BMJ Open

Dementia and vagotomy: A population-based cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019582
Article Type:	Research
Date Submitted by the Author:	12-Sep-2017
Complete List of Authors:	Lin, Shih-Yi ; China Medical University Hospital, Division of Nephrology and Kidney Institute Lin, Cheng-Li; China Medical University Hospital, Management Office for Health Data Wang, I-Kuan; China Medical University Hospital, Division of Nephrology and Kidney Institute Lin, Cheng-Chieh; China Medical University, School of Medicine Lin, Chih-Hsueh ; China Medical University Hospital, Department of Family Medicine Hsu, Wu-Huei; China Medical University Hospital, Department of Internal Medicine Kao, Chia-Hung; China Medical University, School of Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Neurology, Gastroenterology and hepatology, Surgery
Keywords:	Parkinson disease, Dementia < NEUROLOGY, Vagotomy, Cohort study

Dementia and vagotomy: A population-based cohort study

RUNNING TITLE: Dementia and Vagotomy

Shih-Yi Lin, MD

Cheng-Li Lin, MSc

I-Kuan Wang, MD

Cheng-Chieh Lin, MD

Chih-Hsueh Lin, MD

Wu-Huei Hsu, MD

Chia-Hung Kao, MD

Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, Taichung, Taiwan (S.-Y. L., I-K. W., C.-C. L., C.-H. L., W.-H. H., C.-H. K.); Division of Nephrology and Kidney Institute, China Medical University Hospital, Taichung, Taiwan (S.-Y. L., I-K. W.); Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan (C.-L. L.); College of Medicine, China Medical University, Taichung, Taiwan (C.-L. L.); Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan (C.-C. L., C.-H. L.); Division of Pulmonary and Critical Care Medicine, China Medical University

Hospital and China Medical University, Taichung, Taiwan (W.-H. H.); Department of Nuclear Medicine, China Medical University Hospital, Taichung, Taiwan (C.-H. K.); Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan (C.-H. K.).

Correspondence: Chia-Hung Kao, M.D., Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 40447, Taiwan. Tel.: +886-4-22052121 ext.7461, E-mail: d10040@mail.cmuh.org.tw

Author contributions:

Conceptualization: SYL, CHK

Methodology: CLL, CHK.

Software: CLL, CHK.

Validation: SYL, CLL, IKW, CCL, CHL, WHH, CHK

Formal analysis: SYL, CLL, IKW, CCL, CHL, WHH, CHK

Investigation: CLL, CHK.

Resources: CLL, CHK.

Data curation: SYL, CLL, IKW, CCL, CHL, WHH, CHK

Writing (original draft preparation): SYL, CLL, IKW, CCL, CHL, WHH, CHK

Writing (review and editing): SYL, CLL, IKW, CCL, CHL, WHH, CHK

Visualization: SYL, CLL, IKW, CCL, CHL, WHH, CHK

Supervision: CHK.

Project administration: CHK

Funding acquisition: CHK.

Acknowledgments:

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW106-TDU-B-212-113004), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10601010036), Taiwan Clinical Trial Consortium for Stroke (MOST 106-2321-B-039-005), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo AoshimaMemorial Funds, Japan. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

Conflict of Interest: The authors have no proprietary or commercial interest in any of

the materials discussed in this article.

List of abbreviations

PD: Parkinson disease; AD: Alzheimer disease; HRs: hazard ratios; CI: confidence interval; NHIRD: National Health Insurance Research Database; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

Word count: 237 words in abstract; 2026 words in text

Number of reference/tables/supplemental figure: 35/5/1

Abstract

Objective: Truncal vagotomy is associated with a decreased risk of subsequent Parkinson disease (PD), although the effect of vagotomy on dementia is unclear. In response, we investigated the risk of dementia in patients who underwent vagotomy.

Methods: A total of 3077 patients who underwent vagotomy (vagotomy cohort) and 3077 age-, sex-, and comorbidity-matched controls (nonvagotomy cohort) were identified between 2003 and 2011. All patient data were tracked until the diagnosis of cataracts, death, or the end of 2011. The cumulative incidence of subsequent PD and hazard ratios (HRs) were calculated.

Results: The mean ages of the study patients in the vagotomy and nonvagotomy cohorts were 61.3 ± 18.2 and 62.0 ± 17.1 years, respectively. The overall incidence density rate for dementia was similar in the vagotomy and nonvagotomy cohorts (9.52 and 10.2 per 100 person-y, respectively). After adjustment for age, sex, and comorbidities such as diabetes, hypertension, hyperlipidemia, stroke, depression, coronary artery disease, and PD, the patients in the vagotomy cohort were determined to not be at a higher risk of dementia than those in the nonvagatomy cohort [adjusted HR = 1.10, 95% confidence interval (CI) = 0.88–1.37]. Moreover, the patients who underwent truncal vagotomy were not at a significantly higher risk of dementia (adjusted HR = 1.07, 95% CI = 0.84–1.37) than were the patients who did not

undergo truncal vagotomy.

Conclusion: Vagotomy, either truncal or selective, does not reduce the risk of dementia.

Keywords: Parkinson disease; Dementia; Vagotomy; Cohort study

Strengths and limitations of this study

1. The strengths of our study are its population-based design, generalizability of findings with a very large sample size including study and control cohorts. All insurance claims should be scrutinized by medical reimbursement specialists and peer review.

2. Although we have considered the major surrogate variables, the information regarding individual-based risk factors for dementia, including smoking, genetic mutation, family history, vitamin D consumption, sleep patterns, caffeine use, and education level, were unavailable in this database.

Introduction

Dementia, a syndrome representing a cluster of disturbances in cognitive functioning, is currently the leading chronic cause of irreversible disability among elderly patients.[1] According to a World Health Organization estimate, more than 30 million people are living with dementia worldwide, and this number is expected to increase by more than three times by 2050.[2,3]

The most common causes of dementia are Alzheimer disease (AD), vascular dementia, Parkinson disease (PD), and neurodegenerative diseases; these conditions have different pathogeneses that lead to a decline in cognition.4 Because dementia is the end result of a complex process involving genetic defects,[5] hypoperfusion, oxidative stress,[6] mitochondrial dysfunction,[7] and protein deposition,[8] the etiology of dementia is multifactorial.

Typically, accumulation of fibrous amyloid-β (Aβ) plaques or protein fibrils of α-synuclein is the hallmark of AD, whereas aggregation of α-synuclein in the Lewy bodies is the hallmark of PD.[9,10] The levels of Aβ are associated with the severity of AD.[11] Bachhuber et al reported that α-synuclein is also associated with the inhibition of Aβ plaque formation; these findings suggest an overlap between the pathogeneses of AD and PD.[12]

In murine models, intragastric injection of rotenone-initiated α-synuclein can

reproduce the progression of PD pathology[13] and vagotomy can stop the spread of PD pathology.[14] Liu et al used a Swedish database to investigate the association between vagotomy and the risk of PD, and found that vagotomy was not associated with the risk of PD overall.[15] However, a study by Svensson et al, which was conducted using a database from Denmark, revealed an association between complete truncal vagotomy and a decreased risk for subsequent PD.[16] Thus, the association between vagotomy and PD remains inconclusive. The aforementioned observations also suggest that vagotomy may reduce the risk of other neurodegenerative diseases, such as AD. However, clinical evidence in the form of data supporting this hypothesis is not available. Because dementia is the most common clinical sign and the result of most neurodegenerative diseases, we used the National Health Insurance (NHI) registration database to determine the association between vagotomy and dementia risk.

Methods

Data Source

The Taiwan NHI program, launched in March 1995, currently covers more than 99% of the 23.72 million people in Taiwan.[17] The Longitudinal Health Insurance

Database (LHID) of 2000 (LHID2000) was used for this nationwide population-based retrospective cohort study. The details of the program and LHID have been dicussed in previous studies.[18,19] Diseases were coded according to the 2001 International Classification of Disease, Revision 9, Clinical Modification (ICD-9-CM). The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH104-REC2-115-CR2). The IRB also specifically waived the consent requirement.

Data Sharing Statement

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The Ministry of Health and Welfare must approve our application to access this data. Any researcher interested in accessing this dataset can submit an application form to the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848. All relevant data are within the paper.

Sampled Participants

Patients aged more than 20-years-old who had undergone vagotomy (ICD-9-OP codes 44.71–44.78, 44.11–44.16, 44.18–44.19, 44.51, and 44.53) formed the vagotomy cohort. The dates of the first hospitalization for vagotomy were defined as the index dates of the vagotomy patients. Patients with a history of dementia (ICD-9-CM codes 290, 294.1, and 331.0) before the index date were excluded.

Using the same exclusion criterion, we selected the nonvagotomy cohort from the LHID2000 by propensity score matching at a 1:1 ratio with the vagotomy patients.[20] The propensity scores were calculated using logistic regression to estimate the probability of the surgery status using baseline variables of sex; age; comorbidities such as diabetes, hypertension, hyperlipidemia, stroke, coronary artery disease (CAD), chronic kidney disease (CKD), liver disease, osteoarthritis, chronic obstructive pulmonary disease (COPD), depression, head injury, PD, cancer, or peptic ulcer disease (PUD); and medication with benzodiazepine (BZD)/zolpidem, anesthesia, or a proton-pump inhibitor (PPI). All of the study participants were followed up from the index date to the occurrence of dementia, withdrawal from the NHI program, or the end of 2011, whichever occurred first.

Statistical analysis

The frequency and percentage for categorical variables as well as the mean and

standard deviation (SD) for continuous variables were calculated for the vagotomy and nonvagotomy cohorts. The differences in distribution between the two cohorts were assessed using standardized mean differences. A standardized mean difference of ≤0.1 indicated a negligible difference between the two cohorts.[21] The follow-up time in person-years estimated the incidence density of dementia among different risk factors and incidence density stratified by age, sex, comorbidity, and follow-up period. Univariable and multivariable Cox proportional hazard regression models were used to examine the effects of vagotomy on the risk of dementia, expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The multivariable Cox models were adjusted for age; sex; comorbidities such as diabetes, hypertension, hyperlipidemia, stroke, CAD, CKD, osteoarthritis, COPD, depression, PD, and PUD; and BZD/zolpidem medication use. When the patients were stratified according to sex, age, comorbidity, and follow-up period, the relative risk of dementia in the vagotomy and nonvagotomy cohorts was also compared using Cox regression models. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and statistical significance was set $p < 0.05$.

Results

Table 1 lists the characteristics of the study cohort. We identified 2570 patients with vagotomy; hence, 2570 patients were recruited for the nonvagotomy cohort. Men accounted for approximately 63% of the patients in each cohort and most of the patients were aged ≥65 years (52.3% vs. 51.9%). Specifically, the mean age of the patients was 61.3 ±18.2 years for the vagotomy cohort and 62.0 ± 17.1 years for the nonvagotomy cohort. The major comorbidities in both cohorts were PUD (76.4% vs. 79.3%), hypertension (47.6% vs. 49.0%), and CAD (28.3% vs. 29.0%), and BZD/zolpidem (79.5% vs. 80.4%) was the major medication used by both cohorts. The mean follow-up periods were 5.80 ± 4.12 and 6.97 ± 3.24 years for the vagotomy and nonvagotomy cohorts, respectively. Figure 1 indicates that the cumulative incidence curve of dementia of the vagotomy cohort was not significantly higher than that of the nonvagotomy cohort (p = 0.52). The incidence of dementia was 9.52 and 10.2 per 1000 person-years in the vagotomy and nonvagotomy cohorts, respectively. After adjustment for age; sex; comorbidities such as diabetes, hypertension, hyperlipidemia, stroke, CAD, CKD, osteoarthritis, COPD, depression, PD, and PUD; and BZD/zolpidem medication use, the vagotomy cohort was associated with a 1.10-fold higher risk of cancer than was the nonvagotomy cohort (adjusted HR = 1.10, 95% CI = 0.88–1.37); however, this association was not significant. The risk of dementia in the patients who were ≥65 years old was 9.80-fold higher than in those

who were ≤64 years old (95% CI = 6.59–14.6). Furthermore, the multivariable models showed that dementia was independently associated with comorbidities, particularly stroke (adjusted HR = 2.26, 95% CI = 1.72, 2.97) and depression (adjusted HR = 1.59, 95% CI = 1.04, 2.43).

Table 3 compares the risk of dementia between the vagotomy and nonvagotomy cohorts and also presents the risk stratified by sex, age, comorbidity, and follow-up period. In all the stratifications, the risk of dementia in the vagotomy cohort was not significantly higher than that in the nonvagotomy cohort.

We further assessed the association between vagotomy and dementia risk stratified by sex and age (Table 4). Among the men, the effects of vagotomy on dementia risk decreased nonsignificantly with age (adjusted HR = 2.61, 95% CI = 0.76–8.94 for subgroup aged ≤64 years; adjusted HR = 1.00, 95% CI = 0.71–1.42 for subgroup aged ≥65 years).

