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Tinnitus and Dementia Risk: A Nationwide Population-based Case-control Study

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ABSTRACT

Objective

This study aimed to determine if a history of tinnitus is associated with the risk of developing dementia.

Method

A nationwide population-based case-control study included all eligible adults in Taiwan.

Results

A total of 15,686 patients were included in the study, with 7,843 individuals making up each case and control group. Patients with a history of tinnitus were associated with a statistically significant higher risk of being diagnosed with dementia before reaching the age of 65 years old (50 ≦ Age < 65) (aOR 2.68, 95% CI 1.19-6.05, p=0.017). No statistical significance was found among those 65 years and older (aOR 1.17, 95% CI 0.90-1.51, p=0.235).

Conclusion

A history of tinnitus was associated with a 168% increased risk of being diagnosed with dementia in those aged 50 to 65 years old. This association was not significant in those older than 65 years old.

Keywords: tinnitus, dementia

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INTRODUCTION

Tinnitus, derived from the Latin word *tinnire* "to ring", is a symptom characterized by the perception of sound in the absence of external stimuli. It is a common condition that affects millions of people, with a recent study estimating a contemporary prevalence of one in 10 adults in the United States.[1] Despite its widespread prevalence, there is a lack of consensus on its exact underlying mechanisms. Human functional neuroimaging and other pathophysiological models have provided evidence that tinnitus-related activity changes in the brain involve both auditory and non-auditory structures including limbic system, attention system, as well as other areas related to memory and emotion.[2, 3] Patients with chronic tinnitus often have a concomitant hearing impairment,[4] and a growing body of evidence has linked tinnitus with cognitive impairment in adults.[5]

Dementia is a clinical syndrome characterized by progressive decline in two or more cognitive domains resulting in the loss of abilities to perform instrumental and/or basic activities of daily living.[6, 7] Alzheimer's dementia is the most common cause of dementia worldwide. Recent evidence has also indicated that sensory changes may precede the cognitive symptoms of Alzheimer's dementia (AD), a progressive neurodegenerative disease, by several years.[8] An association between hearing impairment and Alzheimer's dementia has previously been established, and a recently published nationwide population-based retrospective cohort study examining data from Taiwan in the early 2000s has also suggested that tinnitus patients had a higher risk of developing Alzheimer's dementia.[9] Previous studies have not examined whether the association between tinnitus and dementia may be age-dependent, and did not adjust for

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patients with coincident tinnitus and hearing loss. We sought to further evaluate this association using the latest available nationwide data from the National Health Insurance (NHI) system.

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MATERIALS AND METHODS

We designed a large case-control study where cases were defined as patients with a new diagnosis of dementia (diagnosed between 2006 and 2013) and no previous related medical history from the NHIRD (detailed exclusion criteria as described in the Case Selection section and Fig 1). Controls without a dementia diagnosis were randomly selected and matched 1:1 to the cases based on age (by a margin of one month) and sex. We subsequently established the presence or absence of tinnitus prior to the diagnosis of dementia in the case group and the presence or absence of tinnitus using the same index date as the matched case patient in the control group.

Taiwanese National Health Insurance Research Database (NHIRD)

In 1995, the Taiwanese government established the National Health Insurance Program, providing coverage for the vast majority (99.6%) of the country's population. The National Health Research Institute (NHRI) then created the NHIRD, a claims database also overseen by the Taiwanese Department of Health. Within the NHIRD, there are multiple subset databases including the Registry for Catastrophic Illness Patient Database (RCIPD) and the Longitudinal Health Insurance Database (LHID). As dementia is administratively assigned to be a catastrophic illness, a diagnosed patient would therefore apply and be registered within the RCIPD. The LHID includes 1 million randomly selected persons designed to represent the total Taiwanese insured population, which numbered approximately 23,460,000 by the end of 2013.

Case Selection - Dementia

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Case patients were identified from the NHIRD as being newly diagnosed with dementia between 2006 and 2013. Diagnoses for dementia were registered using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD 9-CM) code 290 with a certificate of catastrophic illness or 331.0, 331.1, 331.2, 331.8, which was crosslinked to the NHIRD. We used the presence of the code combined with a certificate of catastrophic illness, to identify our initial pool of 34,387 potential patient cases.

