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Original Article

Autonomic modulation and the risk of dementia in a middle-aged cohort: A 17-year follow-up study

Yu-Tsung Chou [a,b], Zih-Jie Sun [b,c], Shih-Chieh Shao [d,e], Yi-Ching Yang [b,f], Feng-Hwa Lu [b,f], Chih-Jen Chang [b,g], Tzu-Chi Liao [d], Chung-Yi Li [h,i], Tony Hsiu-Hsi Chen [j], Jin-Shang Wu [b,c,f,1,**], Edward Chia-Cheng Lai [d,1,*]

[a] Department of Health Management Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[b] Department of Family Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[c] Department of Family Medicine, National Cheng Kung University Hospital Dou-Liou Branch, College of Medicine, National Cheng Kung University, Yunlin, Taiwan
[d] School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[e] Department of Pharmacy, Chang Gung Memorial Hospital at Keelung, Keelung, Taiwan
[f] Department of Family Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[g] Department of Family Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi, Taiwan
[h] Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[i] Department of Public Health, College of Public Health, China Medical University, Taichung, Taiwan
[j] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

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ABSTRACT

Background: Altered autonomic modulation, measured by heart rate variability (HRV), has been found to be associated with dementia risk in the elderly. However, long-term follow-up study evaluating the association between autonomic modulation from middle-age and the incidence of dementia has been limited.

Methods: This retrospective cohort analyzed data from Taiwan's National Health Insurance Database covering the period from 2001 to 2017, with a linkage to citywide health examinations conducted by Tainan Metropolitan City, Taiwan. We included subjects aged 45–64 years. The mean follow-up period was 15.75 ± 3.40 years. The measurements of HRV included resting heart rate, high frequency (HF), low frequency (LF), standard deviation of normal-to-normal R–R intervals (SDNN), ratio between the 30th and 15th R–R interval after standing up from the supine position (30/15 ratio), ratio between the R–R intervals during

* *Corresponding author*. School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, 1, University Rd., Tainan 701, Taiwan.
** *Corresponding author*. Division of Family Medicine, National Cheng Kung University Hospital Dou-Liou Branch, No.345, Chuang Ching Rd., Yun Lin 64043, Taiwan.
E-mail addresses: jins@mail.ncku.edu.tw (J.-S. Wu), edward_lai@mail.ncku.edu.tw (E.C.-C. Lai).
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[1] Equal corresponding author contribution.
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expiration and inspiration, and the ratio between the high- and low-frequency components (LF/HF). The main study outcome was the incidence of dementia. We performed multivariable Cox proportional hazard regression models to compare the risk of dementia among different HRV subgroups.

Results: We included 565 participants with a mean age of 53 (SD: 6) years, of whom 44% were male. The risk of dementia was significantly increased in association with lower parasympathetic HRV modulation, including SDNN (HR: 3.23, 95% CI: 1.55–6.73) and 30/15 ratio (HR: 3.52, 95%CI: 1.67–7.42). Moreover, the risk of dementia was increased in subjects with higher LF/HF ratios (HR: 2.05, 95% CI: 1.12–3.72).

Conclusions: Lower parasympathetic activity and higher sympathetic-vagal imbalance in middle-age were associated with dementia risk.

At a glance commentary

Scientific background on the subject

The incidence of dementia among the elderly population is increasing rapidly worldwide, causing the huge socioeconomic burden. We conducted a comprehensive search on PubMed for the period from January 01, 1991 to August 31, 2022) whereby the results of cross-sectional studies showed that autonomic modulation, evaluated by heart rate variability (HRV), is associated with dementia in the elderly. However, long-term follow-up study evaluating the association between autonomic modulation from middle-age and the incidence of dementia is limited.