Furthermore, the selective vagotomy patients exhibited a nonsignificantly higher risk of dementia than did the nonvagotomy patients (adjusted HR = 1.16, 95% CI = 0.82–1.65) (Table 5). Similarly, the truncal vagotomy patients were at a nonsignificantly higher risk of dementia than were the non-truncal-vagotomy patients.

Discussion

Vagotomy is the surgical resection of the vagus nerve, and it is performed to reduce acid secretion for managing complicated PUD.[22] Two surgical strategies of vagotomy are available: truncal vagotomy, in which the trunk of the vagus nerve is cut to innervate the abdomen, and selective vagotomy, in which the vagus nerve is resected to innervate the fundus and body of the stomach.[23] In addition to the regulation of acid secretion and enteric motility, recent studies have reported that the vagus nerve is associated with the transport of α-synuclein and progression of PD.[14,24] A nationwide population-based study by Svensson et al revealed that truncal vagotomy is associated with a decreased risk of subsequent PD.[16] However, Liu et al reported that neither truncal nor selective vagotomy is associated with a protective effect against PD.[17] Similar to the findings of Liu et al,[15] our study revealed that neither truncal nor selective vagotomy is associated with a lower risk of dementia.

Several explanations for these results are possible. First, dementia has several etiologies, including PD, AD, vascular dementia, and other neurodegenerative diseases. Braak et al proposed that the pathogenic process of PD originates when an environmental insult enters the body and is transmitted to the brain. Furthermore, the pathogenic process is mediated by the neurontransport of α-synuclein.[25] Sevenson et al reported that truncal vagotomy is associated with a decreased risk of PD,[16] which

thus supported the hypothesis of Braak et al.[25] A major component of Lewy bodies in PD, α-synuclein, was first isolated from plaques in the brains of patients with AD.[26] Although α-synuclein is associated with the development of PD and AD, the enteric route might be a spread source for neurodegenerative diseases.[27] Thus, vagotomy might not significantly reduce the risk of dementia.

Another possible explanation is the microbiome effect of vagotomy. In animal models of sepsis, the vagal nerve has been proposed to be involved in the regulation of inflammatory responses.[28] Li et al described a case of impaired intestinal microbiota barrier following vagotomy, and subsequent rescue after microbiota transplantation.[29] Recently, it has been recognized that the human microbiome of the gastrointestinal tract may affect the brain and behavior, an association that has been named the gut–brain axis.[30] The brains of patients with Parkinson-dementia and AD were found to have elevated levels of beta-N-methylamino-L-alanine.[31] Schwartz et al proposed that the host bacteria amyloid contribute to misfolding and amyloidegenic diseases such as AD.[32] Thus, vagotomy might alter the microbiome of the gastrointestinal tract. However, the negative effects of an altered microbiome following vagotomy may attenuate the possible positive effects discussed by Braak et al. The effect of vagotomy on neurological dysfunction therefore remains only vaguely defined.

This study has several limitations. First, we defined dementia as an outcome instead of a specific neurodegenerative disease. Dementia is the most common presentation of neurodegenerative diseases, including AD and PD. The diagnosis of AD is stricter than that of dementia and requires distinct clinical and laboratory features.[33] Thus, in this study, we used dementia as an outcome and adjusted cardiovascular-related comorbidities for vascular dementia to avoid the possible bias of underdiagnosis related to AD and other neurodegenerative diseases. Second, although we have considered the major surrogate variables, the information regarding individual-based risk factors for dementia, including smoking, genetic mutation, family history, vitamin D consumption, sleep patterns, caffeine use, and education level, were unavailable in this database. Third, the study has limited statistical power despite using a nationwide database because the follow-up period was only 10 years. Finally, most of the study population is Taiwanese, and caution is necessary when generalizing our results to other populations.

In conclusion, the current nationwide cohort study revealed that vagotomy, either truncal or selective,does not reduce the risk of dementia. This study also demonstrated that vagotomy is not associated with an increased risk of dementia, despite possible alteration of bowel motility and enteric microbiota in patients who receive this surgery. Although one previous study showed that truncal vagotomy reduces the risk of PD,[17]

our study offers preliminary evidence that the association between vagotomy and dementia is not direct.

Reference:

1 Wimo A, Jönsson L, Bond J, et al. The worldwide economic impact of dementia 2010. Alzheimers Dement. 2013;9:1-11.e3.

2 http://www.who.int/mental_health/publications/dementia_report_2012/en/.

3 Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement. 2013 ;9:63-75.e2.

4 Irvine GB, El-Agnaf OM, Shankar GM, Walsh DM. Protein aggregation in the brain: the molecular basis for Alzheimer's and Parkinson's diseases. Mol Med. 2008 ;14:451-64.

5 Spillantini MG, Murrell JR, Goedert M, Farlow MR, Klug A, Ghetti B. Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. Proc Natl Acad Sci U S A. 1998 ;95:7737-41.

6 Aliev G, Smith MA, Obrenovich ME, de la Torre JC, Perry G. Role of vascular hypoperfusion-induced oxidative stress and mitochondria failure in the pathogenesis of Azheimer disease. Neurotox Res. 2003;5:491-504.

7 Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 2006;443: 787-795.

8 Thal DR, Capetillo-Zarate E, Del Tredici K, Braak H. The development of

amyloid beta protein deposits in the aged brain. Sci Aging Knowledge Environ. 2006;2006:re1.

9 Kelly JW. Structural biology: proteins downhill all the way. Nature. 2006;442: 255-256.

10 Knowles TP, Vendruscolo M, Dobson CM. The amyloid state and its association with protein misfolding diseases. Nat Rev Mol Cell Biol. 2014 ;15:384-96.

11 McLean CA, Cherny RA, Fraser FW, et al. Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. Ann Neurol. 1999;46:860-6.

12 Bachhuber T, Katzmarski N, McCarter JF, et al. Inhibition of amyloid-β plaque formation by α-synuclein. Nat Med. 2015;21:802-7.

13 Pan-Montojo F, Anichtchik O, Dening Y, et al. Progression of Parkinson's disease pathology is reproduced by intragastric administration of rotenone in mice. PLoS One. 2010;5:e8762.

14 Pan-Montojo F, Schwarz M, Winkler C, et al. Environmental toxins trigger PD-like progression via increased alpha-synuclein release from enteric neurons in mice. Sci Rep. 2012;2:898.

15 Liu B, Fang F, Pedersen NL, et al. Vagotomy and Parkinson disease: A

Swedish register-based matched-cohort study. Neurology. 2017;88:1996-2002.

16 Svensson E, Horváth-Puhó E, Thomsen RW, et al. Vagotomy and subsequent risk of Parkinson's disease. Ann Neurol. 2015;78:522-9.

17 Database NHIR. Taiwan, http://nhird.nhri.org.tw/en/index.html (cited in 2015).

18 Lin SY, Hsu WH, Lin CC, Lin CL, Tsai CH, Kao CH. Effect of acute pancreatitis on the risk of developing osteoporosis: A nationwide cohort study. PLoS One. 2017;12:e0179358.

19 Kuan YC, Huang KW, Lin CL, Hu CJ, Kao CH. Effects of metformin exposure on neurodegenerative diseases in elderly patients with type 2 diabetes mellitus. Prog Neuropsychopharmacol Biol Psychiatry. 2017 ;79:77-83.

20 Parsons LS, Ovation Research Group, Seattle, Washingto. Performing a 1:N Case-Control Match on Propensity Score. SUGI. 2009;29: 165.

21 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28: 3083-3107.

22 Johnston D, Wilkinson AR. Highly selective vagotomy without a drainage procedure in the treatment of duodenal ulcer. Br J Surg. 1970;57:289-96.

23 Wilkinson AR, Johnston D. Effect of truncal, selective and highly selective vagotomy on gastric emptying and intestinal transit of a food-barium meal in man. Ann Surg. 1973;178:190-3.

24 Phillips RJ, Walter GC, Wilder SL, Baronowsky EA, Powley TL. Alpha-synuclein-immunopositive myenteric neurons and vagal preganglionic terminals: autonomic pathway implicated in Parkinson's disease? Neuroscience. 2008;153:733-50.

25 Braak H, Rüb U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm (Vienna). 2003 ;110:517-36.

26 Masliah E, Rockenstein E, Veinbergs I, et al. Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders. Science. 2000 ;287:1265-9.

27 Visanji NP, Brooks PL, Hazrati LN, Lang AE. The prion hypothesis in Parkinson's disease: Braak to the future. Acta Neuropathol Commun. 2013;1:2.

28 Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 2000;405:458-62.

29 Li Q, Wang C, Tang C, et al. Successful treatment of severe sepsis and diarrhea after vagotomy utilizing fecal microbiota transplantation: a case report. Crit Care. 2015;19:37.

30 Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012 ;13:701-12.

31 Brenner SR. Blue-green algae or cyanobacteria in the intestinal micro-flora may produce neurotoxins such as Beta-N-Methylamino-L-Alanine (BMAA) which may be related to development of amyotrophic lateral sclerosis, Alzheimer's disease and Parkinson-Dementia-Complex in humans and Equine Motor Neuron Disease in horses. Med Hypotheses. 2013;80:103.

32 Schwartz K, Boles BR. Microbial amyloids--functions and interactions within the host. Curr Opin Microbiol. 2013;16:93-9.

33 Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007 ;6:734-46.

Figure Legends:

Figure 1. Cumulative incidence of dementia in the vagotomy and nonvagotomy cohorts.

Table 1. Demographic characteristics and comorbidities in the vagotomy and nonvagotomy cohorts

	Vagotomy		Standard mean difference[§]
	No (N =2570)	Yes (N =2570)	
Sex			
Women	954(37.1)	961(37.4)	0.01
Men	1616(62.9)	1609(62.6)	0.01
Age stratified			
≤ 49	687(26.7)	678(26.4)	0.01
50-64	550(21.4)	549(21.4)	0.001
65+	1333(51.9)	1343(52.3)	0.01
Age, mean±SD [a]	62.0(17.1)	61.3(18.2)	0.04
Comorbidity			
Diabetes	347(13.5)	382(14.9)	0.04
Hypertension	1258(49.0)	1222(47.6)	0.03
Hyperlipidemia	546(21.3)	560(21.8)	0.01
Stroke	236(9.18)	253(9.84)	0.02
CAD	745(29.0)	726(28.3)	0.02
CKD	107(4.16)	117(4.55)	0.02
Liver disease	605(23.5)	580(22.6)	0.02
Osteoarthritis	661(25.7)	663(25.8)	0.002
COPD	577(22.5)	567(22.1)	0.01
Depression	127(4.94)	117(4.55)	0.02
Head injury	80(3.11)	75(2.92)	0.01
Parkinson's disease	46(1.79)	62(2.41)	0.04
Cancer	113(4.40)	126(4.90)	0.02
PUD	2039(79.3)	1963(76.4)	0.07
Medication			
BZD/ZOLPIDEM	2065(80.4)	2043(79.5)	0.02
Anaesthesia	511(19.9)	528(20.5)	0.02
PPI	553(21.5)	609(23.7)	0.05

[§]A standardized mean difference of ≤0.10 indicates a negligible difference between the two cohorts.

