bacteria (*Chlamydia pneumonia*), or even parasites (*T. gondii*) [8, 9].

Several previous studies have shown that chronic toxoplasmic infection may be associated with the human behavior alterations, obsessive-compulsive disorder, or even schizophrenia [10, 11]. It could also lead to other neurodegenerative symptoms including memory impairment [12], and cognitive decline [13]. The cysts' location in the brain [14], the immune response [15] or changes of brain metabolism [16], could have effects on the cognitive dysfunction. However, Mahami et al., (2016) showed that there were no significant relations between toxoplasmosis and AD from a case-control study [17], and Perry et al., (2016) found no difference of serum *T. gondii* antibody titer between the AD group and control group of the latent toxoplasmosis [18]. No previous nationwide cohort studies have been conducted to investigate the association among toxoplasmosis, antibiotics treatment, and the risk of dementia. Therefore, we conducted the present study, by using Taiwan's National Health Insurance Research Database (NHIRD), to investigate whether toxoplasmosis is associated with the risk of dementia, along with the role of antibiotics treatment in the risk of dementia in patients with toxoplasmic infections.

Methods

Design and study methods

This retrospective cohort study is based on the NHIRD, provided by the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW). The National Health Insurance (NHI) was established in 1995, and as of June 2009, it included contracts with 97% of the medical providers with approximately 23 million people of the program, or more than 99% of the entire population [19, 20]. The details of this program have been documented in previous studies [21-28]. The NHIRD registration files and the original claims data, including the overall data of personal information and the disease coding.

The NHIRD also recorded inpatient care, ambulatory care, dental care, and prescription drugs availed by the insured and their date of birth. Pursuant to the Personal Information Protection Act, individual identifiers are encrypted before release for research. Patients diagnosed with genital warts during the study period (2000-2015) were enrolled, and those recorded in the NHI program are coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM), as ICD-9 codes of 130.

All diagnoses of dementia were made by board-certified psychiatrists or neurologists. Toxoplasmosis were confirmed by serum antibody screening and avidity test or polymerase chain reaction (PCR) [4]. Since several previous studies have revealed a high accuracy and validity of the diagnoses in the NHIRD [29-31], and the licensed medical records technicians verified the coding before claiming the reimbursements in hospitals and clinics [32]. Furthermore, the NHI

Administration appoints several senior external specialists in psychiatry, neurology, infection medicine, and other related medical specialties for randomly reviewing the records of ambulatory care visits and inpatient claims to verify the accuracy of the diagnoses [33]. Thus, it is therefore suitable to use the NHIRD to examine the longitudinal association between the toxoplasmosis and the potential risk of developing dementia afterward.

Ethical approval

This study was approved by the Institutional Review Board of the Tri-Service General Hospital (TSGH IRB No. 2-107-05-026). Because the patient identifiers were encrypted before their data were used for research purposes to protect confidentiality, the requirement for written or verbal consent from patients for data linkage was waived.

Study population

This was a retrospective cohort study. From the LHID of two million individuals, a sub-database, randomly stratified retrieved from the NHIRD, we identified individuals as being ≥ 50 years old with a diagnoses as toxoplasmosis, that were selected between January 1, 2000, and December 31, 2015, according to ICD-9-CM code of 130.x. In this 15-year follow-up study, patients diagnosed with dementia or toxoplasmosis before 2000 or before the first visit for toxoplasmosis, and all patients aged < 50 were excluded. The date of the toxoplasmosis diagnosed was defined as the index date. Figure 1 depicts the flow chart of this study for the comparison of patients with toxoplasmosis and the controls. In addition, Figure S1 depicts the flow chart of this study for the comparison of patients with toxoplasmosis with and without antibiotics treatment.

Covariates

The covariates included sex, age group (50-64, ≥ 65 years), geographical area of residence (north, center, south, and east of Taiwan), urbanization level of residence (levels 1 to 4), levels of hospitals as medical centers, regional and local hospitals, and monthly income (in New Taiwan Dollars [NT\$]; $< 18,000$, $18,000-34,999$, $\geq 35,000$). The urbanization level of residence was defined according to the population, along with various indicators of the level of political, economic, cultural, and metropolitan development. Level 1 was defined as a population of $> 1,250,000$, and a specific designation as political, economic, cultural, and metropolitan development. Level 2 was defined as a population between 500,000 and 1,249,999, and as playing an important role in the political system, economy, and culture. Urbanization levels 3 and 4 were defined as a population between 149,999 and 499,999, and $< 149,999$, respectively.

The comorbidities in this study were diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, human immunodeficiency virus infections/ acquired immune deficiency syndrome, and other immune deficiency diseases. All the ICD codes of the comorbidities are as listed in Table S1.