What this study adds to the field

This cohort study including subjects aged 45–64 years from the database and receiving HRV examination in Tainan, Taiwan, suggested that altered autonomic modulation, including low parasympathetic activity and high sympathetic-vagal imbalance in middle-aged adults may precede the incidence of dementia. Our findings add to the evidence that autonomic modulation in midlife may be associated with the risk of dementia

Dementia causes significant decline of one's cognitive functions which may profoundly impair basic activities of daily living as well as domestic and social functioning [1]. The incidence of dementia among the elderly population is rising rapidly worldwide [2,3]. It is estimated that worldwide, in 2015, there were around 47 million people suffering from dementia, and the numbers are expected to triple by 2050 [2]. Common causes of dementia include Alzheimer's disease, Parkinson's disease, vascular dementia, and dementia with Lewy bodies [1,4]. The symptoms of dementia include cognitive and functional decline, with significant detrimental impact on both the patient's and their family's life and huge global socioeconomic burden [5]. Several modifiable risk factors for dementia such as diabetes, hypertension, dyslipidemia, atherosclerosis and smoking have been recognized [6–10]. However, considering the negative impact of dementia on the whole society, early detection of its risk factors is clinically relevant for the prevention of dementia.

In the human body, sympathetic and parasympathetic systems constitute the autonomic system by acting antagonistically to maintain equilibrium of vital functions [11]. Dysregulated autonomic function is related to the development of hypertension [12], diabetes [13], atherosclerosis [14,15], arrhythmia [16] and even increased risk of mortality [17]. Heart rate variability (HRV), measured as the variation between two consecutive heart beats, is one of several non-invasive and reliable methods for the assessment of cardiac autonomic neuropathy [18]. The HRV parameters may change with age and decline in the elderly [19–21]. In addition, the HRV values may be also influenced by certain medications [22,23], disease [24] and exercise [25,26]. Several indices have been established to evaluate HRV, measured by time domain and frequency domain. For evaluation of parasympathetic activity in the time domain, the resting heart rate, the ratio between the 30th and 15th R–R interval after standing up from the supine position (30/15 ratio), the ratio between the R–R intervals during expiration and inspiration (E/I ratio), and the standard deviation of normal-to-normal R–R intervals (SDNN) have been used [27,28]. The low-frequency component (LF) has been used to evaluate sympathetic activity [29]. Furthermore, in the frequency domain, the ratio between the high- and low-frequency components (LF/HF ratio) has been used to investigate sympathetic-vagal imbalance [29].

The relationship between autonomic modulation and dementia has been reported [30–32]. Reduced parasympathetic tone, increased sympathetic activity, and sympathetic-vagal imbalance have been found to be associated with cognitive decline, Alzheimer's disease or vascular dementia [30–34]. Cohort studies have demonstrated that some parameters of HRV, such as resting heart rate, SDNN or the root mean square of successive differences are associated with the development of cognitive impairment or Alzheimer's disease in elderly patients [32,35,36]. However, autonomic modulation in middle-aged people and its association with the incidence of dementia have not been proven, possibly because of a lack hitherto of a sample with long enough follow-up data and of sufficient size. Therefore, this study aimed to use a nationwide longitudinal database with 17-year follow-up data to evaluate autonomic modulation in subjects, starting from middle age, and its association with long-term development of dementia. Specifically, we linked the data from a citywide

health examination (CHE) campaign to obtain information about subjects' autonomic function, including parasympathetic and sympathetic activity, and sympathetic-vagal imbalance.

Methods

Citywide health examinations

We used data from aCHE to capture information about the subjects' autonomic function. Residents of Tainan Metropolitan City, Taiwan, were recruited for a CHE in 1996, originally as part of an epidemiological study on chronic diseases [37]. After a 3-stage sampling method was executed, a total of 1638 had completed the sample recruitment procedure for the survey, which has been described elsewhere [37,38]. All the subjects were required to avoid consumption of cigarettes, alcohol, coffee and tea on the examination day. A structured questionnaire was used to collect each participant's personal information including demographic characteristics, socioeconomic status, medical history, current medication use, cigarette smoking, alcohol use, physical activity and dietary habits within the past 12 months.