We then excluded individuals whose ages and sexes were not known and those younger than 18 or older than 120. Finally, we excluded those who presented a diagnosis of syphilis (ICD 9-CM code: 091), HIV (ICD 9-CM code: 042), dementia (ICD 9-CM codes: 290.0-290.4, 294.1, 294.2, 331.0-331.2), Huntington's disease (ICD 9-CM code: 333.4), Creutzfeldt-Jakob disease (ICD 9-CM codes: 046.11, 046.19), cerebral degeneration (ICD 9-CM code: 331.8), or Parkinson's disease (ICD 9-CM codes: 332.0, 332.1) before their diagnosis of dementia considering the possibility of having dementia-like symptoms or diagnosis. Based on these criteria, a total of 7,843 cases were identified.

Case-Control Match

A total of 7,843 policy holders were selected as controls in a 1:1 match with the case group, randomly paired for age, sex, and the same index date (the month and year of dementia diagnosis in the case group) from the 2013 version (consistent with our study time frame) of the LHID. Similar to the case group, we excluded individuals whose ages and sexes were not known, those

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under 18 or above 120 years old, those who were diagnosed with the diseases as defined in the case group, and those who were deceased before the index date.

Tinnitus

To identify patients with a tinnitus diagnosis, we searched for the ICD 9-CM code 338.30. Additional criteria for inclusion were as follows: The same diagnosis in at least three outpatient visits or one inpatient diagnosis followed by either another inpatient or outpatient visit with the same diagnosis. Patients with a diagnosis strictly from a single inpatient visit were excluded. The first diagnosis of tinnitus must occur at least one year before the first dementia diagnosis in the case group or before the index date in the control group. (Figure 1)

Other Adjustments

We adjusted for age, sex, a history of hypertension, diabetes, coronary artery disease, depression, hyperlipidemia, alcohol dependence syndrome, thyroid disorders, hearing loss and radioactive iodine treatment. History of obesity was omitted from the analysis due to the small number.

Statistics

We used the Student's t-test to analyze continuous variables and the chi-square test to analyze categorical variables in order to observe differences in clinical characteristics between the case and control groups. A conditional logistic regression analysis was applied to examine the relationship between tinnitus and the risk of developing dementia where we controlled for

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possible confounders. Statistical tests were all two-sided using a significance level of 0.05 and reported using a 95% confidence interval and/or p values. All analyses were run using SAS V.9.4.

This study has been approved by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan (IRB # CE13152B-8).

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RESULTS AND ANALYSIS

A total of 15,686 patients were included in our study, 7,843 in the case group and 7,843 in the control group. The mean ages for those with dementia and those without dementia were 74.9 and 74.5, respectively. Between the case and control groups, there were significant differences ($p < 0.05$) in the proportion of patients who had a history of tinnitus, had a history of hearing loss, had a history of hypertension, had a history of diabetes, had a history of coronary artery disease, had a history of depression, had a history of alcohol dependence syndrome, and had a history of thyroid disorders. (Table 1)

After adjusting for age, sex, history of hypertension, diabetes, coronary artery disease, depression, hyperlipidemia, alcohol dependence syndrome, thyroid disorders, and hearing loss by logistic regression analysis (history of obesity was omitted from the analysis due to small number), having a history of tinnitus was associated with a statistically significant higher risk of being diagnosed with dementia before reaching the age of 65 years old ($50 \leqq \text{Age} < 65$) (aOR 2.68, 95% CI 1.19-6.05, p=0.017). No statistical significance was found among those 65 years and older (aOR 1.17, 95% CI 0.90-1.51, p=0.235). (Table 2)

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DISCUSSION

In this case-control study of 15,868 patients, we found an increased risk of dementia associated with a history of tinnitus in patients aged 50 to 65 (aOR = 2.68, p = 0.017). Consistent with current literature, dementia diagnoses were also associated with a number of conditions and illnesses, including hearing loss ($p < 0.001$), hypertension ($p < 0.001$), diabetes ($p < 0.001$), coronary artery disease ($p < 0.001$), depression ($p < 0.001$), alcohol dependence syndrome ($p < 0.001$), and thyroid disorders ($p < 0.001$).