Data on the usage of antibiotics, sulfadiazine and clindamycin, were collected. The data of the defined daily dose (DDD) were obtained from the WHO Collaborating Centre for Drug Statistics Methodology (<https://www.whocc.no/>), and the duration of the usage of antibiotics was calculated by dividing the cumulative doses by the DDD of the antibiotics. While we analyzed the effects on the risk of dementia between the two subgroups with or without the antibiotics treatment, the sample was divided by the covariates with the references of previous studies using the NHIRD, regarding the treatment effects of medications medication [34-36]. The yearly times of the visits for psychiatry, neurology, and infection medicine clinics were also recorded.

Study Outcomes

All the participants were followed from the index date until the onset of dementia, withdrawal from the NIHRD, or the end of 2015. The patients with dementia were grouped as Alzheimer dementia (AD), vascular dementia (VaD). At least three visits in one consecutive year in the NIHRD records would be regarded as a diagnosis of dementia. All the ICD codes of dementia are as listed in Table S1.

Statistical Analysis

All analyses were performed using the SPSS software version 22 (SPSS Inc., Chicago, Illinois, USA). χ^2 and t tests were used to evaluate the distribution of the categorical and continuous variables, respectively. The Fisher exact test for categorical variables was used to statistically examine the differences between the two cohorts. The Fine and Gray's survival analysis was used to determine the risk of dementia, and the results are presented as a hazard ratio (HR) with a 95% confidence interval (CI). A sensitivity analysis by excluding the diagnosis of dementia within the first year, and the first five years, was conducted to avoid protopathic bias. The difference in the risk of dementia, between the genital warts subjects and control groups was estimated using the Kaplan-Meier method with the log-rank test. A 2-tailed P value < 0.05 was considered to indicate the statistical significance.

Results

Sample characteristics

Table 1 shows that a total of 800 patients that were enrolled, including 200 subjects with toxoplasmosis and 600 controls without toxoplasmosis, which were 1:3 matched for age, sex, and index year. There were no differences in sex and age. The toxoplasmosis cohort tended to have a higher percentage in the comorbidities of DM, but a slightly lower percentage of HIV/AIDS and other immunodeficiency diseases, in comparison to the non-toxoplasmosis controls. The patients with toxoplasmosis tended to have the monthly insurance premiums of NT\$18,000-34,999, live in the middle, eastern, and the outlying islands, residing in areas of urbanization levels 2, 3, and 4, and seek medical care from the medical center and regional hospital. In addition, patients with toxoplasmosis have visited more clinics of infection disease and neurology, than the control group.

Kaplan-Meier model for the cumulative incidence of dementia

Of the toxoplasmosis patients, 21 in 200 (457.84 per 10⁵ person-years) developed dementia, when compared to 56 in 600 (323.42 per 10⁵ person-years) in the control group, and the difference was statistically significant in the Kaplan-Meier survival analysis (log-rank, p =0.030, Figure 2).

Of the toxoplasmosis patients, 20 in 191 with antibiotics treatment (455.72 per 10⁵ person-years) developed dementia when compared to 1 in 9 without antibiotics treatment (507.67 per 10⁵ person-years) in the control group, and the difference was statistically significant in the Kaplan-Meier survival analysis (log-rank, p =0.099, Figure S2).

HR analysis of dementia in the patients with toxoplasmosis

Table 2 shows that Fine and Gray's competing risk model analysis revealed that the study subjects were more likely to develop psychiatric disorders (crude hazard ratio [HR]: 2.570 (95% CI= 1.511-4.347, p <0.001). After adjusting for gender, age, monthly insurance premiums, urbanization level, geographic region, and comorbidities, the adjusted HR was 2.878 (95% CI= 1.709-4.968, p <0.001). Male patients and higher CCI were associated with a higher risk of developing dementia. The toxoplasmosis patients aged ≥ 65 years were associated with a higher risk of developing dementia, in comparison to the patients aged 50-64.

Types and sensitivity analysis of dementia after toxoplasmosis

Table 3 reveals that the toxoplasmosis patients were associated with overall dementia, AD, and other degenerative dementia, with an adjusted HR as 2.878 ($p < 0.001$), 6.675 ($p < 0.001$), and 3.162 ($p < 0.001$), respectively.

Toxoplasmosis was noted as being associated with VaD. Table 3 also depicts that, after the exclusion of diagnosis within the first year or first five years, toxoplasmosis was only associated with the other degenerative dementia.

The effects of antiprotozoal medications for toxoplasmosis and the risk of toxoplasmosis

Antiprotozoal medications usage for toxoplasmosis was associated with a lower risk than the comparison group, both sulfadiazine and clindamycin, either monotherapy or combination treatment, were associated with a lower risk of dementia (Table 4).