Data source

We used Taiwan's National Health Insurance Database (NHID) from 1999 to 2017 for obtaining the diagnosis of dementia in this study. The details of NHID have been described elsewhere [39]. Briefly, the NHID derives from the National Health Insurance (NHI) program, covering over 99% of the entire Taiwanese population. The NHI is a mandatory health insurance program initiated in 1995 [39]. This single-payer health care program covers participant's expenditures including outpatient care, inpatient care, prescribed medications and dental care. The NHID contains personal information of NHI beneficiaries, including medical visit records (inpatient, outpatient and emergency visits), prescription records, and death records. This study was approved by the research committee of National Cheng Kung University Hospital, Taiwan (IRB number: A-ER-108-025).

Study cohort assembly

We linked the NHID and the CHE data by subjects' ID. The HRV evaluation was performed in 1996. The dementia evaluations occurred between 2001 and 2017, and the index date was defined as 1st Jan 2001. A 5-year washout period from 1996 to 2000 was applied to avoid capturing patients' underlying disease after health examination, and to minimize the uncertainty of dementia diagnosis. This was based on previous studies which indicated the mean time between first symptom to dementia diagnosis to be around 5 years [40–45]. We included subjects aged 45–65 on the index date for this study. We excluded subjects with incomplete information about birth date or sex, subjects who had a history of cerebral vascular accidents, subjects who had received treatment for arrhythmia when recruited, and those who were diagnosed with dementia or died within 5 years before the index date. The exclusion process for selecting eligible participants is shown in [Supplementary Fig. 1] and all the included subjects from the original cohort had completed the follow-up course.

Study groups

Study subjects were classified on the basis of HRV, which was examined in the CHE in 1996. The electrocardiography (ECG) and HRV analyses were performed for all participants by well trained technicians. The participants were asked to rest in supine position for at least 15 min before assessment of HRV. The cardiac cycle was evaluated by an ECG monitor (Cardi-Suny 800, Fukuda M-E Kogyo Inc., Tokyo, Japan) on a personal computer-based data acquisition system with the following examinations: 1) normal breathing for 5 min in supine position, 2) an active standing up from the lying position, and then 3) six deep breaths over 1 min long while sitting. The protocol and meaning of the HRV examinations are shown in [Supplementary Table 1 38,46].

HRV may change with age and there is no universal cutoff value for each parameter. We therefore categorized subjects into quartiles of HRV values, following the example of previous studies [47–51]. Those in the highest quartile of parasympathetic parameters, and those in the lowest quartile of sympathetic-vagal imbalance and sympathetic parameters, were defined as the reference group for comparison. The resting heart rate (RHR) (Q2-Q4 versus Q1), HF (Q1-Q3 versus Q4), SDNN (Q1-Q3 versus Q4), 30/15 ratio (Q1-Q3 versus Q4), and E/I ratio (Q1-Q3 versus Q4) were analyzed for parasympathetic activity. We also classified subjects based on LF/HF ratio, an indicator for sympathetic-vagal imbalance (Q2-Q4 versus Q1), and LF, an indicator of predominantly sympathetic with some parasympathetic activity (Q2-Q4 versus Q1).

Study endpoints and follow-up

The primary study endpoint was dementia (documented in the NHIRD), which was defined by the following ICD-9-CM codes: 290, 294.1, 331.0, 331.1, 331.2, 331.82 or ICD-10 codes: F01.50, F01.51, F02.80, F02.81, F03.90, F03.91, G30.0, G30.1, G30.8, G30.9, G31.1, G31.83 and ACODE codes: A222, A210, A213. We followed up subjects from the index date to the occurrence of dementia, death or the last date of the NHIRD (12/31/2017).