A previous study by Cheng *et al.* established a 1.675-fold increase in the risk of early-onset dementia among those aged 30-64 in the same population using the NHIRD.[10] However, to our knowledge, no study has expounded whether this association extends between tinnitus and dementia in adults aged 65 or older—especially in an East Asian population. Our study reveals that tinnitus is not associated with dementia in elderly patients (p = 0.235) and support the assertion that this correlation exclusively operates in the context of early-onset dementia.

The pathophysiological relationship between the development of dementia and tinnitus remains tenuously studied. Numerous mechanisms and external factors potentially underlie our results. For example, although tinnitus does not cause hearing loss, loss of hearing can amplify the severity of tinnitus.[11] Hearing loss has long been established as a significant risk factor with incident all-cause dementia, with Lin *et al.* proposing that the former can contribute to the depletion of cognitive reserve.[12-14] Echoing this idea, a systematic review found that subjective tinnitus is associated with significantly diminished function in cognitive performance for general

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short-term memory, response time, processing accuracy, and general learning and retrieval tasks.[15] Cognitive reserve has been postulated as one of the keys to understanding the disconnect between obvious brain pathologies and remarkably unimpaired neurophysical performance in patients.[16] Consequently, tinnitus may exhaust this cognitive reserve. In one out of five patients, tinnitus can be so severe that it contributes to depression, insomnia, anxiety, irritability, and hyperacusis, which all can serve as risk factors lending greater susceptibility to patients to develop cognitive impairment in the future.[17-20]

As previous work has suggested, there is a significant likelihood that both tinnitus and dementia are clinical indicators of shared, underlying dysfunction in the patient's neurochemistry. The root causes of tinnitus have yet to be illuminated. Researchers have proposed that the ear's ringing, whooshing, or buzzing perception stems from three primary sources: alterations to the brain's temporal patterns, an uptick in abnormal spontaneous firing rates in the auditory pathway, and restructuring of the tonotopic maps.[21-23] Imaging techniques such as PET, diffusion MRI, and BOLD-fMRI in human and animal studies have mapped a significant portion of the central mechanisms involved in tinnitus.[3] Both auditory and non-auditory networks have been found to play a role in failing to compensate for symptoms via maladaptive homeostatic plasticity. These areas include the inferior colliculus, dorsal cochlear nucleus, the paraflocculus lobe in the cerebellum, posteroventral cochlear nucleus, medial prefrontal cortex, basal ganglia, dorsal prefrontal regions, parietal cortex, the medial and caudolateral orbital cortex, insula, posterior thalamus, the anterior and posterior cingulate cortex, amygdala, parahippocampus, hippocampus, and nucleus accumbens.[23-37] Given that the amygdala, hippocampus, and posterior cortices are the three most affected sites in MRI studies of early-onset Alzheimer's, there are indeed

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confounding multifaceted pathways that may connect dementia to tinnitus.[38] For example, in a small percentage of the population, traumatic brain injuries or forms of brain damage can directly trigger both tinnitus and dementia.[39-41] Whether tinnitus precisely precedes or develops concurrently concerning cognitive impairment remains vital to study.

Though Alzheimer's disease is still the most common cause of dementia in young onset dementia, other etiologies such as frontotemporal dementia and vascular dementia are more prevalent in this group.[42] Even in Alzheimer's disease patients, atypical phenotypes, such as posterior cortical atrophy, are more common in young-onset patient population. Our study showed a history of tinnitus is associated with increased risk of dementia only in the younger (< 65 year-old) population, but not in the elderly population. This could suggest the effect of tinnitus varies in different age group. Alternatively, this could be related to the underlying differences in the pathophysiology and anatomical areas affected by the etiologies of dementia.

Strength and Limitations

As the NHIRD encompasses nearly the entirety of the Taiwanese population, one of the greatest strengths of the study is the large and representative sample size. The nature of insurance claims discourages selection bias, recall bias, and underreporting. Furthermore, we accounted for confounders in our case-control study by implementing logistic regression analysis for age, sex, hearing loss, hypertension, coronary artery disease, depression, hyperlipidemia, alcohol dependence syndrome, and thyroid disorders (history of obesity was omitted due to small sample size).