Discussion

In this retrospective cohort study, there are several noteworthy findings. First, the patients with toxoplasmosis had a nearly 2.8-fold increased risk of the development of dementia, that is, after the sensitivity analysis by excluding the diagnosis of dementia the first year and the first five years since toxoplasmosis was diagnosed, the patients with toxoplasmosis still had a two-fold increased risk for developing dementia. Second, the sensitivity analysis revealed that, by excluding the AD diagnosis in the first year and first five years after toxoplasmosis, the association became insignificant, but VaD and other degenerative dementia were still associated with toxoplasmosis. However, other types of degenerative dementia were found to be proportionately higher than AD and VaD, and most of the community studies revealed that Alzheimer-type dementia is the most common cause of dementia (40–60% in all dementias), followed by vascular dementia (20–30% in all dementias), and mixed or other dementias (7–15%) in Taiwan [37–39]. One possible explanation for this disparity is that some subjects were classified as other degenerative type of dementia, similar to the findings of previous studies [32, 35]. Thirdly, the usage of medications such as sulfadiazine and clindamycin, either monotherapy or combination treatment, were associated with a lower risk of dementia. To the best of our knowledge, this is the first nationwide, population-based study on the topic about the association between the toxoplasmosis and the risk of dementia, and the effects of antibiotics usage in the reducing risk after toxoplasmosis infections.

In previous studies, the brain is the main target organ in *T. gondii* infection and may cause life-threatening encephalitis in immunosuppressed patients [40]. In healthy individuals, the tachyzoites of the parasite could be cleaned by cellular immune response in the proliferative stage of the systemic infection [41]. In the infected mice brain model, the interferon-gamma (IFN- γ) produced by lymphocyte, microglial cell and blood-derived macrophage could mediate the cell-immune response to the proliferating tachyzoites [42]. The IFN- γ could also activate the astrocytes which inhibit the tachyzoites replication by nitric oxide (NO) production [42]. The microglial are also the resident innate immune cells in the CNS which are the main cause of the inflammatory process. Uncontrolled activation of microglial cells may cause neurotoxicity due to the releasing of inflammatory cytokines, NO or superoxide (SOD). In addition to the acute toxoplasmosis caused by tachyzoites, there were also bradyzoites of the parasite which could produce a tissue cyst and slowly replicate in the brain or muscles and become latent toxoplasmosis [41]. Although the tachyzoites could induce more obvious inflammatory cytokine production than bradyzoites [42], the dormant parasite could resume the pathogenic activity and kill the host with immune deficiency. The latent toxoplasmosis revealed the asymptomatic in a normal condition. However, in comparison with the acute toxoplasmosis, the latent toxoplasmosis might cause a slow and cumulative effect that decreased the psychomotor performance [43]. The early animal model study had already discovered the pathological change in the cyst-

containing region of the brain in mice including the granulomatous change of the perivascular areas and necrotic tissue deposition with vascular sclerosis [44].

Torres et al., (2018) had designed another mice model and argued that Möhle et al., didn't evaluate the advanced signs of AD which could be caused by cerebral amyloid angiopathy (CAA) driven by *T. gondii*, and there is the A β immunoreactivity co-localized with the *T. gondii* cysts as early as day 15 post infection and widespread A β immunoreactivity. They were detected in other areas of the brain where they didn't co-localize with cysts at days 60 to 90 post infection [45]. Moreover, Torres et al., pointed out that A β immunoreactivity may lead to N-methyl-D-aspartate receptor (NMDAR) loss. In the CNS system, the glutamate plays the role of neuron excitation and could be endocytosed or released at the synapse through NMDAR on neural cells. Therefore, the NMDAR plays an important role of the synaptic connection which controls the function of learning and memory. The NMDAR dysfunction is highly associated with AD [46]. There was also strong evidence that the NMDAR antagonist could avoid the neuron dysfunction by A β immunoreactivity [47]. However, some studies had found that the countries with high seropositivity of *T. plasma* didn't have a higher AD prevalence. For example, in the 1970s, the seroprevalance of France was 70% [1], but only 3% prevalence of AD in people more than 60 years old were noted in 2012 [48]. Möhle et al., (2016) had declared a mice model study and discovered that there were reduced A β plaques in *T. plasma* infected mice compared to the non-infected mice [49]. The association between toxoplasmosis and AD, as well as the underlying mechanisms, is as yet to be clarified.

Our study has several strengths: First, we used Taiwan's NHIRD, which is a valuable resource to cover a nationwide population, to address this issue. Second, several previous studies have demonstrated the accuracy and validity of several diagnoses of neuropsychiatric disorders in the NHIRD, such as Tourette syndrome [50], stroke [29, 51-53], sleep apnea [54], and major depressive disorder [55]. Besides, as aforementioned, the in-hospital licensed medical records technicians and the NHI Administration would have verified the diagnoses in the claims dataset [56, 57] for the diagnosis. Third, previous studies have also demonstrated the concordance between Taiwan's National Health Survey and the NHIRD on a variety of diagnoses [58], medication usage [58], and health system utilizations [58, 59]. Therefore, this study was conducted in a large, nationwide, and reliable database for the association between toxoplasmosis and psychiatric morbidities in an Asian country.