BZD, benzodiazepine; CAD, coronary artery disease; CKD, chronic kidney disease, PPI, proton-pump inhibitor

Table 2. Incidences of and risk factors for dementia

Variable	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[&] (95% CI)
Vagotomy					
No	182	17907	10.2	1.00	1.00
Yes	142	14915	9.52	0.93(0.75, 1.16)	1.10(0.88, 1.37)
Age group, year					
20−64	31	19254	1.61	1.00	1.00
≥ 65	293	13568	21.6	13.4(9.26, 19.5)***	9.80(6.59, 14.6)***
Sex					
Female	143	12707	11.3	1.26(1.01, 1.57)*	1.13(0.90, 1.42)
Male	181	20115	9.00	1.00	1.00
Comorbidity					
Diabetes					
No	258	29028	8.89	1.00	1.00
Yes	66	3794	17.4	1.92(1.47, 2.52)***	1.18(0.88,1 .58)
Hypertension					
No	87	18683	4.66	1.00	1.00
Yes	237	14139	16.8	3.57(2.79, 4.56)***	1.09(0.82, 1.46)
Hyperlipidemia					
No	224	25802	8.68	1.00	1.00
Yes	100	7020	14.2	1.64(1.29, 2.07)***	0.96(0.74, 1.25)
Stroke					
No	251	30861	8.13	1.00	1.00
Yes	73	1961	37.2	4.43(3.41, 5.76)***	2.26(1.72, 2.97)***
CAD					
No	169	24453	6.91	1.00	1.00
Yes	155	8368	18.5	2.65(2.13, 3.30)***	1.10(0.86, 1.40)
CKD					
No	299	31810	9.40	1.00	1.00
Yes	25	1013	24.7	2.55(1.69, 3.83)***	1.45(0.96, 2.20)
Liver disease					
No	257	25249	10.2	1.00	1.00
Yes	67	7574	8.85	0.87(0.66, 1.14)	-
Osteoarthritis					
No	183	25132	7.28	1.00	1.00
Yes	141	7690	18.3	2.50(2.00, 3.11)***	1.19(0.94, 1.51)
COPD					

No	210	26809	7.83	1.00	1.00
Yes	114	6013	19.0	2.38(1.89, 2.99)***	1.19(0.93, 1.52)
Depression					
No	300	31400	9.55	1.00	1.00
Yes	24	1422	16.9	1.76(1.16, 2.66)**	1.59(1.04, 2.43)*
Head injury					
No	311	31885	9.75	1.00	1.00
Yes	13	938	13.9	1.41(0.81, 2.46)	-
Parkinson's disease					
No	311	32351	9.61	1.00	1.00
Yes	13	471	27.6	2.78(1.60, 4.85)***	0.99(0.56, 1.75)
Cancer					
No	315	31973	9.85	1.00	1.00
Yes	9	849	10.6	1.04(0.54, 2.02)	-
PUD					
No	46	6124	7.51	1.00	1.00
Yes	278	26699	10.4	1.39(1.02, 1.90)*	1.18(0.85, 1.63)
Medication					
BZD/ZOLPIDEM					
No	37	7452	4.97	1.00	1.00
Yes	287	25370	11.3	2.25(1.60, 3.17)***	1.15(0.80, 1.65)
Anaesthesia					
No	269	27299	9.85	1.00	1.00
Yes	55	5524	9.96	1.00(0.74, 1.33)	-
PPI					
No	262	26369	9.94	1.00	1.00
Yes	62	6453	9.61	0.96(0.72, 1.26)	-

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PD, Parkinson disease; PUD, peptic ulcer disease; PY, person-years; PPI, proton-pump inhibitor

[#] Incidence rate per 1000 person-years

[&]Model was adjusted for age, sex, comorbidities, and benzodiazepine/zolpidem medication by using Cox proportional hazard regression

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 3. Incidence densities of dementia hazard ratios between the vagotomy and nonvagotomy cohorts based on demographic characteristics and comorbidities

	Vagotomy							
	No			Yes				
	Event	PY	Rate[#]	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[&] (95% CI)
Sex								
Women	75	6672	11.2	68	6035	11.3	1.00(0.72, 1.39)	1.14(0.81, 1.58)
Men	107	11235	9.52	74	8880	8.33	0.87(0.65, 1.17)	1.07(0.79, 1.45)
Stratify age								
≤ 64	14	10001	1.40	17	9254	1.84	1.28(0.63, 2.59)	0.97(0.47, 2.00)
≥ 65	168	7906	21.3	125	5661	22.1	1.03(0.82, 1.30)	1.01(0.80, 1.28)
Comorbidity[‡]								
No	3	1356	2.21	0	901	0.00	-	-
Yes	179	16551	10.8	142	14015	10.1	0.93(0.75, 1.16)	1.09(0.88, 1.37)
Follow-up period								
<4	107	9171	11.7	78	7454	10.5	0.89(0.66, 1.19)	1.03(0.76, 1.38)
4-8	51	6600	7.73	46	5331	8.63	1.11(0.75, 1.65)	1.31(0.87, 1.96)
≥8	24	2136	11.2	18	2130	8.45	0.77(0.42, 1.42)	0.92(0.49, 1.73)

Rate[#], incidence rate per 1000 person-years; crude HR, crude hazard ratio

Adjusted HR[&]: mutually adjusted for age, sex, comorbidities, and benzodiazepine/zolpidem medication use in the Cox proportional hazard regression

Comorbidity[‡]: Patients with any one of the listed comorbidities were classified as the comorbidity group

Table 4. Incidence and hazard ratios of dementia, stratified by age and sex, between the vagotomy and nonvagotomy cohorts

	Men						Women					
	Vagotomy						Vagotomy					
	No		Yes				No		Yes			
Variables	Event	Rate[#]	Event	Rate[#]	Crude HR (95% CI)	Adjusted HR[&] (95% CI)	Event	Rate[#]	Event	Rate[#]	Crude HR (95% CI)	Adjusted HR[&] (95% CI)
Age												
≤64	4	1.09	10	2.78	2.57(0.81,8.20)	2.61(0.76, 8.94)	10	1.58	7	1.24	0.74(0.28, 1.95)	0.56(0.19, 1.65)
≥ 65	71	23.7	58	23.7	0.99(0.70, 1.40)	1.00(0.71, 1.42)	97	19.8	67	20.8	1.05(0.77, 1.44)	1.02(0.74, 1.39)

Abbreviations: HR, hazard ratio; PY, person-years

Rate[#], incidence rate per 1000 person-years

Adjusted HR[&] multivariable analysis including age, sex, comorbidities, and benzodiazepine/zolpidem medication use in the Cox proportional hazard regression

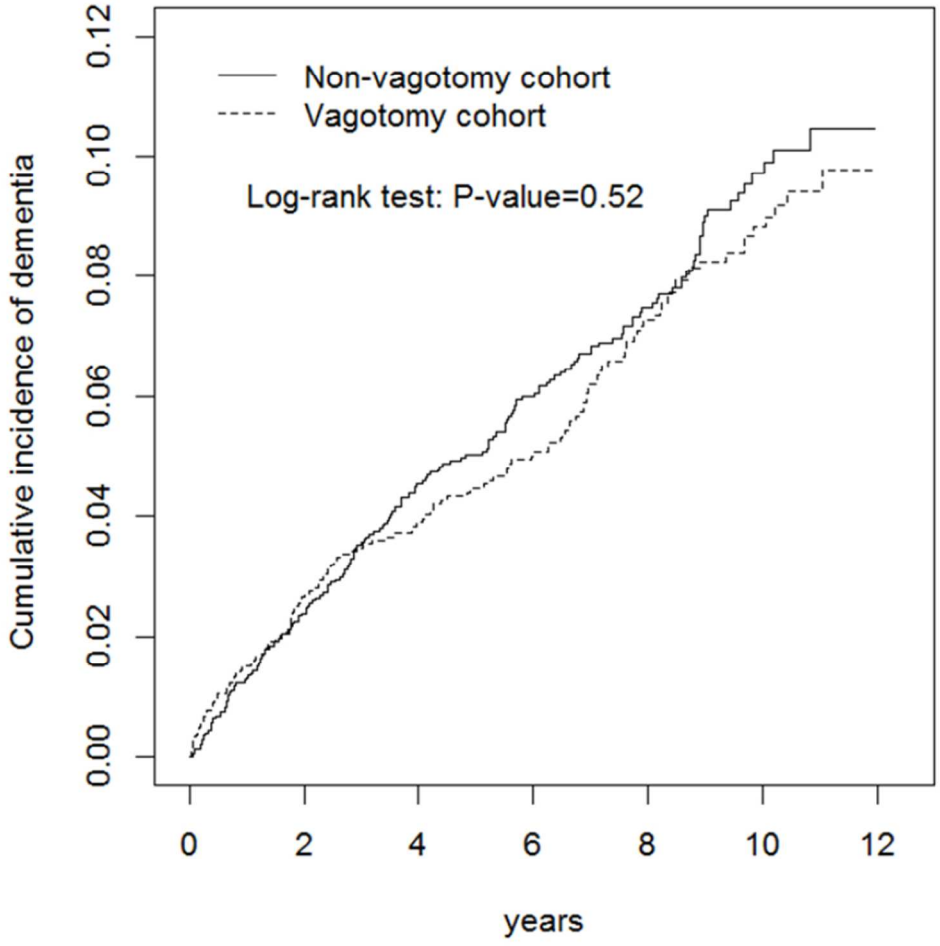
Table 5. Incidence and hazard ratios of dementia among the vagotomy and nonvagotomy cohorts

Variable	Event	PY	Rate[#]	cHR (95% CI)	aHR (95% CI)[a]
Control	182	17907	10.2	1(Reference)	1(Reference)
Vagotomy					
Truncal	104	12103	8.59	0.84(0.66, 1.07)	1.07(0.84, 1.37)
Selective	38	2812	13.5	1.30(0.92, 1.85)	1.16(0.82, 1.65)

Abbreviation: PY, person-years

Rate[#], incidence rate per 1000 person-years

Adjusted HR[&] multivariable analysis including age, sex, comorbidities, and benzodiazepine/zolpidem medication use in the Cox proportional hazard regression



78x76mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Included on page:
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,5,6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5,6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7,8
Objectives	3	State specific objectives, including any pre-specified hypotheses	7.8
Methods			
Study design	4	Present key elements of study design early in the paper	8-11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-11
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	8-11
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	8-11
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	8-11
		Case-control study—For matched studies, give matching criteria and the number of controls per case	8-11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-11
Bias	9	Describe any efforts to address potential sources of bias	8-11
Study size	10	Explain how the study size was arrived at	8-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-11
		(*b*) Describe any methods used to examine subgroups and interactions	8-11

		(*c*) Explain how missing data were addressed	8-11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	8-11
		Case-control study—If applicable, explain how matching of cases and controls was addressed	8-11
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	8-11
		(*e*) Describe any sensitivity analyses	8-11
Continued on next page			
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-13
		(b) Give reasons for non-participation at each stage	11-13
		(c) Consider use of a flow diagram	11-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-13
		(b) Indicate number of participants with missing data for each variable of interest	11-13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11-13
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11-13
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	11-13
		Cross-sectional study—Report numbers of outcome events or summary measures	11-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	11-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-17

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Dementia and vagotomy: A population-based cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019582.R1
Article Type:	Research
Date Submitted by the Author:	14-Dec-2017
Complete List of Authors:	Lin, Shih-Yi ; China Medical University Hospital, Division of Nephrology and Kidney Institute Lin, Cheng-Li; China Medical University Hospital, Management Office for Health Data Wang, I-Kuan; China Medical University Hospital, Division of Nephrology and Kidney Institute Lin, Cheng-Chieh; China Medical University, School of Medicine Lin, Chih-Hsueh ; China Medical University Hospital, Department of Family Medicine Hsu, Wu-Huei; China Medical University Hospital, Department of Internal Medicine Kao, Chia-Hung; China Medical University, School of Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Neurology, Gastroenterology and hepatology, Surgery
Keywords:	Parkinson disease, Dementia < NEUROLOGY, Vagotomy, Cohort study

Dementia and vagotomy: A population-based cohort study

RUNNING TITLE: Dementia and Vagotomy

Shih-Yi Lin[1,2], Cheng-Li Lin[3,4], I-Kuan Wang[1,2], Cheng-Chieh Lin[1,5], Chih-Hsueh Lin[1,5], Wu-Huei Hsu[1,6], Chia-Hung Kao[1,7,8]

[1]Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, Taichung, Taiwan

[2]Division of Nephrology and Kidney Institute, China Medical University Hospital, Taichung, Taiwan

[3]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan

[4]College of Medicine, China Medical University, Taichung, Taiwan

[5]Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan

[6]Division of Pulmonary and Critical Care Medicine, China Medical University Hospital and China Medical University, Taichung, Taiwan

[7]Department of Nuclear Medicine, China Medical University Hospital, Taichung, Taiwan

[8]Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan.

Correspondence: Chia-Hung Kao, M.D., Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 40447, Taiwan. Tel.: +886-4-22052121 ext.7461, E-mail: d10040@mail.cmuh.org.tw

Author contributions:

Conceptualization: SYL, CHK

Methodology: CLL, CHK.

Software: CLL, CHK.

Validation: SYL, CLL, IKW, CCL, CHL, WHH, CHK

Formal analysis: SYL, CLL, IKW, CCL, CHL, WHH, CHK

Investigation: CLL, CHK.

Resources: CLL, CHK.

Data curation: SYL, CLL, IKW, CCL, CHL, WHH, CHK

Writing (original draft preparation): SYL, CLL, IKW, CCL, CHL, WHH, CHK

Writing (review and editing): SYL, CLL, IKW, CCL, CHL, WHH, CHK

Visualization: SYL, CLL, IKW, CCL, CHL, WHH, CHK

Supervision: CHK.

Project administration: CHK

Funding acquisition: CHK.

Funding Statement:

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW106-TDU-B-212-113004), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10601010036), Taiwan Clinical Trial Consortium for Stroke (MOST 106-2321-B-039-005), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo AoshimaMemorial Funds, Japan. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

Conflict of Interest: The authors have no proprietary or commercial interest in any of the materials discussed in this article.

List of abbreviations

PD: Parkinson disease; AD: Alzheimer disease; HRs: hazard ratios; CI: confidence interval; NHIRD: National Health Insurance Research Database; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

Abstract

Objective: Truncal vagotomy is associated with a decreased risk of subsequent Parkinson disease (PD), although the effect of vagotomy on dementia is unclear. In response, we investigated the risk of dementia in patients who underwent vagotomy.

Setting: Population-based cohort study

Participants: A total of 155,944 patients who underwent vagotomy (vagotomy cohort) and 155,944 age-, sex-, and comorbidity-matched controls (nonvagotomy cohort) were identified between 2000 and 2011.