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The source of strength of this study also coincides with a limitation, as Taiwan's ethnic population is effectively homogenous, consisting of overwhelmingly Han Chinese. Additionally, without imaging or laboratory data (e.g., brain MRI scans, genetic results, cerebrospinal fluid (CSF) Aβ42, or tau protein), diagnoses of dementia do not elucidate the severity of the disease or its developmental timing in individuals in the database. Likewise, the severity, progressive onset, and specificity of tinnitus are not fully captured by the ICD-9 code. For instance, unlike subjective tinnitus, objective tinnitus is not technically a true hearing disorder, as the hearing organs and neuropathology are not strictly dysfunctional. Though very few tinnitus patients have this mechanical problem, our inability to exclude them may slightly skew results. Furthermore, by the nature of observational studies, we can only determine the association, not biological causality, between tinnitus and dementia.

Conclusions

In this East-Asian nationwide case-control study, a history of tinnitus was associated with a 168% increased risk of being diagnosed with dementia in those aged 50 to 65 years old. This association was not significant in those older than 65 years old ($p = 0.235$). The hope of this study is that future physicians and patients will utilize these findings in learning predictive factors of early dementia. For now, the connection between tinnitus and dementia has been primarily explored through correlative studies. Future pathophysiological and prospective longitudinal studies may be beneficial to uncover causality and any underlying biochemical mechanisms between the two.

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2. Competing interests: The authors declare none.
3. This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Department of Health or National Health Research Institutes.
4. The datasets generated during and/or analyzed during the current study are not publicly available due to patient confidentiality and government policy but are available from the corresponding author on reasonable request.
5. Funding/financial support: None.

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REFERENCES

1 Bhatt JM, Lin HW, Bhattacharyya N. Prevalence, Severity, Exposures, and Treatment Patterns of Tinnitus in the United States. *JAMA Otolaryngol Head Neck Surg* 2016;**142:**959-65

2 Langguth B, Kreuzer PM, Kleinjung T, De Ridder D. Tinnitus: causes and clinical management. *Lancet Neurol* 2013;**12:**920-30

3 Hu J, Cui J, Xu JJ, Yin X, Wu Y, Qi J. The Neural Mechanisms of Tinnitus: A Perspective From Functional Magnetic Resonance Imaging. *Front Neurosci* 2021;**15:**621145

4 Oosterloo BC, Croll PH, Baatenburg de Jong RJ, Ikram MK, Goedegebure A. Prevalence of Tinnitus in an Aging Population and Its Relation to Age and Hearing Loss. *Otolaryngol Head Neck Surg* 2021;**164:**859-68

5 Tegg-Quinn S, Bennett RJ, Eikelboom RH, Baguley DM. The impact of tinnitus upon cognition in adults: A systematic review. *Int J Audiol* 2016;**55:**533-40

6 Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. *F1000Res* 2018;**7:**F1000 Faculty Rev-1161

7 Wieland DR, Wieland JR, Wang H, Chen YH, Lin CH, Wang JJ, et al. Thyroid Disorders and Dementia Risk: A Nationwide Population-Based Case-Control Study. *Neurology* 2022;**99:**e679-e87

8 Albers MW, Gilmore GC, Kaye J, Murphy C, Wingfield A, Bennett DA, et al. At the interface of sensory and motor dysfunctions and Alzheimer's disease. *Alzheimers Dement* 2015;**11:**70-98

9 Liu CM, Lee CT. Association of Hearing Loss With Dementia. *JAMA Netw Open* 2019;**2:**e198112

10 Cheng YF, Xirasagar S, Yang TH, Wu CS, Kao YW, Lin HC. Risk of early-onset dementia among persons with tinnitus: a retrospective case-control study. *Sci Rep* 2021;**11:**13399

11 Han BI, Lee HW, Kim TY, Lim JS, Shin KS. Tinnitus: characteristics, causes, mechanisms, and treatments. *J Clin Neurol* 2009;**5:**11-9