The present study has several limitations that warrant consideration. Firstly, similar to the previous studies, not all data were recorded in the NHIRD, and we were unable to evaluate the family history, neurological severity, types, laboratory parameters, the availability of rehabilitation, and the additional examination findings (e.g., neuroimaging). Therefore, the lack of data about the clinical and radiological course and treatment of the disease was a limitation. Secondly, other factors, such as genetic, psychosocial, and environmental, were not included in the dataset. However, since the present study had covered all of Taiwan's hospitals and > 99% of the Taiwanese population during a 15-year period, which thereby increased the likelihood of our data being valid and representative. Thirdly, the prevalence of the Toxoplasma infection in Taiwan was about 10% in 2006 (<https://nidss.cdc.gov.tw>) but only focused on pregnant women, and it couldn't represent the general prevalence of the total population. Therefore, we couldn't correlate the current prevalence of dementia with the prevalence of toxoplasmosis in the past.

Conclusion

To the best of our knowledge, we have provided the first evidence that toxoplasmosis is associated with AD and other dementia in Taiwan, but the association between toxoplasmosis and VaD is not significant. The antibiotics for toxoplasmosis treatment had the effect to prevent the potential risk of dementia in the future. Clinicians should pay more attention on the risk of dementia in the patients with toxoplasmosis.

Declarations

Acknowledgements:

This study was supported by the Tri-Service General Hospital Research Foundation under the grants from the Medical Affairs Bureau, the Ministry of Defense of Taiwan (MAB-107-084 and MND-MAB-110-087), the Tri-Service General Hospital Research Foundation (TSGH-C108-003, TSGH-C108-151, TSGH-B-109-010, TSGH-E-110240, and TSGH-B-110-012), and the Taoyuan Armed Forces General Hospital (TYAFGH-A-110020). The sponsor had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. We also appreciate the provision of the National Health Insurance Research Database by the Taiwan's Health and Welfare Data Science Center and Ministry of Health and Welfare (HWDC, MOW).

Data Availability:

The data on the study population that were obtained from the NHIRD (<http://nhird.nhri.org.tw/en/index.html>) are maintained in the NHIRD (<http://nhird.nhri.org.tw/>). The NHRI is a nonprofit foundation established by the government. Only citizens of the Taiwan who fulfill the requirements of conducting research projects are eligible to apply for the NHIRD. The use of the NHIRD is limited to research purposes only. Applicants must follow the Computer-Processed Personal Data Protection Law (<http://www.winklerpartners.com/?p=987>) and the related regulations of the National Health Insurance Administration and NHRI, and an agreement must be signed by the applicant and their supervisor upon application submission. All applications are reviewed for approval of data release.

Conflicts of Interest: none

References

1. Robert-Gangneux F, Darde ML. Epidemiology of and diagnostic strategies for toxoplasmosis. Clin Microbiol Rev. 2012;25:264-96.
2. Tenter AM, Heckeroth AR, Weiss LM. Toxoplasma gondii: from animals to humans. Int J Parasitol. 2000;30:1217-58.
3. Wilking H, Thamm M, Stark K, Aebischer T, Seeber F. Prevalence, incidence estimations, and risk factors of Toxoplasma gondii infection in Germany: a representative, cross-sectional, serological study. Sci Rep. 2016;6:22551.
4. Center for Disease Control. Introduction to Toxoplasmosis. https://www.cdc.gov.tw/File/Get/sqrAKrJg_Uq8Ki5B0HtO3g?path=CbQtr9efAo_2E10ZEstd2J5QKlu34aEmG6X1BdPpNeDQ2CtHDScOGTGOxIBjpnXUeeo3R86xYnUzhEWslPu-qA&name=G5tHATu3PN9vCZCYnPRueSNsD98p1kmxpv6tOg-nNrs (2010). Accessed February, 11 2021.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text-Revision. Philadelphia, United States of America: American Psychiatric Association Publishing; 1994.
6. Hickey EM, Bourgeois MC. Dementia: Person-Centered Assessment and Intervention. Abingdon: Routledge, United Kingdom; 2018.
7. Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimers Dement. 2015;11:332-84.
8. Zhou L, Miranda-Saksena M, Saksena NK. Viruses and neurodegeneration. Virol J. 2013;10:172.
9. Mattson MP. Infectious agents and age-related neurodegenerative disorders. Ageing Res Rev. 2004;3:105-20.