Primary and secondary outcome measures: All patient data were tracked until the diagnosis of dementia, death, or the end of 2011. The cumulative incidence of subsequent dementia and hazard ratios (HRs) were calculated.

Results: The mean ages of the study patients in the vagotomy and nonvagotomy cohorts were 56.6±17.4 and 56.7±17.3 years, respectively. The overall incidence density rate for dementia was similar in the vagotomy and nonvagotomy cohorts (2.43 and 2.84 per 1000 person-years, respectively). After adjustment for age, sex, and comorbidities such as diabetes, hypertension, hyperlipidemia, stroke, depression, coronary artery disease, and PD, the patients in the vagotomy cohort were determined to not be at a higher risk of dementia than those in the nonvagatomy cohort [adjusted HR = 1.09, 95% confidence interval (CI) = 0.87–1.36]. Moreover, the patients who

underwent truncal vagotomy were not associated with risk of dementia (adjusted HR = 1.04, 95% CI = 0.87–1.25), compared with the patients who did not undergo vagotomy.

Conclusion: Vagotomy, either truncal or selective, is not associated with risk of dementia.

Keywords: Parkinson disease; Dementia; Vagotomy; Cohort study

Strengths and limitations of this study

1. The strengths of our study are its population-based design, generalizability of findings with a very large sample size including study and control cohorts. All insurance claims should be scrutinized by medical reimbursement specialists and peer review.

2. Although we have considered the major surrogate variables, the information regarding individual-based risk factors for dementia, including smoking, genetic mutation, family history, vitamin D consumption, sleep patterns, caffeine use, and education level, were unavailable in this database.

Introduction

Dementia, a syndrome representing a cluster of disturbances in cognitive functioning, is currently the leading chronic cause of irreversible disability among elderly patients [1]. According to a World Health Organization estimate, more than 30 million people are living with dementia worldwide, and this number is expected to increase by more than three times by 2050 [2,3].

The most common causes of dementia are Alzheimer disease (AD), vascular dementia, Parkinson disease (PD), and neurodegenerative diseases; these conditions have different pathogeneses that lead to a decline in cognition [4]. Because dementia is the end result of a complex process involving genetic defects [5], hypoperfusion, oxidative stress [6], mitochondrial dysfunction [7], and protein deposition [8], the etiology of dementia is multifactorial.

Typically, accumulation of fibrous amyloid-β (Aβ) plaques or protein fibrils of α-synuclein is the hallmark of AD, whereas aggregation of α-synuclein in the Lewy bodies is the hallmark of PD [9,10]. The levels of Aβ are associated with the severity of AD [11]. Bachhuber et al reported that α-synuclein is also associated with the inhibition of Aβ plaque formation; these findings suggest an overlap between the pathogeneses of AD and PD [12].

In murine models, intragastric injection of rotenone-initiated α-synuclein can

reproduce the progression of PD pathology [13] and vagotomy can stop the spread of PD pathology [14]. Vagotomy is the surgical resection of the vagus nerve, and it is performed to reduce acid secretion for managing complicated PUD [15]. Two surgical strategies of vagotomy are available: truncal vagotomy, in which the trunk of the vagus nerve is cut to innervate the abdomen, and selective vagotomy, in which the vagus nerve is resected to innervate the fundus and body of the stomach [16]. Liu et al used a Swedish database to investigate the association between vagotomy and the risk of PD, and found that vagotomy was not associated with the risk of PD overall [17]. However, a study by Svensson et al, which was conducted using a database from Denmark, revealed an association between complete truncal vagotomy and a decreased risk for subsequent PD [18]. Thus, the association between vagotomy and PD remains inconclusive. The aforementioned observations also suggest that vagotomy may reduce the risk of other neurodegenerative diseases, such as AD. However, clinical evidence in the form of data supporting this hypothesis is not available. Because dementia is the most common clinical sign and the result of most neurodegenerative diseases, we used the National Health Insurance (NHI) registration database to determine the association between vagotomy and dementia risk.

Methods

Data Source

The Taiwan NHI program, launched in March 1995, currently covers more than 99% of the 23.72 million people in Taiwan [19]. The inpatient database was used for this nationwide population-based retrospective cohort study. The details of the program and inpatient databases have been dicussed in previous studies [20,21].

Diseases were coded according to the 2001 International Classification of Disease, Revision 9, Clinical Modification (ICD-9-CM). The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH104-REC2-115-CR2). The Institutional Review Board (IRB) also specifically waived the consent requirement.

Data Sharing Statement

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The Ministry of Health and Welfare must approve our application to access this data. Any researcher interested in accessing this dataset can submit an application form to the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd.,

Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848. All relevant data are within the paper.

Sampled Participants

Patients aged more than 20-years-old who had undergone vagotomy (ICD-9-OP codes 44.0) formed the vagotomy cohort. The dates of the first hospitalization for vagotomy were defined as the index dates of the vagotomy patients. Patients with a history of dementia (ICD-9-CM codes 290, 294.1, and 331.0) before the index date were excluded.

Using the same exclusion criterion, we selected the nonvagotomy cohort by propensity score matching at a 1:1 ratio with the vagotomy patients [22]. The date of enrollment in non-vagotomy cohort was matched with the same year and month of the vagotomy cohort, by the random assignment method. The propensity scores were calculated using logistic regression to estimate the probability of the surgery status using baseline variables of sex; age; comorbidities such as diabetes, hypertension, hyperlipidemia, stroke, coronary artery disease (CAD), chronic kidney disease (CKD), liver disease, osteoarthritis, chronic obstructive pulmonary disease (COPD), depression, head injury, PD, cancer, or peptic ulcer disease (PUD). The samples were matched with sex, age, comorbidities, and index year to reduce confounding effects of

sex, age, and comorbidities, and to have a valid measure of follow up person-years. All of the study participants were followed up from the index date to the occurrence of dementia, withdrawal from the NHI program, or the end of 2011, whichever occurred first.

Statistical analysis

The frequency and percentage for categorical variables as well as the mean and standard deviation (SD) for continuous variables were calculated for the vagotomy and nonvagotomy cohorts. The differences in distribution between the two cohorts were assessed using standardized mean differences. A standardized mean difference of ≤0.1 indicated a negligible difference between the two cohorts [23]. The follow-up time in person-years estimated the incidence density of dementia among different risk factors and incidence density stratified by age, sex, comorbidity, and follow-up period. To address the concern of constant proportionality, we examined the proportional hazard model assumption using a test of scaled Schoenfeld residuals. Results showed that there was no significant relationship between Schoenfeld residuals for vagotomy and follow-up time (p-value = 0.07) in the model evaluating the dementia risk. Cox proportional hazards models stratifying on the matched pairs were performed to estimate the hazard ratio (HR) and 95% confidence intervals (CI) of developing

dementia associated with vagotomy cohort, compared with non-vagotomy cohort. When the patients were stratified according to sex, age, comorbidity, and follow-up period (using the first quartile and second quartile as a cut off), the relative risk of dementia in the vagotomy and nonvagotomy cohorts was also compared using Cox regression models. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and statistical significance was set $p < 0.05$.

Results

Table 1 lists the characteristics of the study cohort. We identified 155944 patients with vagotomy; hence, 155944 patients were recruited for the nonvagotomy cohort. Men accounted for approximately 79% of the patients in each cohort and most of the patients were aged ≥50 years (61.7% vs. 61.7%). Specifically, the mean age of the patients was 56.6 ±17.4 years for the vagotomy cohort and 56.7 ± 17.3 years for the nonvagotomy cohort. The major comorbidities in both cohorts were PUD (96.2% vs. 96.2%), hypertension (21.1% vs. 21.1%), and diabetes (15.2% vs. 15.1%). The mean follow-up periods were 5.88 ± 3.80 and 6.58 ± 3.35 years for the vagotomy and nonvagotomy cohorts, respectively. The incidence of dementia was 2.43 and 2.84 per 1000 person-years in the vagotomy and nonvagotomy cohorts, respectively. The

vagotomy cohort was not associated with dementia compared with the nonvagotomy cohort (HR = 1.09, 95% CI = 0.87–1.36). The risk of dementia in the patients who were ≥65 years old was 74.4-fold higher than in those who were ≤49 years old (95% CI = 36.8–150.5). Furthermore, the multivariable models showed that dementia was independently associated with comorbidities, particularly stroke (HR = 1.84, 95% CI = 1.47, 2.29), head injury (HR = 1.66, 95% CI = 1.23, 2.24), and Parkinson's disease (HR = 2.00, 95% CI = 1.19, 3.38) (Table 2).

Table 3 compares the risk of dementia between the vagotomy and nonvagotomy cohorts and also presents the risk stratified by sex, age, comorbidity, and follow-up period. Female vagotomy patients had a 1.56-fold higher risk of dementia than female patients from the non-vagotomy cohort did (HR = 1.56, 95% CI = 1.00–2.44). When compared with the non-vagotomy patients, the vagotomy patients had higher risk of dementia in those aged ≤64 years (HR = 2.07, 95% CI = 1.12-3.83).

We further assessed the association between vagotomy and dementia risk stratified by sex and age (Table 4). Among the men, the effects of vagotomy on dementia risk was not associated with age (HR = 1.77, 95% CI = 0.90–3.49 for subgroup aged ≤64 years; HR = 0.85, 95% CI = 0.64–1.14 for subgroup aged ≥65 years).

Furthermore, the truncal vagotomy patients exhibited no association with risk of

dementia, compared with the nonvagotomy patients (HR = 1.05, 95% CI = 0.87–1.25) (Table 5). Similarly, compared with non-vagotomy cohort, the types of vagotomy, including trunk, highly selective, and other selective vagotomy were not associated with risk of dementia. (Table 5) Figure 1 shows the cumulative incidence for vagotomy group compared with non-vagotomy cohort. (log-rank test p =0.08)

Discussion

Vagotomy, in addition to the regulation of acid secretion and enteric motility, recent studies have reported that the vagus nerve is associated with the transport of α-synuclein and progression of PD [14,24]. A nationwide population-based study by Svensson et al revealed that truncal vagotomy is associated with a decreased risk of subsequent PD [16]. However, Liu et al reported that neither truncal nor selective vagotomy is associated with a protective effect against PD [17]. Similar to the findings of Liu et al [15], our study revealed that vagotomy is not associated with overall risk of dementia. However, vagotomy, in those women or patients aged ≤ 64 years-old, is associated with higher risk of dementia.

Several explanations for these results are possible. First, dementia has several etiologies, including PD, AD, vascular dementia, and other neurodegenerative

diseases. Braak et al proposed that the pathogenic process of PD originates when an environmental insult enters the body and is transmitted to the brain. Furthermore, the pathogenic process is mediated by the neurontransport of α-synuclein [25]. Sevenson et al reported that truncal vagotomy is associated with a decreased risk of PD [16], which thus supported the hypothesis of Braak et al [25]. A major component of Lewy bodies in PD, α-synuclein, was first isolated from plaques in the brains of patients with AD [26]. Although α-synuclein is associated with the development of PD and AD, the enteric route might be a spread source for neurodegenerative diseases [27]. Thus, vagotomy might not correlate directly with the risk of dementia.

Another possible explanation is the microbiome effect of vagotomy. In animal models of sepsis, the vagal nerve has been proposed to be involved in the regulation of inflammatory responses [28]. Li et al described a case of impaired intestinal microbiota barrier following vagotomy, and subsequent rescue after microbiota transplantation [29]. Recently, it has been recognized that the human microbiome of the gastrointestinal tract may affect the brain and behavior, an association that has been named the gut–brain axis [30]. The brains of patients with Parkinson-dementia and AD were found to have elevated levels of beta-N-methylamino-L-alanine [31]. Schwartz et al proposed that the host bacteria amyloid contribute to misfolding and amyloidegenic diseases such as AD [32]. Thus, vagotomy might alter the microbiome

of the gastrointestinal tract. However, the negative effects of an altered microbiome following vagotomy may attenuate the possible positive effects discussed by Braak et al. The effect of vagotomy on neurological dysfunction therefore remains only vaguely defined. One interesting finding of this study is that vagotomy, in those women or patients aged ≤ 64 years-old, is associated with higher risk of dementia. Further studies needed to be carried out to clarify whether and why vagotomy had harm effects on the risk of dementia in women and aged ≤ 64 years-old.

This study has several limitations. First, we defined dementia as an outcome instead of a specific neurodegenerative disease. Dementia is the most common presentation of neurodegenerative diseases, including AD and PD. The diagnosis of AD is stricter than that of dementia and requires distinct clinical and laboratory features [33]. Thus, in this study, we used dementia as an outcome and adjusted cardiovascular-related comorbidities for vascular dementia to avoid the possible bias of underdiagnosis related to AD and other neurodegenerative diseases. Since the discrimination and validity of dementia had been difficult especially in such coding-based study, we did not analyze the association between vagotomy and subtypes of dementia. Second, although we have considered the major surrogate variables, the information regarding individual-based risk factors for dementia, including smoking, genetic mutation, family history, vitamin D consumption, sleep

patterns, caffeine use, and education level, were unavailable in this database. Further, the vagotomy cohort might have more medical visits and more chances to be diagnosed with dementia, possible surveillance and detection bias should be mentioned here. Finally, the follow up period of this study is relatively short. Since our data showed that vagotomy had no association with dementia before 7 years, but maybe provide protection for dementia after 7 years, it would be possible that vagotmy might be protective for dementia once the follow up duration is longer. Further, the number of dementia events are small in this study, thus the conclusion and presumption would not be precise and valid. Longitudinal cohort studies of longer follow up duration are necessary to clarify the possible protective role of vagotomy for dementia.