12 Loughrey DG, Kelly ME, Kelley GA, Brennan S, Lawlor BA. Association of Age-Related Hearing Loss With Cognitive Function, Cognitive Impairment, and Dementia: A Systematic Review and Meta-analysis. *JAMA Otolaryngol Head Neck Surg* 2018;**144:**115-26

13 Chern A, Golub JS. Age-related Hearing Loss and Dementia. *Alzheimer Dis Assoc Disord* 2019;**33:**285-90

14 Lin FR, Metter EJ, O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L. Hearing loss and incident dementia. *Arch Neurol* 2011;**68:**214-20

15 Clarke NA, Henshaw H, Akeroyd MA, Adams B, Hoare DJ. Associations Between Subjective Tinnitus and Cognitive Performance: Systematic Review and Meta-Analyses. *Trends Hear* 2020;**24:**2331216520918416

16 Stern Y. Cognitive reserve. *Neuropsychologia* 2009;**47:**2015-28

17 Lockwood AH, Salvi RJ, Burkard RF. Tinnitus. *N Engl J Med* 2002;**347:**904-10

18 de Almondes KM, Costa MV, Malloy-Diniz LF, Diniz BS. Insomnia and risk of dementia in older adults: Systematic review and meta-analysis. *J Psychiatr Res* 2016;**77:**109-15

19 Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? *Maturitas* 2014;**79:**184-90

20 Santabarbara J, Lipnicki DM, Olaya B, Villagrasa B, Gracia-Garcia P, Bueno-Notivol J, et al. Association between Anxiety and Vascular Dementia Risk: New Evidence and an Updated Meta-Analysis. *J Clin Med* 2020;**9**

21 Lanting CP, de Kleine E, van Dijk P. Neural activity underlying tinnitus generation: results from PET and fMRI. *Hear Res* 2009;**255:**1-13

22 Shore SE, Roberts LE, Langguth B. Maladaptive plasticity in tinnitus--triggers, mechanisms and treatment. *Nat Rev Neurol* 2016;**12:**150-60

23 Haider HF, Bojic T, Ribeiro SF, Paco J, Hall DA, Szczepek AJ. Pathophysiology of Subjective Tinnitus: Triggers and Maintenance. *Front Neurosci* 2018;**12:**866

24 Cacace AT, Brozoski T, Berkowitz B, Bauer C, Odintsov B, Bergkvist M, et al. Manganese enhanced magnetic resonance imaging (MEMRI): a powerful new imaging method to study tinnitus. *Hear Res* 2014;**311:**49-62

25 Lan L, Li J, Chen Y, Chen W, Li W, Zhao F, et al. Alterations of brain activity and functional connectivity in transition from acute to chronic tinnitus. *Hum Brain Mapp* 2021;**42:**485-94

26 Rauschecker JP, Leaver AM, Muhlau M. Tuning out the noise: limbic-auditory interactions in tinnitus. *Neuron* 2010;**66:**819-26

27 Leaver AM, Seydell-Greenwald A, Turesky TK, Morgan S, Kim HJ, Rauschecker JP. Cortico-limbic morphology separates tinnitus from tinnitus distress. *Front Syst Neurosci* 2012;**6:**21

28 Chen YC, Liu S, Lv H, Bo F, Feng Y, Chen H, et al. Abnormal Resting-State Functional Connectivity of the Anterior Cingulate Cortex in Unilateral Chronic Tinnitus Patients. *Front Neurosci* 2018;**12:**9

29 Araneda R, Renier L, Dricot L, Decat M, Ebner-Karestinos D, Deggouj N, et al. A key role of the prefrontal cortex in the maintenance of chronic tinnitus: An fMRI study using a Stroop task. *Neuroimage Clin* 2018;**17:**325-34

30 San Juan JD, Zhai T, Ash-Rafzadeh A, Hu XS, Kim J, Filipak C, et al. Tinnitus and auditory cortex: using adapted functional near-infrared spectroscopy to measure resting-state functional connectivity. *Neuroreport* 2021;**32:**66-75

31 Mirz F, Gjedde A, Sodkilde-Jrgensen H, Pedersen CB. Functional brain imaging of tinnitus-like perception induced by aversive auditory stimuli. *Neuroreport* 2000;**11:**633-7