10. Henriquez SA, Brett R, Alexander J, Pratt J, Roberts CW. Neuropsychiatric disease and *Toxoplasma gondii* infection. *Neuroimmunomodulation*. 2009;16:122-33.
11. Xiao J, Prandovszky E, Kannan G, Pletnikov MV, Dickerson F, Severance EG, et al. *Toxoplasma gondii*: Biological Parameters of the Connection to Schizophrenia. *Schizophr Bull*. 2018;44:983-92.
12. Gajewski PD, Falkenstein M, Hengstler JG, Golka K. *Toxoplasma gondii* impairs memory in infected seniors. *Brain Behav Immun*. 2014;36:193-9.
13. Nimgaonkar VL, Yolken RH, Wang T, Chang CC, McClain L, McDade E, et al. Temporal Cognitive Decline Associated With Exposure to Infectious Agents in a Population-based, Aging Cohort. *Alzheimer Dis Assoc Disord*. 2016;30:216-22.
14. McConkey GA, Martin HL, Bristow GC, Webster JP. *Toxoplasma gondii* infection and behaviour - location, location, location? *J Exp Biol*. 2013;216:113-9.
15. Hamdani N, Daban-Huard C, Lajnef M, Gadel R, Le Corvoisier P, Delavest M, et al. Cognitive deterioration among bipolar disorder patients infected by *Toxoplasma gondii* is correlated to interleukin 6 levels. *J Affect Disord*. 2015;179:161-6.
16. Carruthers VB, Suzuki Y. Effects of *Toxoplasma gondii* infection on the brain. *Schizophr Bull*. 2007;33:745-51.
17. Mahami-Oskouei M, Hamidi F, Talebi M, Farhoudi M, Taheraghdam AA, Kazemi T, et al. Toxoplasmosis and Alzheimer: can *Toxoplasma gondii* really be introduced as a risk factor in etiology of Alzheimer? *Parasitol Res*. 2016;115:3169-74.
18. Perry CE, Gale SD, Erickson L, Wilson E, Nielsen B, Kauwe J, et al. Seroprevalence and Serointensity of Latent *Toxoplasma gondii* in a Sample of Elderly Adults With and Without Alzheimer Disease. *Alzheimer Dis Assoc Disord*. 2016;30:123-6.
19. Ho Chan WS. Taiwan's healthcare report 2010. *EPMA J*. 2010;1:563-85.
20. Hsieh C-Y, Su C-C, Shao S-C, Sung S-F, Lin S-J, Kao Yang Y-H, et al. Taiwan's National Health Insurance Research Database: past and future. *Clinical epidemiology*. 2019;11:349-58.
21. Yang CC, Chien WC, Chung CH, Liu YP, Yeh CB, Chen KH, et al. No Association Between Human Immunodeficiency Virus Infections And Dementia: A Nationwide Cohort Study In Taiwan. *Neuropsychiatr Dis Treat*. 2019;15:3155-66.
22. Chen TY, Huang CH, Chung CH, Mao WC, Yeh CB, Yang CCH, et al. Sex and age differences in the association between anxiety disorders and narcolepsy: A nationwide population-based case control study. *Journal of Affective Disorders*. 2020;264:130-7.
23. Lin CH, Chien WC, Chung CH, Chiang CP, Wang WM, Chang HA, et al. Increased Risk of Dementia in Patients with Genital Warts—A Nationwide Cohort Study in Taiwan. *J Dermatol*. 2020;Accepted: Jan 27, 2020.
24. Lin YC, Chen TY, Chien WC, Chung CH, Chang HA, Kao YC, et al. Stimulants associated with reduced risk of hospitalization for motor vehicle accident injury in patients with obstructive sleep apnea-a nationwide cohort study. *BMC Pulm Med*. 2020;Accepted Dec 24, 2019.
25. Liu YP, Chien WC, Chung CH, Chang HA, Kao YC, Tzeng NS. Are Anticholinergic Medications Associated With Increased Risk of Dementia and Behavioral and Psychological Symptoms of Dementia? A Nationwide 15-Year Follow-Up Cohort Study in Taiwan. *Front Pharm*. 2020;11.
26. Wan FJ, Chien WC, Chung CH, Yang YJ, Tzeng NS. Association between traumatic spinal cord injury and affective and other psychiatric disorders—A nationwide cohort study and effects of rehabilitation therapies. *Journal of Affective Disorders*. 2020;265:381-8.