In conclusion, the current nationwide cohort study revealed that vagotomy, either truncal or selective, was not associated risk of dementia. Although one previous study showed that truncal vagotomy reduces the risk of PD [17], our study offers preliminary evidence that the association between vagotomy and dementia is not direct.

Reference:

1 Wimo A1, Jönsson L, Bond J, Prince M, Winblad B; Alzheimer Disease International. The worldwide economic impact of dementia 2010. Alzheimers Dement. 2013;9:1-11.e3.

2 http://www.who.int/mental_health/publications/dementia_report_2012/en/.

3 Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement. 2013 ;9:63-75.e2.

4 Irvine GB, El-Agnaf OM, Shankar GM, Walsh DM. Protein aggregation in the brain: the molecular basis for Alzheimer's and Parkinson's diseases. Mol Med. 2008 ;14:451-64.

5 Spillantini MG, Murrell JR, Goedert M, Farlow MR, Klug A, Ghetti B. Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. Proc Natl Acad Sci U S A. 1998 ;95:7737-41.

6 Aliev G, Smith MA, Obrenovich ME, de la Torre JC, Perry G. Role of vascular hypoperfusion-induced oxidative stress and mitochondria failure in the pathogenesis of Azheimer disease. Neurotox Res. 2003;5:491-504.

7 Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 2006;443: 787-795.

8 Thal DR, Capetillo-Zarate E, Del Tredici K, Braak H. The development of amyloid beta protein deposits in the aged brain. Sci Aging Knowledge Environ. 2006;2006:re1.

9 Kelly JW. Structural biology: proteins downhill all the way. Nature. 2006;442: 255-256.

10 Knowles TP, Vendruscolo M, Dobson CM. The amyloid state and its association with protein misfolding diseases. Nat Rev Mol Cell Biol. 2014 ;15:384-96.

11 McLean CA, Cherny RA, Fraser FW, Fuller SJ, Smith MJ, Beyreuther K, et al. Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. Ann Neurol. 1999;46:860-6.

12 Bachhuber T, Katzmarski N, McCarter JF, Loreth D, Tahirovic S, Kamp F, et al. Inhibition of amyloid-β plaque formation by α-synuclein. Nat Med. 2015;21:802-7.

13 Pan-Montojo F, Anichtchik O, Dening Y, Knels L, Pursche S, Jung R, et al. Progression of Parkinson's disease pathology is reproduced by intragastric administration of rotenone in mice. PLoS One. 2010;5:e8762.

14 Pan-Montojo F, Schwarz M, Winkler C, Arnhold M, O'Sullivan GA, Pal A, et al. Environmental toxins trigger PD-like progression via increased

alpha-synuclein release from enteric neurons in mice. Sci Rep. 2012;2:898.

15 Johnston D, Wilkinson AR. Highly selective vagotomy without a drainage procedure in the treatment of duodenal ulcer. Br J Surg. 1970;57:289-96.

16 Wilkinson AR, Johnston D. Effect of truncal, selective and highly selective vagotomy on gastric emptying and intestinal transit of a food-barium meal in man. Ann Surg. 1973;178:190-3.

17 Liu B, Fang F, Pedersen NL, Tillander A, Ludvigsson JF, Ekbom A, et al. Vagotomy and Parkinson disease: A Swedish register-based matched-cohort study. Neurology. 2017;88:1996-2002.

18 Svensson E, Horváth-Puhó E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, et al. Vagotomy and subsequent risk of Parkinson's disease. Ann Neurol. 2015;78:522-9.

19 Database NHIR. Taiwan, http://nhird.nhri.org.tw/en/index.html (cited in 2015).

20 Peng YC, Lin CL, Yeh HZ, Tung CF, Chang CS, Kao CH. Diverticular disease and additional comorbidities associated with increased risk of dementia. J Gastroenterol Hepatol. 2016;31:1816-1822.

21 Chen YT, Su JS, Tseng CW, Chen CC, Lin CL, Kao CH. Inflammatory bowel disease on the risk of acute pancreatitis: A population-based cohort study. J

Gastroenterol Hepatol. 2016;31:782-7.

22 Parsons LS, Ovation Research Group, Seattle, Washingto. Performing a 1:N Case-Control Match on Propensity Score. SUGI. 2009;29: 165.

23 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28: 3083-3107.

24 Phillips RJ, Walter GC, Wilder SL, Baronowsky EA, Powley TL. Alpha-synuclein-immunopositive myenteric neurons and vagal preganglionic terminals: autonomic pathway implicated in Parkinson's disease? Neuroscience. 2008;153:733-50.

25 Braak H, Rüb U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm (Vienna). 2003 ;110:517-36.

26 Masliah E, Rockenstein E, Veinbergs I, Mallory M, Hashimoto M, Takeda A, et al. Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders. Science. 2000 ;287:1265-9.

27 Visanji NP, Brooks PL, Hazrati LN, Lang AE. The prion hypothesis in Parkinson's disease: Braak to the future. Acta Neuropathol Commun.

2013;1:2.

28 Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 2000;405:458-62.

29 Li Q, Wang C, Tang C, He Q, Zhao X, Li N, et al. Successful treatment of severe sepsis and diarrhea after vagotomy utilizing fecal microbiota transplantation: a case report. Crit Care. 2015;19:37.

30 Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012 ;13:701-12.

31 Brenner SR. Blue-green algae or cyanobacteria in the intestinal micro-flora may produce neurotoxins such as Beta-N-Methylamino-L-Alanine (BMAA) which may be related to development of amyotrophic lateral sclerosis, Alzheimer's disease and Parkinson-Dementia-Complex in humans and Equine Motor Neuron Disease in horses. Med Hypotheses. 2013;80:103.

32 Schwartz K, Boles BR. Microbial amyloids--functions and interactions within the host. Curr Opin Microbiol. 2013;16:93-9.

33 Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007 ;6:734-46.

Figure Legends:

Figure 1. Cumulative incidence of dementia in the vagotomy and nonvagotomy cohorts.

Table 1. Demographic characteristics and comorbidities in the vagotomy and nonvagotomy cohorts

	Vagotomy		Standard mean difference[§]
	No (N =155944)	Yes (N =155944)	
Sex			
Women	3409(21.4)	3397(21.3)	0.002
Men	12535(78.6)	12547(78.7)	0.002
Age stratified			
≤ 49	6115(38.4)	6114(38.4)	0.000
50-64	3938(24.7)	3939(24.7)	0.000
65+	5891(37.0)	5891(37.0)	0.000
Age, mean±SD [a]	56.7±17.3	56.6±17.4	0.01
Comorbidity			
Diabetes	2399(15.1)	2421(15.2)	0.004
Hypertension	3359(21.1)	3360(21.1)	0.000
Hyperlipidemia	584(3.66)	613(3.84)	0.01
Stroke	1334(8.37)	1340(8.40)	0.001
CAD	1379(8.65)	1381(8.66)	0.000
CKD	613(3.84)	632(3.96)	0.01
Liver disease	1834(11.5)	1846(11.6)	0.002
Osteoarthritis	498(3.12)	521(3.27)	0.01
COPD	158(0.99)	153(0.96)	0.003
Depression	191(1.20)	190(1.19)	0.001
Head injury	976(6.12)	994(6.23)	0.01
Parkinson's disease	117(0.73)	108(0.68)	0.01
Cancer	597(3.74)	619(3.88)	0.01
PUD	15343(96.2)	15343(96.2)	0.000

[§]A standardized mean difference of ≤0.10 indicates a negligible difference between the two cohorts.

CAD, coronary artery disease; CKD, chronic kidney disease

Table 2. Incidences of and risk factors for dementia

Variable	Event	PY	Rate[#]	HR(95% CI)
Vagotomy				
No	298	104932	2.84	1.00
Yes	228	93707	2.43	1.09(0.87, 1.36)
Age group, year				
≤ 49	8	91483	0.09	1.00
50-64	51	51513	0.99	10.3(4.86, 21.6)***
65+	467	55643	8.39	74.4(36.8, 150.5)***
Sex				
Female	143	39468	3.62	1.00(0.06, 16.0)
Male	383	159171	2.41	1.00
Comorbidity				
Diabetes				
No	405	177247	2.28	1.00
Yes	121	21391	5.66	1.01(0.82, 1.25)
Hypertension				
No	289	169471	1.71	1.00
Yes	237	29168	8.13	1.44(1.18, 1.75)***
Hyperlipidemia				
No	497	193049	2.57	1.00
Yes	29	5590	5.19	3.00(0.31, 28.8)
Stroke				
No	400	188269	2.12	1.00
Yes	126	10370	12.2	1.84(1.47, 2.29)***
CAD				
No	416	187358	2.22	1.00
Yes	110	11281	9.75	2.00(0.18, 22.1)
CKD				
No	494	194635	2.54	1.00
Yes	32	4004	7.99	1.33(0.93, 1.92)
Liver disease				
No	442	180865	2.44	1.00
Yes	84	17774	4.73	1.20(0.95, 1.52)
Osteoarthritis				
No	502	194322	2.58	1.00
Yes	24	4317	5.56	0.76(0.50, 1.15)
COPD				

No	513	197076	2.60	1.00
Yes	13	1562	8.32	1.67(0.96, 2.90)
Depression				
No	420	196769	2.64	1.00
Yes	6	1869	3.21	1.03(0.46, 2.32)
Head injury				
No	478	188290	2.54	1.00
Yes	48	10349	4.64	1.66(1.23, 2.24)***
Parkinson's disease				
No	511	197771	2.58	1.00
Yes	15	868	17.3	2.00(1.19, 3.38)**
Cancer				
No	516	194585	2.65	1.00
Yes	10	4054	2.47	0.52(0.05, 5.51)
PUD				
No	10	6542	1.53	1.00
Yes	516	192096	2.69	2.11(1.13, 3.95)*

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PD, Parkinson disease; PUD, peptic ulcer disease; PY, person-years;

[#] Incidence rate per 1000 person-years

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 3. Incidence densities of dementia hazard ratios between the vagotomy and nonvagotomy cohorts based on demographic characteristics and comorbidities

	Vagotomy						
	No			Yes			
	Event	PY	Rate[#]	Event	PY	Rate[#]	HR (95% CI)
Sex							
Women	77	21364	3.60	66	18104	3.65	1.56(1.00, 2.44)*
Men	221	83568	2.64	162	75603	2.14	0.96(0.74, 1.24)
Stratify age							
≤ 64	24	73656	0.33	35	69339	0.50	2.07(1.12, 3.83)*
≥ 65	274	31275	8.76	193	24367	7.92	0.97(0.76, 1.24)
Comorbidity[‡]							
No	1	2156	0.46	1	1493	0.67	-
Yes	297	102776	2.89	227	92214	2.46	1.08(0.86, 1.35)
Follow-up period							
<4	131	43502	3.01	116	38634	3.00	1.24(0.94, 1.63)
4-7	119	34038	3.50	87	30274	2.87	0.91(0.59, 1.40)
≥7	48	19534	2.46	25	17780	1.41	0.50(0.17, 1.46)

Rate[#], incidence rate per 1000 person-years; HR, hazard ratio

Comorbidity[‡]: Patients with any one of the listed comorbidities were classified as the comorbidity group

Table 4. Incidence and hazard ratios of dementia, stratified by age and sex, between the vagotomy and nonvagotomy cohorts

	Men					Women				
	Vagotomy					Vagotomy				
	No		Yes			No		Yes		
Variables	Event	Rate#	Event	Rate#	HR(95% CI)	Event	Rate#	Event	Rate#	HR(95% CI)
Age										
≤64	19	0.31	27	0.46	1.77(0.90, 3.49)	5	0.42	8	0.73	4.00(0.85, 18.8)
≥ 65	202	9.23	135	7.87	0.85(0.64, 1.14)	72	7.68	58	8.05	1.40(0.88, 2.24)