Covariates

We determined the covariates based on literature review and experts' opinions [1]. The covariates included participants' age, sex, social economic status, lifestyle information (such as smoking status, alcohol consumption and exercise habits), anthropometric measurements, blood pressure, and blood biochemical examination reports. Smoking habit was defined as smoking at least 1 pack/month in the past 6 months. Alcohol use was the consumption of at least 1 alcoholic drink per week for the preceding 6 months. Regular exercise was defined as exercising at least 3 times/week. The socioeconomic status of each participant was categorized into

one of 3 groups (low, medium, high), according to their self-reported occupation. The body weight (to the nearest 0.1 kg) and body height (to the nearest 0.1 cm) were measured by trained nurses. BMI was then calculated as weight/square of height (m^2). Subjects were asked to rest in a supine position for 10 min and blood pressure and heart rate of the right upper arm were subsequently measured by a DINAMAP^{TM} vital sign monitor (Model 1846SX, Critikon Inc., Irvine, CA, U.S.A.). Hypertension was defined as a positive personal history of hypertension, a right brachial SBP $\geq$140 mmHg or DBP $\geq$ 90 mmHg. After overnight fasting for at least 10 h, a blood sample was taken for laboratory analysis including fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), 2 h post-load glucose (2h-PG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and apolipoprotein E genotyping [52]. Diabetes mellitus was diagnosed if at least one of the following conditions was fulfilled: 1) a positive history of diabetes, 2) FPG level $\geq$ 126 mg/dL, 3) HbA1c $\geq$ 6.5% or 4) 2-h PG $\geq$ 200 mg/dL [53].

Statistics analysis

We described categorical variables by numbers and percentages and continuous variables by means and standard deviations. We calculated the incidence rate of dementia as the number of events divided by the follow-up time in 1000 person-years. We used a cumulative incidence function to compare the incidence rate of dementia among different subgroups by various HRV parameters. We performed multivariable Cox proportional hazard regression models with adjustment for the aforementioned covariates to compare the risk of dementia among different HRV subgroups. In addition, to minimize potential selection bias, we applied the propensity score method to create two more homogenous subgroups with balanced distribution of covariates for comparisons. The propensity score was calculated using logistic regression models conditional on all covariates. We applied inverse probability of treatment weighting (IPTW) and standardized mortality ratio weighting (SMRW) with propensity score [54] to generate risk comparisons on the basis of the average effects from autonomic modulation. The IPTW created two pseudo-populations sharing similar propensity scores and provided the average effects, based on the entire study population. The SMRW created a pseudo-population of reference group that had similar propensity score to the comparison group, and provided the average effects based on the characteristics of the comparison group [54]. The covariates used for calculating propensity score included age, sex, socio-economic status, BMI, SBP, FPG, TC/HDL-C ratio, apolipoprotein E genotype, cigarette smoking, alcohol consumption, and exercise. We used SAS V.9.4 (SAS Institute) for all the data analysis.

Results

A total of 565 participants were included in the final analysis (Supplementary Fig. 1). Table 1 shows the baseline characteristics of the participants in this study. The mean age at examination was 53 with a standard deviation of 6 years, and 44% were male. The detailed comparison of demographic information between different subgroups of autonomic parameters before and after adjustment with the propensity score methods (including IPTW and SMRW approaches) is presented in the supplementary material [Supplementary Tables 2–8].

Table 2 demonstrates the relationship between parasympathetic activity and dementia. The number of events, event follow-up period and incidence rates of dementia in each subgroup analysis are presented. Among parasympathetic parameters, subjects had a relatively lower (Q1-Q3) SDNN and a higher risk of dementia, compared to those with the highest quartiles of SDNN in both models using IPTW (HR: 3.23, 95% CI: 1.55–6.73) and SMRW (HR: 3.46, 95% CI: 1.51–7.96) with propensity score. The IPTW and SMRW models also showed an increased risk of dementia in subjects with lower 30/15 ratio, compared to those with the highest

Table 1 Baseline characteristics of the study sample.