32 Landgrebe M, Langguth B, Rosengarth K, Braun S, Koch A, Kleinjung T, et al. Structural brain changes in tinnitus: grey matter decrease in auditory and non-auditory brain areas. *Neuroimage* 2009;**46:**213-8

33 Jastreboff PJ. Phantom auditory perception (tinnitus): mechanisms of generation and perception. *Neurosci Res* 1990;**8:**221-54

34 Leaver AM, Seydell-Greenwald A, Rauschecker JP. Auditory-limbic interactions in chronic tinnitus: Challenges for neuroimaging research. *Hear Res* 2016;**334:**49-57

35 Leaver AM, Turesky TK, Seydell-Greenwald A, Morgan S, Kim HJ, Rauschecker JP. Intrinsic network activity in tinnitus investigated using functional MRI. *Hum Brain Mapp* 2016;**37:**2717-35

36 Leaver AM, Renier L, Chevillet MA, Morgan S, Kim HJ, Rauschecker JP. Dysregulation of limbic and auditory networks in tinnitus. *Neuron* 2011;**69:**33-43

37 Muhlau M, Rauschecker JP, Oestreicher E, Gaser C, Rottinger M, Wohlschlager AM, et al. Structural brain changes in tinnitus. *Cereb Cortex* 2006;**16:**1283-8

38 Contador J, Perez-Millan A, Tort-Merino A, Balasa M, Falgas N, Olives J, et al. Longitudinal brain atrophy and CSF biomarkers in early-onset Alzheimer's disease. *Neuroimage Clin* 2021;**32:**102804

39 R AA. Risk factors for Alzheimer's disease. *Folia Neuropathol* 2019;**57:**87-105

40 Luo H, Pace E, Zhang J. Blast-induced tinnitus and hyperactivity in the auditory cortex of rats. *Neuroscience* 2017;**340:**515-20

41 Clifford RE, Baker D, Risbrough VB, Huang M, Yurgil KA. Impact of TBI, PTSD, and Hearing Loss on Tinnitus Progression in a US Marine Cohort. *Mil Med* 2019;**184:**839-46

42 Rossor MN, Fox NC, Mummery CJ, Schott JM, Warren JD. The diagnosis of young-onset dementia. *Lancet Neurol* 2010;**9:**793-806

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Figure: Flow Diagram of Participant Selection and Study Design