Abbreviations: HR, hazard ratio; PY, person-years

Rate#, incidence rate per 1000 person-years

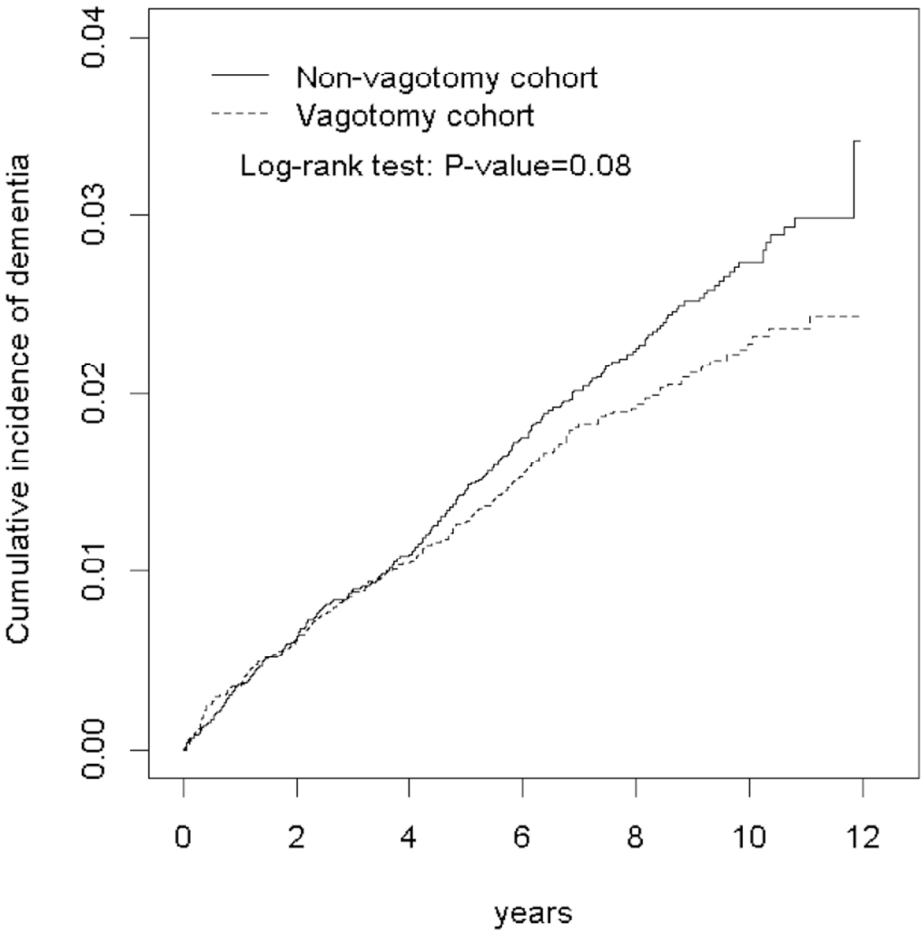
Adjusted HR& multivariable analysis including age, sex, comorbidities, and benzodiazepine/zolpidem medication use in the Cox proportional hazard regression

Table 5. Incidence and hazard ratios of dementia among the vagotomy and nonvagotomy cohorts

Variable	N	Event	PY	Rate[#]	HR (95% CI)
Control	15944	298	104932	2.84	1(Reference)
Vagotomy					
Truncal vagotomy	12999	192	77219	2.49	1.04(0.87, 1.25)
Highly selective	1035	8	6141	1.30	0.84(0.42,1 .69)
Other selective vagotomy	101	1	529	1.89	0.80(0.11, 5.73)

Abbreviation: PY, person-years

Rate[#], incidence rate per 1000 person-years



78x76mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Included on page:
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,5,6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5,6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7,8
Objectives	3	State specific objectives, including any pre-specified hypotheses	7.8
Methods			
Study design	4	Present key elements of study design early in the paper	8-11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-11
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	8-11
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	8-11
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	8-11
		Case-control study—For matched studies, give matching criteria and the number of controls per case	8-11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-11
Bias	9	Describe any efforts to address potential sources of bias	8-11
Study size	10	Explain how the study size was arrived at	8-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-11
		(*b*) Describe any methods used to examine subgroups and interactions	8-11

		(*c*) Explain how missing data were addressed	8-11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	8-11
		Case-control study—If applicable, explain how matching of cases and controls was addressed	8-11
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	8-11
		(*e*) Describe any sensitivity analyses	8-11
Continued on next page			
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-13
		(b) Give reasons for non-participation at each stage	11-13
		(c) Consider use of a flow diagram	11-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-13
		(b) Indicate number of participants with missing data for each variable of interest	11-13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11-13
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11-13
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	11-13
		Cross-sectional study—Report numbers of outcome events or summary measures	11-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	11-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-17

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Dementia and vagotomy in Taiwan: A population-based cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019582.R2
Article Type:	Research
Date Submitted by the Author:	19-Jan-2018
Complete List of Authors:	Lin, Shih-Yi ; China Medical University Hospital, Division of Nephrology and Kidney Institute Lin, Cheng-Li; China Medical University Hospital, Management Office for Health Data Wang, I-Kuan; China Medical University Hospital, Division of Nephrology and Kidney Institute Lin, Cheng-Chieh; China Medical University, School of Medicine Lin, Chih-Hsueh ; China Medical University Hospital, Department of Family Medicine Hsu, Wu-Huei; China Medical University Hospital, Department of Internal Medicine Kao, Chia-Hung; China Medical University, School of Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Neurology, Gastroenterology and hepatology, Surgery
Keywords:	Parkinson disease, Dementia < NEUROLOGY, Vagotomy, Cohort study

Dementia and vagotomy in Taiwan: A population-based cohort study

RUNNING TITLE: Dementia and Vagotomy

Shih-Yi Lin[1,2], Cheng-Li Lin[3,4], I-Kuan Wang[1,2], Cheng-Chieh Lin[1,5], Chih-Hsueh Lin[1,5], Wu-Huei Hsu[1,6], Chia-Hung Kao[1,7,8]

[1]Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, Taichung, Taiwan

[2]Division of Nephrology and Kidney Institute, China Medical University Hospital, Taichung, Taiwan

[3]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan

[4]College of Medicine, China Medical University, Taichung, Taiwan

[5]Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan

[6]Division of Pulmonary and Critical Care Medicine, China Medical University Hospital and China Medical University, Taichung, Taiwan

[7]Department of Nuclear Medicine, China Medical University Hospital, Taichung,

Taiwan

[8]Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan.

Correspondence: Chia-Hung Kao, M.D., Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 40447, Taiwan. Tel.: +886-4-22052121 ext.7461, E-mail: d10040@mail.cmuh.org.tw

Author contributions:

Conceptualization: SYL, CHK

Methodology: CLL, CHK.

Software: CLL, CHK.

Validation: SYL, CLL, IKW, CCL, CHL, WHH, CHK

Formal analysis: SYL, CLL, IKW, CCL, CHL, WHH, CHK

Investigation: CLL, CHK.

Resources: CLL, CHK.

Data curation: SYL, CLL, IKW, CCL, CHL, WHH, CHK

Writing (original draft preparation): SYL, CLL, IKW, CCL, CHL, WHH, CHK

Writing (review and editing): SYL, CLL, IKW, CCL, CHL, WHH, CHK

Visualization: SYL, CLL, IKW, CCL, CHL, WHH, CHK

Supervision: CHK.

Project administration: CHK

Funding acquisition: CHK.

Funding Statement:

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW106-TDU-B-212-113004), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10601010036), Taiwan Clinical Trial Consortium for Stroke (MOST 106-2321-B-039-005), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo AoshimaMemorial Funds, Japan. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

Conflict of Interest: The authors have no proprietary or commercial interest in any of the materials discussed in this article.

List of abbreviations

PD: Parkinson disease; AD: Alzheimer disease; HRs: hazard ratios; CI: confidence interval; NHIRD: National Health Insurance Research Database; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

Abstract

Objective: Truncal vagotomy is associated with a decreased risk of subsequent Parkinson disease (PD), although the effect of vagotomy on dementia is unclear. In response, we investigated the risk of dementia in patients who underwent vagotomy.

Setting: Population-based cohort study

Participants: A total of 155,944 patients who underwent vagotomy (vagotomy cohort) and 155,944 age-, sex-, and comorbidity-matched controls (nonvagotomy cohort) were identified between 2000 and 2011.

Primary and secondary outcome measures: All patient data were tracked until the diagnosis of dementia, death, or the end of 2011. The cumulative incidence of subsequent dementia and hazard ratios (HRs) were calculated.

Results: The mean ages of the study patients in the vagotomy and nonvagotomy cohorts were 56.6±17.4 and 56.7±17.3 years, respectively. The overall incidence density rate for dementia was similar in the vagotomy and nonvagotomy cohorts (2.43 and 2.84 per 1000 person-years, respectively). After adjustment for age, sex, and comorbidities such as diabetes, hypertension, hyperlipidemia, stroke, depression, coronary artery disease, and PD, the patients in the vagotomy cohort were determined to not be at a higher risk of dementia than those in the nonvagatomy cohort [adjusted HR = 1.09, 95% confidence interval (CI) = 0.87–1.36]. Moreover, the patients who

underwent truncal vagotomy were not associated with risk of dementia (adjusted HR = 1.04, 95% CI = 0.87–1.25), compared with the patients who did not undergo vagotomy.

Conclusion: Vagotomy, either truncal or selective, is not associated with risk of dementia.

Keywords: Parkinson disease; Dementia; Vagotomy; Cohort study

Strengths and limitations of this study

1. The strengths of our study are its population-based design, generalizability of findings with a very large sample size including study and control cohorts.

2. All insurance claims should be scrutinized by medical reimbursement specialists and peer review.

3. Although we have considered the major surrogate variables, the information regarding individual-based risk factors for dementia, including smoking, genetic mutation, family history, vitamin D consumption, sleep patterns, caffeine use, and education level, were unavailable in this database.

Introduction

Dementia, a syndrome representing a cluster of disturbances in cognitive functioning, is currently the leading chronic cause of irreversible disability among elderly patients [1]. According to a World Health Organization estimate, more than 30 million people are living with dementia worldwide, and this number is expected to increase by more than three times by 2050 [2,3].

The most common causes of dementia are Alzheimer disease (AD), vascular dementia, Parkinson disease (PD), and neurodegenerative diseases; these conditions have different pathogeneses that lead to a decline in cognition [4]. Because dementia is the end result of a complex process involving genetic defects [5], hypoperfusion, oxidative stress [6], mitochondrial dysfunction [7], and protein deposition [8], the etiology of dementia is multifactorial.

Typically, accumulation of fibrous amyloid-β (Aβ) plaques or protein fibrils of α-synuclein is the hallmark of AD, whereas aggregation of α-synuclein in the Lewy bodies is the hallmark of PD [9,10]. The levels of Aβ are associated with the severity of AD [11]. Bachhuber et al reported that α-synuclein is also associated with the inhibition of Aβ plaque formation; these findings suggest an overlap between the pathogeneses of AD and PD [12].

In murine models, intragastric injection of rotenone-initiated α-synuclein can

reproduce the progression of PD pathology [13] and vagotomy can stop the spread of PD pathology [14]. Vagotomy is the surgical resection of the vagus nerve, and it is performed to reduce acid secretion for managing complicated PUD [15]. Two surgical strategies of vagotomy are available: truncal vagotomy, in which the trunk of the vagus nerve is cut to innervate the abdomen, and selective vagotomy, in which the vagus nerve is resected to innervate the fundus and body of the stomach [16]. Liu et al used a Swedish database to investigate the association between vagotomy and the risk of PD, and found that vagotomy was not associated with the risk of PD overall [17]. However, a study by Svensson et al, which was conducted using a database from Denmark, revealed an association between complete truncal vagotomy and a decreased risk for subsequent PD [18]. Thus, the association between vagotomy and PD remains inconclusive. The aforementioned observations also suggest that vagotomy may reduce the risk of other neurodegenerative diseases, such as AD. However, clinical evidence in the form of data supporting this hypothesis is not available. Because dementia is the most common clinical sign and the result of most neurodegenerative diseases, we used the National Health Insurance (NHI) registration database to determine the association between vagotomy and dementia risk.

Methods

Data Source

The Taiwan NHI program, launched in March 1995, currently covers more than 99% of the 23.72 million people in Taiwan [19]. The inpatient database was used for this nationwide population-based retrospective cohort study. The details of the program and inpatient databases have been dicussed in previous studies [20,21].

Diseases were coded according to the 2001 International Classification of Disease, Revision 9, Clinical Modification (ICD-9-CM). The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH104-REC2-115-CR2). The Institutional Review Board (IRB) also specifically waived the consent requirement.

Data Sharing Statement

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The Ministry of Health and Welfare must approve our application to access this data. Any researcher interested in accessing this dataset can submit an application form to the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd.,

Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848. All relevant data are within the paper.

Sampled Participants

Patients aged more than 20-years-old who had undergone vagotomy (ICD-9-OP codes 44.0) formed the vagotomy cohort. The dates of the first hospitalization for vagotomy were defined as the index dates of the vagotomy patients. Patients with a history of dementia (ICD-9-CM codes 290, 294.1, and 331.0) before the index date were excluded.