27. Wang DS, Chung CH, Chang HA, Kao YC, Chu DM, Wang CC, et al. Association between child abuse exposure and the risk of psychiatric disorders: A nationwide cohort study in Taiwan. *Child Abuse Negl.* 2020;101:104362.
28. Yeh TC, Chien WC, Chung CH, Liang CS, Chang HA, Kao YC, et al. Psychiatric Disorders After Traumatic Brain Injury: A Nationwide Population-Based Cohort Study and the Effects of Rehabilitation Therapies. *Arch Phys Med Rehabil.* 2020.
29. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf.* 2011;20:236-42.
30. Hsieh CY, Chen CH, Li CY, Lai ML. Validating the diagnosis of acute ischemic stroke in a National Health Insurance claims database. *J Formos Med Assoc.* 2015;114:254-9.
31. Liang JA, Sun LM, Muo CH, Sung FC, Chang SN, Kao CH. The analysis of depression and subsequent cancer risk in Taiwan. *Cancer Epidemiol Biomarkers Prev.* 2011;20:473-5.
32. Tzeng NS, Chung CH, Yeh CB, Huang RY, Yuh DY, Huang SY, et al. Are Chronic Periodontitis and Gingivitis Associated with Dementia? A Nationwide, Retrospective, Matched-Cohort Study in Taiwan. *Neuroepidemiology.* 2016;47:82-93.
33. Ministry of Justice. National Health Insurance Reimbursement Regulations. <http://law.moj.gov.tw/LawClass/LawAllIf.aspx?PCode=L0060006> (2014). Accessed March 7 2018.
34. Chao PC, Chien WC, Chung CH, Chu CW, Yeh CB, Huang SY, et al. Cognitive enhancers associated with decreased risk of injury in patients with dementia: a nationwide cohort study in Taiwan. *J Investig Med.* 2017.
35. Tzeng NS, Chung CH, Lin FH, Huang CF, Yeh CB, Huang SY, et al. Magnesium oxide use and reduced risk of dementia: a retrospective, nationwide cohort study in Taiwan. *Curr Med Res Opin.* 2018;34:163-9.
36. Tzeng NS, Chung CH, Lin FH, Chiang CP, Yeh CB, Huang SY, et al. Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections-a Nationwide, Population-Based Cohort Study in Taiwan. *Neurotherapeutics.* 2018;15:417-29.
37. Liu HC, Lin KN, Teng EL, Wang SJ, Fuh JL, Guo NW, et al. Prevalence and subtypes of dementia in Taiwan: a community survey of 5297 individuals. *J Am Geriatr Soc.* 1995;43:144-9.
38. Lin RT, Lai CL, Tai CT, Liu CK, Yen YY, Howng SL. Prevalence and subtypes of dementia in southern Taiwan: impact of age, sex, education, and urbanization. *J Neurol Sci.* 1998;160:67-75.
39. Liu CK, Lai CL, Tai CT, Lin RT, Yen YY, Howng SL. Incidence and subtypes of dementia in southern Taiwan: impact of socio-demographic factors. *Neurology.* 1998;50:1572-9.
40. Creuzet C, Robert F, Roisin MP, Van Tan H, Benes C, Dupouy-Camet J, et al. Neurons in primary culture are less efficiently infected by *Toxoplasma gondii* than glial cells. *Parasitol Res.* 1998;84:25-30.
41. Denkers EY, Gazzinelli RT. Regulation and function of T-cell-mediated immunity during *Toxoplasma gondii* infection. *Clin Microbiol Rev.* 1998;11:569-88.
42. Suzuki Y, Orellana MA, Schreiber RD, Remington JS. Interferon-gamma: the major mediator of resistance against *Toxoplasma gondii*. *Science.* 1988;240:516-8.
43. Havlicek J, Gasova ZG, Smith AP, Zvara K, Flegr J. Decrease of psychomotor performance in subjects with latent 'asymptomatic' toxoplasmosis. *Parasitology.* 2001;122:515-20.
44. Werner H, Masihi KN, Senk U. Latent toxoplasma-infection as a possible risk factor for CNS-disorders. *Zentralbl Bakteriol Mikrobiol Hyg A.* 1981;250:368-75.
45. Torres L, Robinson SA, Kim DG, Yan A, Cleland TA, Bynoe MS. *Toxoplasma gondii* alters NMDAR signaling and induces signs of Alzheimer's disease in wild-type, C57BL/6 mice. *J Neuroinflammation.* 2018;15:57.

46. Foster TC, Kyritsopoulos C, Kumar A. Central role for NMDA receptors in redox mediated impairment of synaptic function during aging and Alzheimer's disease. *Behav Brain Res.* 2017;322:223-32.
47. Gunn AP, Wong BX, Johanssen T, Griffith JC, Masters CL, Bush AI, et al. Amyloid-beta Peptide Abeta3pE-42 Induces Lipid Peroxidation, Membrane Permeabilization, and Calcium Influx in Neurons. *J Biol Chem.* 2016;291:6134-45.
48. Takizawa C, Thompson PL, van Walssem A, Faure C, Maier WC. Epidemiological and economic burden of Alzheimer's disease: a systematic literature review of data across Europe and the United States of America. *J Alzheimers Dis.* 2015;43:1271-84.
49. Mohle L, Israel N, Paarmann K, Krohn M, Pietkiewicz S, Muller A, et al. Chronic Toxoplasma gondii infection enhances beta-amyloid phagocytosis and clearance by recruited monocytes. *Acta Neuropathol Commun.* 2016;4:25.
50. Chou IC, Lin HC, Lin CC, Sung FC, Kao CH. Tourette syndrome and risk of depression: a population-based cohort study in Taiwan. *J Dev Behav Pediatr.* 2013;34:181-5.
51. Cheng CL, Chien HC, Lee CH, Lin SJ, Yang YH. Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in National Health Insurance Research Database in Taiwan. *Int J Cardiol.* 2015;201:96-101.
52. Sung SF, Hsieh CY, Lin HJ, Chen YW, Yang YH, Li CY. Validation of algorithms to identify stroke risk factors in patients with acute ischemic stroke, transient ischemic attack, or intracerebral hemorrhage in an administrative claims database. *Int J Cardiol.* 2016;215:277-82.
53. Tseng HP, Lin FJ, Chen PT, Mou CH, Lee SP, Chang CY, et al. Derivation and validation of a discharge disposition predicting model after acute stroke. *J Stroke Cerebrovasc Dis.* 2015;24:1179-86.
54. Su VY, Liu CJ, Wang HK, Wu LA, Chang SC, Perng DW, et al. Sleep apnea and risk of pneumonia: a nationwide population-based study. *CMAJ.* 2014;186:415-21.
55. Wu CS, Kuo CJ, Su CH, Wang SH, Dai HJ. Using text mining to extract depressive symptoms and to validate the diagnosis of major depressive disorder from electronic health records. *J Affect Disord.* 2020;260:617-23.
56. Hsieh CY, Su CC, Shao SC, Sung SF, Lin SJ, Kao Yang YH, et al. Taiwan's National Health Insurance Research Database: past and future. *Clin Epidemiol.* 2019;11:349-58.
57. Ministry of Justice. National Health Insurance Reimbursement Regulations. <https://law.moj.gov.tw/LawClass/LawAll.aspx?pcode=L0060035> (2019). Accessed December 18, 2019.
58. Wu CS, Lai MS, Gau SS, Wang SC, Tsai HJ. Concordance between patient self-reports and claims data on clinical diagnoses, medication use, and health system utilization in Taiwan. *PLoS One.* 2014;9:e112257.
59. Yu ST, Chang HY, Lin MC, Lin YH. Agreement between self-reported and health insurance claims on utilization of health care: A population study. *J Clin Epidemiol.* 2009;62:1316-22.