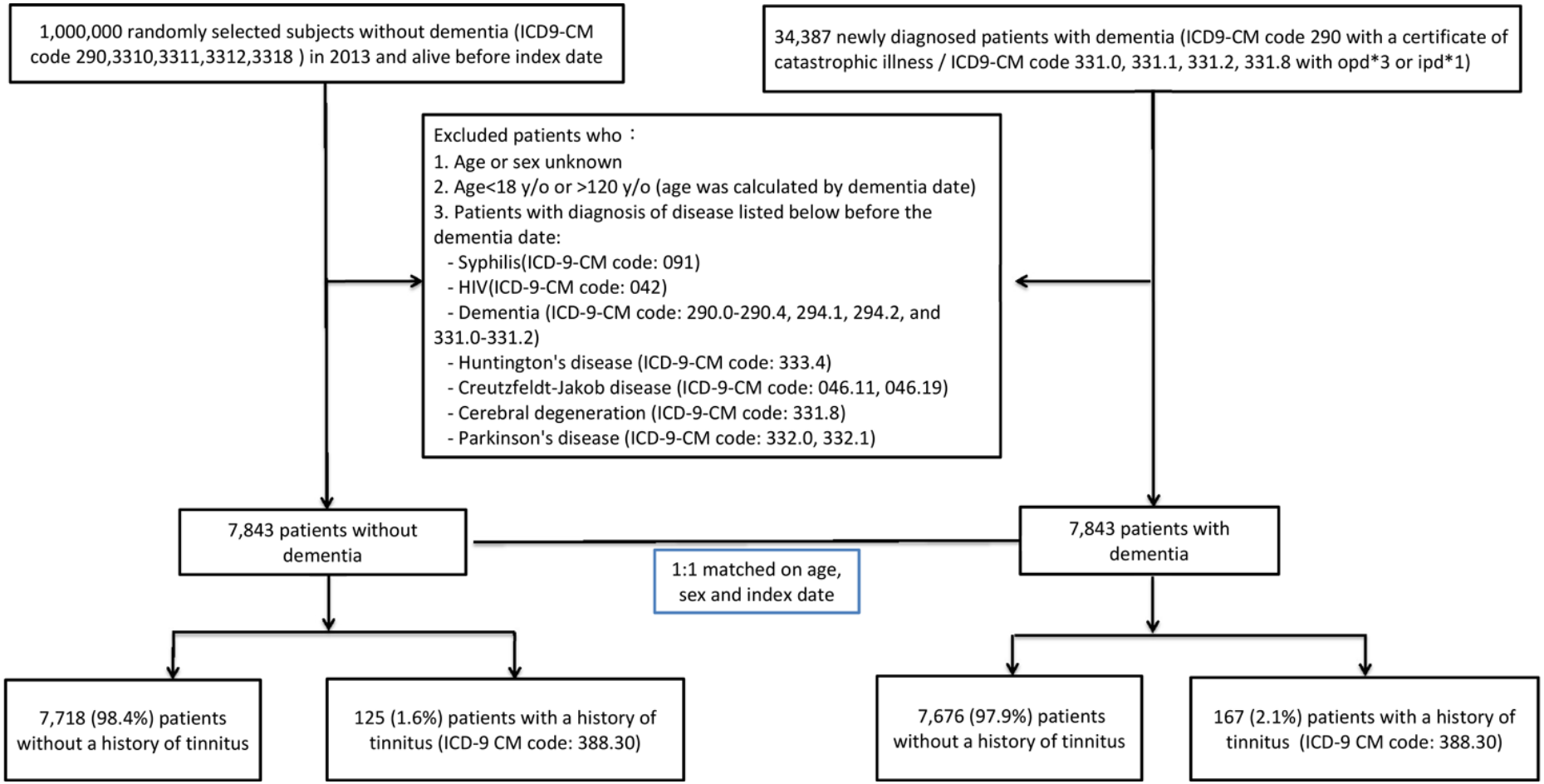

Table 1.Clinical characteristics of study subjects with and without dementia							
Variable	Total (n=15686)		Without dementia (n=7843)		With dementia (n=7843)		*p* value
	N	%	n	%	n	%	
Age, years (mean ± SD)	74.7±11.3		74.5±11.3		74.9±11.3		—
Gender							—
Female	8132	(51.8)	4066	(51.8)	4066	(51.8)	
Male	7554	(48.2)	3777	(48.2)	3777	(48.2)	
History of tinnitus							0.013
No	15394	(98.1)	7718	(98.4)	7676	(97.9)	
Yes	292	(1.9)	125	(1.6)	167	(2.1)	
History of hearing loss							<0.001
No	15408	(98.2)	7746	(98.8)	7662	(97.7)	
Yes	278	(1.8)	97	(1.2)	181	(2.3)	
History of hypertension							<0.001
No	8763	(55.9)	4632	(59.1)	4131	(52.7)	
Yes	6923	(44.1)	3211	(40.9)	3712	(47.3)	
History of obesity							0.617
No	15670	(99.9)	7834	(99.9)	7836	(99.9)	
Yes	16	(0.1)	9	(0.1)	7	(0.1)	
History of diabetes							<0.001
No	12147	(77.4)	6449	(82.2)	5698	(72.7)	
Yes	3539	(22.6)	1394	(17.8)	2145	(27.3)	
History of coronary artery disease							<0.001

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	No	13509	(86.1)	6842	(87.2)	6667	(85.0)	
	Yes	2177	(13.9)	1001	(12.8)	1176	(15.0)	
History of depression								<0.001
	No	15503	(98.8)	7819	(99.7)	7684	(98.0)	
	Yes	183	(1.2)	24	(0.3)	159	(2.0)	
History of hyperlipidemia								0.422
	No	12791	(81.5)	6415	(81.8)	6376	(81.3)	
	Yes	2895	(18.5)	1428	(18.2)	1467	(18.7)	
History of alcohol dependence syndrome								<0.001
	No	15646	(99.7)	7841	(100.0)	7805	(99.5)	
	Yes	40	(0.3)	2	(0.0)	38	(0.5)	
Thyroid disorders								0.001
	No	15122	(96.4)	7604	(97.0)	7518	(95.9)	
	With Hypothyroidism	102	(0.7)	34	(0.4)	68	(0.9)	
	With Hyperthyroidism	133	(0.8)	57	(0.7)	76	(1.0)	
	With Acquired Hypothyroidism	5	(0.0)	3	(0.0)	2	(0.0)	
	Others	324	(2.1)	145	(1.8)	179	(2.3)	