Patients who had undergone vagotomy were matched (1:1 ratio) with those who did not undergo vagotomy according to their propensity score through nearest neighbor matching, initially to the eighth digit and then as required to the first digit [22]. Therefore, matches were first made within a caliper width of 0.0000001, and then the caliper width was increased for unmatched cases to 0.1. We considered the matching criteria and performed a rematch (greedy algorithm) using without replacement. For each vagotomy patient, the corresponding comparisons were selected based on the nearest propensity score. The date of enrollment in non-vagotomy cohort was matched with the same year and month of the vagotomy cohort, by the random assignment method. The propensity scores were calculated

using logistic regression to estimate the probability of the surgery status using baseline variables of sex; age; comorbidities such as diabetes, hypertension, hyperlipidemia, stroke, coronary artery disease (CAD), chronic kidney disease (CKD), liver disease, osteoarthritis, chronic obstructive pulmonary disease (COPD), depression, head injury, PD, cancer, or peptic ulcer disease (PUD). The samples were matched with sex, age, comorbidities, and index year to reduce confounding effects of sex, age, and comorbidities, and to have a valid measure of follow up person-years. All of the study participants were followed up from the index date to the occurrence of dementia, withdrawal from the NHI program, or the end of 2011, whichever occurred first. Most important of all, there would be no any event of vagotomy in the control cohort during the follow-up period.

Statistical analysis

The frequency and percentage for categorical variables as well as the mean and standard deviation (SD) for continuous variables were calculated for the vagotomy and nonvagotomy cohorts. The differences in distribution between the two cohorts were assessed using standardized mean differences. A standardized mean difference of ≤0.1 indicated a negligible difference between the two cohorts [23]. The follow-up time in person-years estimated the incidence density of dementia among different risk

factors and incidence density stratified by age, sex, comorbidity, and follow-up period. Cox proportional hazards models stratifying on the matched pairs were performed to estimate the hazard ratio (HR) and 95% confidence intervals (CI) of developing dementia associated with vagotomy cohort, compared with non-vagotomy cohort. When the patients were stratified according to sex, age, comorbidity, and follow-up period (using the first quartile and second quartile as a cut off), the relative risk of dementia in the vagotomy and nonvagotomy cohorts was also compared using Cox regression models. To address the concern of constant proportionality, we examined the proportional hazard model assumption using a test of scaled Schoenfeld residuals. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and statistical significance was set $p < 0.05$ [24].

Results

Table 1 lists the characteristics of the study cohort. We identified 155944 patients with vagotomy; hence, 155944 patients were recruited for the nonvagotomy cohort. Men accounted for approximately 79% of the patients in each cohort and most of the patients were aged ≥50 years (61.7% vs. 61.7%). Specifically, the mean age of the patients was 56.6 ±17.4 years for the vagotomy cohort and 56.7 ± 17.3 years for the

nonvagotomy cohort. The major comorbidities in both cohorts were PUD (96.2% vs. 96.2%), hypertension (21.1% vs. 21.1%), and diabetes (15.2% vs. 15.1%). The mean follow-up periods were 5.88 ± 3.80 and 6.58 ± 3.35 years for the vagotomy and nonvagotomy cohorts, respectively. The incidence of dementia was 2.43 and 2.84 per 1000 person-years in the vagotomy and nonvagotomy cohorts, respectively. Results showed that there was no significant relationship between Schoenfeld residuals for vagotomy and follow-up time (p-value = 0.07) in the model evaluating the dementia risk. The vagotomy cohort was not associated with dementia compared with the nonvagotomy cohort (HR = 1.09, 95% CI = 0.87–1.36). The risk of dementia in the patients who were ≥65 years old was 74.4-fold higher than in those who were ≤49 years old (95% CI = 36.8–150.5). Furthermore, the multivariable models showed that dementia was independently associated with comorbidities, particularly stroke (HR = 1.84, 95% CI = 1.47, 2.29), head injury (HR = 1.66, 95% CI = 1.23, 2.24), and Parkinson's disease (HR = 2.00, 95% CI = 1.19, 3.38) (Table 2).

Table 3 compares the risk of dementia between the vagotomy and nonvagotomy cohorts and also presents the risk stratified by sex, age, comorbidity, and follow-up period. Female vagotomy patients had a 1.56-fold higher risk of dementia than female patients from the non-vagotomy cohort did (HR = 1.56, 95% CI = 1.00–2.44). When compared with the non-vagotomy patients, the vagotomy patients had higher risk of

dementia in those aged ≤64 years (HR = 2.07, 95% CI = 1.12-3.83).

We further assessed the association between vagotomy and dementia risk stratified by sex and age (Table 4). Among the men, the effects of vagotomy on dementia risk was not associated with age (HR = 1.77, 95% CI = 0.90–3.49 for subgroup aged ≤64 years; HR = 0.85, 95% CI = 0.64–1.14 for subgroup aged ≥65 years).

Furthermore, the truncal vagotomy patients exhibited no association with risk of dementia, compared with the nonvagotomy patients (HR = 1.05, 95% CI = 0.87–1.25) (Table 5). Similarly, compared with non-vagotomy cohort, the types of vagotomy, including trunk, highly selective, and other selective vagotomy were not associated with risk of dementia. (Table 5) Figure 1 shows the cumulative incidence for vagotomy group compared with non-vagotomy cohort. (log-rank test p =0.08)

To address the concern of constant proportionality, we examined the proportional hazard model assumption using a test of scaled Schoenfeld residuals. Results showed that there was no significant relationship between Schoenfeld residuals for vagotomy and follow-up time (p-value = 0.07) in the model evaluating the dementia risk.

Discussion

Recent studies have reported that the vagus nerve is associated with the transport of α-synuclein and progression of PD [14,25]. A nationwide population-based study by Svensson et al revealed that truncal vagotomy is associated with a decreased risk of subsequent PD [16]. However, Liu et al reported that neither truncal nor selective vagotomy is associated with a protective effect against PD [17]. Similar to the findings of Liu et al [15], our study revealed that vagotomy is not associated with overall risk of dementia. However, vagotomy, in those women or patients aged ≤ 64 years-old, is associated with higher risk of dementia.

Several explanations for these results are possible. First, dementia has several etiologies, including PD, AD, vascular dementia, and other neurodegenerative diseases. Braak et al proposed that the pathogenic process of PD originates when an environmental insult enters the body and is transmitted to the brain. Furthermore, the pathogenic process is mediated by the neurontransport of α-synuclein [26]. Sevenson et al reported that truncal vagotomy is associated with a decreased risk of PD [16], which thus supported the hypothesis of Braak et al [26]. A major component of Lewy bodies in PD, α-synuclein, was first isolated from plaques in the brains of patients with AD [27]. Although α-synuclein is associated with the development of PD and AD, the enteric route might be a spread source for neurodegenerative diseases [28].

Thus, vagotomy might not be associated directly with the risk of dementia.

Another possible explanation is the microbiome effect of vagotomy. In animal models of sepsis, the vagal nerve has been proposed to be involved in the regulation of inflammatory responses [29]. Li et al described a case of impaired intestinal microbiota barrier following vagotomy, and subsequent rescue after microbiota transplantation [30]. Recently, it has been recognized that the human microbiome of the gastrointestinal tract may affect the brain and behavior, an association that has been named the gut–brain axis [31]. The brains of patients with Parkinson-dementia and AD were found to have elevated levels of beta-N-methylamino-L-alanine [32]. Schwartz et al proposed that the host bacteria amyloid contribute to misfolding and amyloidegenic diseases such as AD [33]. Thus, vagotomy might alter the microbiome of the gastrointestinal tract. However, the negative effects of an altered microbiome following vagotomy may attenuate the possible positive effects discussed by Braak et al. The effect of vagotomy on neurological dysfunction therefore remains only vaguely defined. One interesting finding of this study is that vagotomy, in those women or patients aged ≤ 64 years-old, is associated with higher risk of dementia. Further studies are needed to clarify whether and why vagotomy are associated with e risk of dementia in group of women or aged ≤ 64 years-old.

This study has several limitations. First, we defined dementia as an outcome

instead of a specific neurodegenerative disease. Dementia is the most common presentation of neurodegenerative diseases, including AD and PD. The diagnosis of AD is stricter than that of dementia and requires distinct clinical and laboratory features [34,35]. Thus, in this study, we used dementia as an outcome and adjusted cardiovascular-related comorbidities for vascular dementia to avoid the possible bias of underdiagnosis related to AD and other neurodegenerative diseases. The discrimination and validity for subtypes of dementia are difficult in this study based on coding. We did not analyze the association between vagotomy and subtypes of dementia. Second, although we have considered the major surrogate variables, the information regarding individual-based risk factors for dementia, including smoking, genetic mutation, family history, vitamin D consumption, sleep patterns, caffeine use, and education level, were unavailable in this database. Further, the vagotomy cohort might have more medical visits and more chances to be diagnosed with dementia, possible surveillance and detection bias should be mentioned here. The follow up period of this study is relatively short. Since our data showed that vagotomy had no association with dementia before 7 years, but maybe provide protection for dementia after 7 years, it would be possible that vagotmy might be protective for dementia once the follow up duration is longer. Further, the number of dementia events are small in this study, thus the conclusion and presumption would not be precise and valid.

Longitudinal cohort studies of longer follow up duration are necessary to clarify the possible protective role of vagotomy for dementia. Finally, most of the study population is Taiwanese, thus it needs cautions to translate and generalize our findings to other population. The generalizability of our results might be limited

In conclusion, the current nationwide cohort study revealed that vagotomy, either truncal or selective, was not associated risk of dementia. Although one study showed that truncal vagotomy reduces the risk of PD [17], our study offers preliminary evidence that the association between vagotomy and dementia is not direct.

Reference:

1 Wimo A1, Jönsson L, Bond J, Prince M, Winblad B; Alzheimer Disease International. The worldwide economic impact of dementia 2010. Alzheimers Dement. 2013;9:1-11.e3.

2 http://www.who.int/mental_health/publications/dementia_report_2012/en/.

3 Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement. 2013 ;9:63-75.e2.

4 Irvine GB, El-Agnaf OM, Shankar GM, Walsh DM. Protein aggregation in the brain: the molecular basis for Alzheimer's and Parkinson's diseases. Mol Med. 2008 ;14:451-64.

5 Spillantini MG, Murrell JR, Goedert M, Farlow MR, Klug A, Ghetti B. Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. Proc Natl Acad Sci U S A. 1998 ;95:7737-41.

6 Aliev G, Smith MA, Obrenovich ME, de la Torre JC, Perry G. Role of vascular hypoperfusion-induced oxidative stress and mitochondria failure in the pathogenesis of Azheimer disease. Neurotox Res. 2003;5:491-504.

7 Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 2006;443: 787-795.

8 Thal DR, Capetillo-Zarate E, Del Tredici K, Braak H. The development of amyloid beta protein deposits in the aged brain. Sci Aging Knowledge Environ. 2006;2006:re1.

9 Kelly JW. Structural biology: proteins downhill all the way. Nature. 2006;442: 255-256.

10 Knowles TP, Vendruscolo M, Dobson CM. The amyloid state and its association with protein misfolding diseases. Nat Rev Mol Cell Biol. 2014 ;15:384-96.

11 McLean CA, Cherny RA, Fraser FW, Fuller SJ, Smith MJ, Beyreuther K, et al. Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. Ann Neurol. 1999;46:860-6.

12 Bachhuber T, Katzmarski N, McCarter JF, Loreth D, Tahirovic S, Kamp F, et al. Inhibition of amyloid-β plaque formation by α-synuclein. Nat Med. 2015;21:802-7.

13 Pan-Montojo F, Anichtchik O, Dening Y, Knels L, Pursche S, Jung R, et al. Progression of Parkinson's disease pathology is reproduced by intragastric administration of rotenone in mice. PLoS One. 2010;5:e8762.

14 Pan-Montojo F, Schwarz M, Winkler C, Arnhold M, O'Sullivan GA, Pal A, et al. Environmental toxins trigger PD-like progression via increased

alpha-synuclein release from enteric neurons in mice. Sci Rep. 2012;2:898.

15 Johnston D, Wilkinson AR. Highly selective vagotomy without a drainage procedure in the treatment of duodenal ulcer. Br J Surg. 1970;57:289-96.

16 Wilkinson AR, Johnston D. Effect of truncal, selective and highly selective vagotomy on gastric emptying and intestinal transit of a food-barium meal in man. Ann Surg. 1973;178:190-3.

17 Liu B, Fang F, Pedersen NL, Tillander A, Ludvigsson JF, Ekbom A, et al. Vagotomy and Parkinson disease: A Swedish register-based matched-cohort study. Neurology. 2017;88:1996-2002.

18 Svensson E, Horváth-Puhó E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, et al. Vagotomy and subsequent risk of Parkinson's disease. Ann Neurol. 2015;78:522-9.

19 Database NHIR. Taiwan, http://nhird.nhri.org.tw/en/index.html (cited in 2015).

20 Peng YC, Lin CL, Yeh HZ, Tung CF, Chang CS, Kao CH. Diverticular disease and additional comorbidities associated with increased risk of dementia. J Gastroenterol Hepatol. 2016;31:1816-1822.

21 Chen YT, Su JS, Tseng CW, Chen CC, Lin CL, Kao CH. Inflammatory bowel disease on the risk of acute pancreatitis: A population-based cohort study. J

Gastroenterol Hepatol. 2016;31:782-7.