Tables

Table 1. Characteristics of study in at the baseline					
<i>Toxoplasmosis</i>	With		Without		<i>P</i>
Variables	n	%	n	%	
Total	200	25.00	600	75.00	
Gender					0.999
Male	87	43.50	261	43.50	
Female	113	56.50	339	56.50	
Age (years)	62.11 ± 8.88		63.18 ± 8.71		0.135
Age groups (yrs)					0.999
50-64	131	65.50	393	65.50	
≥65	69	34.50	207	34.50	
Insured premium (NT\$)					<0.001
<18,000	143	71.50	593	98.83	
18,000-34,999	48	24.00	7	1.17	
≥35,000	9	4.50	0	0	
Diabetes mellitus					0.014
Without	179	89.50	493	82.17	
With	21	10.50	107	17.83	
Hypertension					0.482
Without	155	77.50	479	79.83	
With	45	22.50	121	20.17	
Hyperlipidemia					0.357
Without	196	98.00	578	96.33	
With	4	2.00	22	3.67	
Coronary artery disease					0.885
Without	183	91.50	547	91.17	
With	17	8.50	53	8.83	
Obesity					-
Without	200	100	600	100	
With	0	0	0	0	
HIV					<0.001
Without	196	98.00	596	99.33	
With	4	2.00	4	0.67	

With	4	2.00	4	0.67
Immune deficiency				<0.001
Without	190	95.00	589	98.17
With	10	5.00	11	1.83
CCI_R	0.76 ± 1.84		0.69 ± 1.48	0.596
Location				<0.001
Northern Taiwan	68	34.00	244	40.67
Middle Taiwan	96	48.00	162	27.00
Southern Taiwan	26	13.00	170	28.33
Eastern Taiwan	8	4.00	22	3.67
Outlying islands	2	1.00	2	0.33
Urbanization level				0.003
1 (The highest)	53	26.50	208	34.67
2	96	48.00	260	43.33
3	15	7.50	39	6.50
4 (The lowest)	36	18.00	93	15.50
Level of care				0.002
Hospital center	81	40.50	220	36.67
Regional hospital	75	37.50	172	28.67
Local hospital	44	22.00	208	34.67
Department of visits in study period				
Infection	1.12 ± 1.30		0.85 ± 1.08	0.004
Neurology	2.54 ± 2.69		2.03 ± 2.51	0.015
Psychiatry	3.01 ± 3.47		2.75 ± 2.83	0.289
P: Chi-square / Fisher exact test on category variables and t-test on continue variables, CCI_R: Charlson Comorbidity Index, dementia and HIV removed				

Table 2. Factors of dementia by using Cox regression and Fine & Gray's competing risk model								
	No competing risk in the model				Competing risk in the model			
Variables	Adjusted HR	95% CI	95% CI	P	Adjusted HR	95% CI	95% CI	P
<i>Toxoplasmosis</i> (reference: without)	2.570	1.511	4.347	<0.001	2.878	1.709	4.968	<0.001
Male (reference: female)	1.841	1.123	3.018	0.001	1.989	1.235	3.310	<0.001
Age $\geq$ 65 (reference: age of 40-59)	1.685	1.240	2.006	<0.001	1.703	1.259	2.034	<0.001
CCI_R	1.286	1.032	1.537	0.029	1.335	1.050	1.682	0.007
HR= hazard ratio, CI = confidence interval, Adjusted HR: Adjusted variables listed in the table 1; CCI_R: Charlson Comorbidity Index, dementia and HIV removed								