+ T test; chi-squared test for all other p-values.
Definition of the variables: opd=outpatient visit; ipd=inpatient hospitalization
Tinnitus: ICD 9CM 388.30; opd*3 or ipd*1; diagnosed 1 year prior to index date.
Hearing loss: ICD 9CM 388.1, 388.2, 389.10, 389.0, 389.2, 389.9; opd*3 or ipd*1; diagnosed 1 year prior to index date.
Hypertension: ICD 9CM 401; opd*3 or ipd*1; diagnosed 1 year prior to index date.
Obesity: ICD 9CM 278.0; opd*3 or ipd*1; diagnosed 1 year prior to index date.
Diabetes: ICD 9CM 250, A181; opd*3 or ipd*1; diagnosed 1 year prior to index date.
Coronary artery disease: ICD 9CM 414.0, 414.8, 414.9; opd*3 or ipd*1; diagnosed 1 year prior to index date.
Depression: ICD 9CM 311; opd*3 or ipd*1; diagnosed 1 year prior to index date.
Hyperlipidemia: ICD 9CM 272; opd*3 or ipd*1; diagnosed 1 year prior to index date.
Alcohol dependence syndrome: ICD 9CM 303; opd*3 or ipd*1; diagnosed 1 year prior to index date.

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Hypothyroidism: ICD 9CM 243, 244.8, 244.9; opd*3 or ipd*1; diagnosed 1 year prior to index date.
Hyperthyroidism: ICD 9CM 242; opd*3 or ipd*1; diagnosed 1 year prior to index date.
Acquired hypothyroidism: ICD 9CM 242 & 244.0, 244.1, 244.2, 244.3; opd*3 or ipd*1; diagnosed 1 year prior to index date.

Table 2. Adjusted odds ratio of dementia associated with tinnitus

Variable		Dementia		
		Adjusted odds ratio	95% CI	*p* value
50 ≦ Age < 65 (n=1806)				
History of tinnitus				
	No	1.00	—	—
	Yes	2.68	(1.19-6.05)	0.017
65 ≦ Age (n=13324)				
History of tinnitus				
	No	1.00	—	—
	Yes	1.17	(0.90-1.51)	0.235

Adjusted odds ratio (aOR) was adjusted for sex, age, history of tinnitus, hypertension, diabetes, coronary artery disease, depression, hyperlipidemia, alcohol dependence syndrome, thyroid disorders, hearing loss and radioactive iodine treatment by logistic regression analysis. History of obesity was omitted from the analysis due to small number.
CI: confidence interval.

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SUMMARY

- Tinnitus, a condition impacting 10% of American adults, coincides with the growing prevalence of dementia in the aging population. Yet, there remains a scarcity of evidence exploring the connection between these two conditions across various age groups.
- Researchers leveraged the Taiwanese National Health Insurance Research Database (NHIRD) and conducted a population-based, retrospective case-control study in all eligible adults.
- Dementia patients were 1:1 matched to control patients with the same age, sex, and index date (the month and year of dementia diagnosis in the case group) with further adjustment for known risk factors.
- A total of 15,686 patients were identified. Between the case and control groups, there were significant differences ($p < 0.05$) in the proportion of patients who had a history of tinnitus, had a history of hearing loss, had a history of hypertension, had a history of diabetes, had a history of coronary artery disease, had a history of depression, had a history of alcohol dependence syndrome, and had a history of thyroid disorders.
- This nationwide study shows that a history of tinnitus is associated with a 168% increased risk of being diagnosed with dementia in patients aged 50 to 65 years old, but the association is not significant in those older than 65 years old.