22 Parsons LS, Ovation Research Group, Seattle, Washingto. Performing a 1:N Case-Control Match on Propensity Score. SUGI. 2009;29: 165.

23 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28: 3083-3107.

24. Lori S. Parsons, Ovation Research Group, Seattle, Washington. Performing a 1:N Case-Control Match on Propensity Score. SUGI29, 2001:165-29

25 Phillips RJ, Walter GC, Wilder SL, Baronowsky EA, Powley TL. Alpha-synuclein-immunopositive myenteric neurons and vagal preganglionic terminals: autonomic pathway implicated in Parkinson's disease? Neuroscience. 2008;153:733-50.

26 Braak H, Rüb U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm (Vienna). 2003 ;110:517-36.

27 Masliah E, Rockenstein E, Veinbergs I, Mallory M, Hashimoto M, Takeda A, et al. Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders. Science. 2000 ;287:1265-9.

28 Visanji NP, Brooks PL, Hazrati LN, Lang AE. The prion hypothesis in Parkinson's disease: Braak to the future. Acta Neuropathol Commun. 2013;1:2.

29 Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 2000;405:458-62.

30 Li Q, Wang C, Tang C, He Q, Zhao X, Li N, et al. Successful treatment of severe sepsis and diarrhea after vagotomy utilizing fecal microbiota transplantation: a case report. Crit Care. 2015;19:37.

31 Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012 ;13:701-12.

32 Brenner SR. Blue-green algae or cyanobacteria in the intestinal micro-flora may produce neurotoxins such as Beta-N-Methylamino-L-Alanine (BMAA) which may be related to development of amyotrophic lateral sclerosis, Alzheimer's disease and Parkinson-Dementia-Complex in humans and Equine Motor Neuron Disease in horses. Med Hypotheses. 2013;80:103.

33 Schwartz K, Boles BR. Microbial amyloids--functions and interactions within the host. Curr Opin Microbiol. 2013;16:93-9.

34 Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P,

Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007 ;6:734-46.

35. Nai-Fang Chi, Li-Nien Chien, Hsiao-Lun Ku, et al. Alzheimer disease and risk of stroke: A population-based cohort study. Neurology 2013; 80:

Figure Legends:

Figure 1. Cumulative incidence of dementia in the vagotomy and nonvagotomy cohorts.

Table 1. Demographic characteristics and comorbidities in the vagotomy and nonvagotomy cohorts

	Vagotomy		Standard mean difference[§]
	No (N =155944)	Yes (N =155944)	
Sex			
Women	3409(21.4)	3397(21.3)	0.002
Men	12535(78.6)	12547(78.7)	0.002
Age stratified			
≤ 49	6115(38.4)	6114(38.4)	0.000
50-64	3938(24.7)	3939(24.7)	0.000
65+	5891(37.0)	5891(37.0)	0.000
Age, mean±SD [a]	56.7±17.3	56.6±17.4	0.01
Comorbidity			
Diabetes	2399(15.1)	2421(15.2)	0.004
Hypertension	3359(21.1)	3360(21.1)	0.000
Hyperlipidemia	584(3.66)	613(3.84)	0.01
Stroke	1334(8.37)	1340(8.40)	0.001
CAD	1379(8.65)	1381(8.66)	0.000
CKD	613(3.84)	632(3.96)	0.01
Liver disease	1834(11.5)	1846(11.6)	0.002
Osteoarthritis	498(3.12)	521(3.27)	0.01
COPD	158(0.99)	153(0.96)	0.003
Depression	191(1.20)	190(1.19)	0.001
Head injury	976(6.12)	994(6.23)	0.01
Parkinson's disease	117(0.73)	108(0.68)	0.01
Cancer	597(3.74)	619(3.88)	0.01
PUD	15343(96.2)	15343(96.2)	0.000

[§]A standardized mean difference of ≤0.10 indicates a negligible difference between the two cohorts.

CAD, coronary artery disease; CKD, chronic kidney disease

Table 2. Incidences of and risk factors for dementia

Variable	Event	PY	Rate[#]	HR(95% CI)
Vagotomy				
No	298	104932	2.84	1.00
Yes	228	93707	2.43	1.09(0.87, 1.36)
Age group, year				
≤ 49	8	91483	0.09	1.00
50-64	51	51513	0.99	10.3(4.86, 21.6)***
65+	467	55643	8.39	74.4(36.8, 150.5)***
Sex				
Female	143	39468	3.62	1.00(0.06, 16.0)
Male	383	159171	2.41	1.00
Comorbidity				
Diabetes				
No	405	177247	2.28	1.00
Yes	121	21391	5.66	1.01(0.82, 1.25)
Hypertension				
No	289	169471	1.71	1.00
Yes	237	29168	8.13	1.44(1.18, 1.75)***
Hyperlipidemia				
No	497	193049	2.57	1.00
Yes	29	5590	5.19	3.00(0.31, 28.8)
Stroke				
No	400	188269	2.12	1.00
Yes	126	10370	12.2	1.84(1.47, 2.29)***
CAD				
No	416	187358	2.22	1.00
Yes	110	11281	9.75	2.00(0.18, 22.1)
CKD				
No	494	194635	2.54	1.00
Yes	32	4004	7.99	1.33(0.93, 1.92)
Liver disease				
No	442	180865	2.44	1.00
Yes	84	17774	4.73	1.20(0.95, 1.52)
Osteoarthritis				
No	502	194322	2.58	1.00
Yes	24	4317	5.56	0.76(0.50, 1.15)
COPD				

No	513	197076	2.60	1.00
Yes	13	1562	8.32	1.67(0.96, 2.90)
Depression				
No	420	196769	2.64	1.00
Yes	6	1869	3.21	1.03(0.46, 2.32)
Head injury				
No	478	188290	2.54	1.00
Yes	48	10349	4.64	1.66(1.23, 2.24)***
Parkinson's disease				
No	511	197771	2.58	1.00
Yes	15	868	17.3	2.00(1.19, 3.38)**
Cancer				
No	516	194585	2.65	1.00
Yes	10	4054	2.47	0.52(0.05, 5.51)
PUD				
No	10	6542	1.53	1.00
Yes	516	192096	2.69	2.11(1.13, 3.95)*

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PD, Parkinson disease; PUD, peptic ulcer disease; PY, person-years;

[#] Incidence rate per 1000 person-years

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 3. Incidence densities of dementia hazard ratios between the vagotomy and nonvagotomy cohorts based on demographic characteristics and comorbidities

	Vagotomy						
	No			Yes			
	Event	PY	Rate[#]	Event	PY	Rate[#]	HR (95% CI)
Sex							
Women	77	21364	3.60	66	18104	3.65	1.56(1.00, 2.44)*
Men	221	83568	2.64	162	75603	2.14	0.96(0.74, 1.24)
Stratify age							
≤ 64	24	73656	0.33	35	69339	0.50	2.07(1.12, 3.83)*
≥ 65	274	31275	8.76	193	24367	7.92	0.97(0.76, 1.24)
Comorbidity[‡]							
No	1	2156	0.46	1	1493	0.67	-
Yes	297	102776	2.89	227	92214	2.46	1.08(0.86, 1.35)
Follow-up period							
<4	131	43502	3.01	116	38634	3.00	1.24(0.94, 1.63)
4-7	119	34038	3.50	87	30274	2.87	0.91(0.59, 1.40)
≥7	48	19534	2.46	25	17780	1.41	0.50(0.17, 1.46)

Rate[#], incidence rate per 1000 person-years; HR, hazard ratio

Comorbidity[‡]: Patients with any one of the listed comorbidities were classified as the comorbidity group

Table 4. Incidence and hazard ratios of dementia, stratified by age and sex, between the vagotomy and nonvagotomy cohorts

	Men					Women				
	Vagotomy					Vagotomy				
	No		Yes			No		Yes		
Variables	Event	Rate#	Event	Rate#	HR(95% CI)	Event	Rate#	Event	Rate#	HR(95% CI)
Age										
≤64	19	0.31	27	0.46	1.77(0.90, 3.49)	5	0.42	8	0.73	4.00(0.85, 18.8)
≥ 65	202	9.23	135	7.87	0.85(0.64, 1.14)	72	7.68	58	8.05	1.40(0.88, 2.24)

Abbreviations: HR, hazard ratio; PY, person-years

Rate#, incidence rate per 1000 person-years

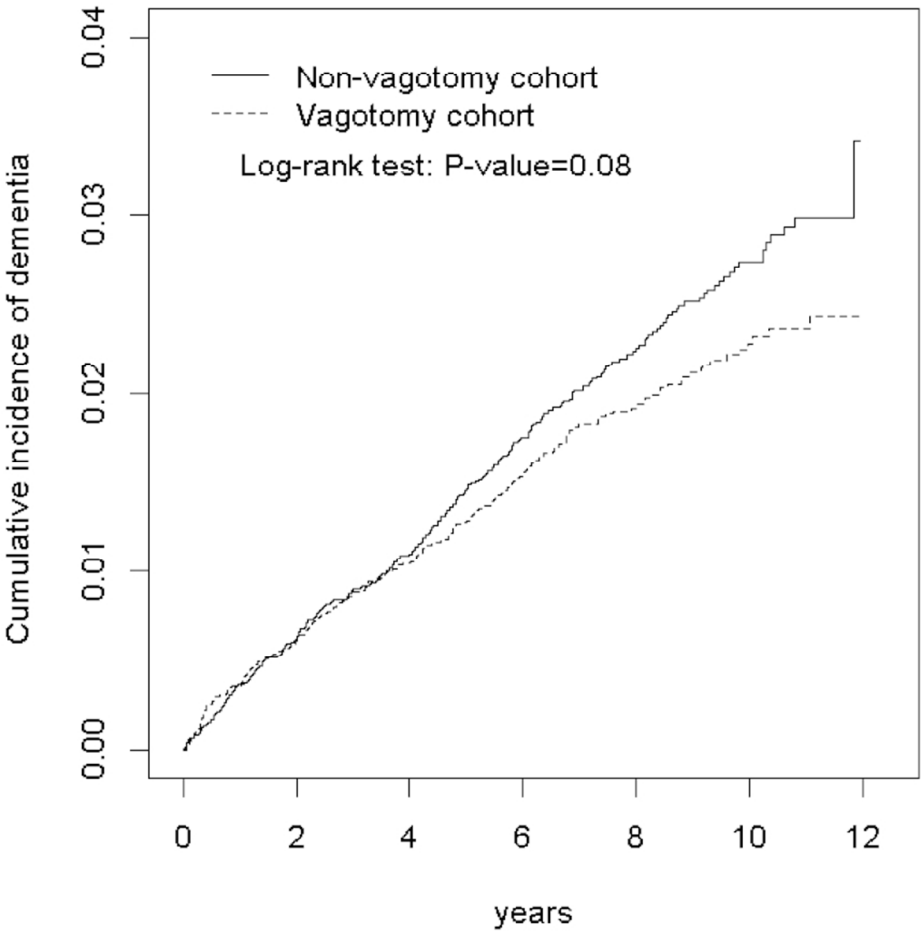
Adjusted HR& multivariable analysis including age, sex, comorbidities, and benzodiazepine/zolpidem medication use in the Cox proportional hazard regression

Table 5. Incidence and hazard ratios of dementia among the vagotomy and nonvagotomy cohorts

Variable	N	Event	PY	Rate[#]	HR (95% CI)
Control	15944	298	104932	2.84	1(Reference)
Vagotomy					
Truncal vagotomy	12999	192	77219	2.49	1.04(0.87, 1.25)
Highly selective	1035	8	6141	1.30	0.84(0.42,1 .69)
Other selective vagotomy	101	1	529	1.89	0.80(0.11, 5.73)

Abbreviation: PY, person-years

Rate[#], incidence rate per 1000 person-years



78x76mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Included on page:
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,5,6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5,6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8,9
Objectives	3	State specific objectives, including any pre-specified hypotheses	8,9
Methods			
Study design	4	Present key elements of study design early in the paper	10-13
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10-13
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10-13
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	10-13
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	10-13
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	10-13
		Case-control study—For matched studies, give matching criteria and the number of controls per case	10-13
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-13
Bias	9	Describe any efforts to address potential sources of bias	10-13
Study size	10	Explain how the study size was arrived at	10-13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-13
		(*b*) Describe any methods used to examine subgroups and interactions	10-13

		(*c*) Explain how missing data were addressed	10-13
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	10-13
		Case-control study—If applicable, explain how matching of cases and controls was addressed	10-13
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	10-13
		(*e*) Describe any sensitivity analyses	10-13
Continued on next page			
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13-15
		(b) Give reasons for non-participation at each stage	13-15
		(c) Consider use of a flow diagram	13-15
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-15
		(b) Indicate number of participants with missing data for each variable of interest	13-15
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	13-15
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	13-15
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	13-15
		Cross-sectional study—Report numbers of outcome events or summary measures	13-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-15
		(*b*) Report category boundaries when continuous variables were categorized	13-15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-19

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.