Table 3. Factors of dementia subgroup and sensitivity test by using Cox regression									
	<i>Toxoplasmosis</i>	With	Without		Competing risk in the model				
Sensitivity test	Dementia subgroup	Events	Rate (per 10 ⁵ PYs)	Events	Rate (per 10 ⁵ PYs)	Adjusted HR	95% CI	95% CI	<i>P</i>
Overall	Overall	21	457.84	56	323.42	2.878	1.709	4.968	<0.001
	AD	1	21.80	1	5.78	6.675	3.157	11.241	<0.001
	VaD	1	21.80	9	51.98	0.956	0.312	1.478	0.570
	Other degenerative dementia	19	414.24	46	265.67	3.162	1.875	5.406	<0.001
In the first year excluded	Overall	15	352.13	47	277.21	2.538	1.345	4.497	<0.001
	AD	0	0	0	0	-	-	-	-
	VaD	0	0	7	41.29	0.000	-	-	0.976
	Other dementia	15	352.13	40	235.92	2.973	1.801	5.213	<0.001
In the first 5 years excluded	Overall	8	219.94	33	239.32	1.862	1.045	3.270	0.007
	AD	0	0	0	0	-	-	-	-
	VaD	0	0	4	29.01	0.000	-	-	0.983
	Other degenerative dementia	8	219.94	29	210.31	2.011	1.099	3.452	0.001
PYs = Person-years; Adjusted HR = Adjusted Hazard ratio: Adjusted for the variables listed in Table 3.; CI = confidence interval									

Table 4. Factors of dementia among different model by using Cox regression and Fine & Gray's competing risk model								
Antibiotics	<i>Toxoplasmosis</i> subgroup	Events	PYs	Rate (per 10 ⁵ PYs)	Competing risk in the model			
					Adjusted HR	95% CI	95% CI	<i>P</i>
Sulfadiazine	With <i>Toxoplasmosis</i> , without Sulfadiazine	5	1,015.10	492.56	Reference			
	With <i>Toxoplasmosis</i> , with Sulfadiazine	16	3,571.66	447.97	0.909	0.887	0.932	0.013
	With <i>Toxoplasmosis</i> , with Sulfadiazine <30 days	5	1,047.15	477.48	0.967	0.943	0.991	0.046
	With <i>Toxoplasmosis</i> , with Sulfadiazine 30-364 days	5	1,257.18	397.72	0.808	0.782	0.845	<0.001
	With <i>Toxoplasmosis</i> , with Sulfadiazine ≥365 days	6	1,267.33	473.44	0.932	0.901	0.986	0.041
Clindamycin	With <i>Toxoplasmosis</i> , without Clindamycin	5	879.28	568.65	Reference			
	With <i>Toxoplasmosis</i> , with Clindamycin	16	3,707.48	431.56	0.759	0.732	0.797	<0.001
	With <i>Toxoplasmosis</i> , with Clindamycin <30 days	5	1,048.48	476.88	0.832	0.784	0.863	<0.001
	With <i>Toxoplasmosis</i> , with Clindamycin 30-364 days	5	1,056.84	473.11	0.821	0.776	0.859	<0.001
	With <i>Toxoplasmosis</i> , with Clindamycin ≥365 days	6	1,602.17	374.49	0.664	0.602	0.692	<0.001
Sulfadiazine	With <i>Toxoplasmosis</i> , without antibiotics	1	198.15	504.67	Reference			
and / or	With <i>Toxoplasmosis</i> , with any of antibiotics	20	4,388.61	455.72	0.927	0.894	0.950	0.022
Clindamycin	With <i>Toxoplasmosis</i> , with any of antibiotics <30 days	5	1,030.45	485.22	0.970	0.942	0.995	0.047
	With <i>Toxoplasmosis</i> , with any of antibiotics 30-364 days	7	1,544.20	453.31	0.965	0.931	0.983	0.041

With <i>Toxoplasmosis</i> , with any of antibiotics ≥365 days	8	1,813.96	441.02	0.864	0.803	0.899	<0.001
With <i>Toxoplasmosis</i> , with both antibiotics	12	2,890.53	415.15	0.812	0.694	0.872	<0.001
With <i>Toxoplasmosis</i> , with both antibiotics <30 days	5	1,065.18	469.40	0.853	0.793	0.901	<0.001
With <i>Toxoplasmosis</i> , with both antibiotics 30- 364 days	3	769.82	389.70	0.750	0.615	0.830	<0.001
With <i>Toxoplasmosis</i> , with both antibiotics ≥365 days	4	1,055.54	378.95	0.721	0.594	0.825	<0.001
PYs = Person-years; Adjusted HR = Adjusted Hazard ratio: Adjusted for the variables listed in Table 1.; CI = confidence interval							

Figures

Figure 1

Toxoplasmosis tracking to dementia

Figure 2

Toxoplasmosis tracking to dementia

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [200215ToxoplasmosistrackingtodementiaFigS1.jpg](#)
- [Graphicabstract.jpg](#)
- [200220ToxoplasmosistrackingtodementiaFigS2.jpg](#)