Variables	Study sample for analysis (n = 565)
Age at start of follow-up, years	52.97 ± 5.82
Age 45–54 y/o at start of follow-up	357 (63.19)
Age 55–64 y/o at start of follow-up	208 (36.81)
Follow-up duration, years	15.75 ± 3.40
Male	248 (43.89)
Socio-economic status	
Low n (%)	154 (27.26)
Median to high	411 (72.74)
Body mass index, kg/m^2	24.51 ± 3.35
Body mass index ≥27	110 (19.47)
Systolic blood pressure	118.5 ± 18.08
Diastolic blood pressure	73.09 ± 10.32
Hypertension	103 (18.23)
Fasting plasma glucose, mg/dL	98.21 ± 24.53
Diabetes mellitus	52 (9.20)
Total cholesterol, mg/dL	200.6 ± 43.52
HDL-C, mg/dL	49.42 ± 14.19
Triglycerides, mg/dL	138.7 ± 161.0
Total cholesterol/HDL-C ratio	4 ± 1.69
Total cholesterol/HDL-C ratio ≥ 5	160 (28.32)
ApoEϵ4	55 (9.73)
Use of diabetes mellitus medication, yes	13 (2.30)
Use of hypertension medication, yes	39 (6.90)
Smoking, yes	117 (20.71)
Alcohol consumption, yes	82 (14.51)
Exercise, yes	73 (12.92)
Resting heart rate, bpm	68.11 ± 11.21
HF	283.3 ± 187.5
SDNN	34.36 ± 89.93
30/15 ratio	1.11 ± 0.10
E/I ratio	1.23 ± 0.11
LF	814.5 ± 445.6
LF/HF ratio	7.15 ± 13.90

Data are expressed as the mean ± standard deviation or number (percent).
HDL-C: high-density lipoprotein-cholesterol, RHR: resting heart rate, HF: high frequency, SDNN: standard deviation of normal-to-normal R–R intervals, LF: low frequency E/I ratio: ratio between the R–R intervals during expiration and inspiration.

Table 2 Relationship between parasympathetic activity indices and dementia risk.

Variables	N	Event	Follow year	Incidence rate (1000 person-years)	Overall population		IPTW with PS		SMRW with PS	
					HR	95% CI	HR	95% CI	HR	95% CI
RHR										
Q2-Q4	404	22	6391.13	3.44	0.95	0.44–2.06	1.06	0.63–1.77	1.10	0.59–2.06
Q1	161	9	2505.41	3.59	1.00	reference	1.00	reference	1.00	reference
HF										
Q1-Q3	424	24	6623.00	3.62	1.19	0.51–2.77	1.05	0.62–1.79	0.97	0.54–1.76
Q4	141	7	2273.54	3.08	1.00	reference	1.00	reference	1.00	reference
SDNN										
Q1-Q3	427	28	6754.52	4.14	2.94	0.89–9.66	3.23	1.55–6.73	3.46	1.51–7.96
Q4	138	3	2142.02	1.40	1.00	reference	1.00	reference	1.00	reference
30/15 ratio										
Q1-Q3	424	28	6652.51	4.21	3.19	0.97–10.50	3.52	1.67–7.42	4.43	1.78–10.99
Q4	141	3	2244.03	1.34	1.00	reference	1.00	reference	1.00	reference
E/I ratio										
Q1-Q3	424	24	6633.16	3.62	1.19	0.51–2.75	0.91	0.53–1.54	0.86	0.48–1.51
Q4	141	7	2263.38	3.09	1.00	reference	1.00	reference	1.00	reference

RHR: resting heart rate, HF: high frequency, SDNN: standard deviation of normal-to-normal R-R intervals, E/I ratio: ratio between the R-R intervals during expiration and inspiration, IPTW: inverse probability of treatment weighting, SMRW: standardized mortality ratio weighting, PS: propensity score, HR: hazard ratio, 95% CI: 95% confidence interval,

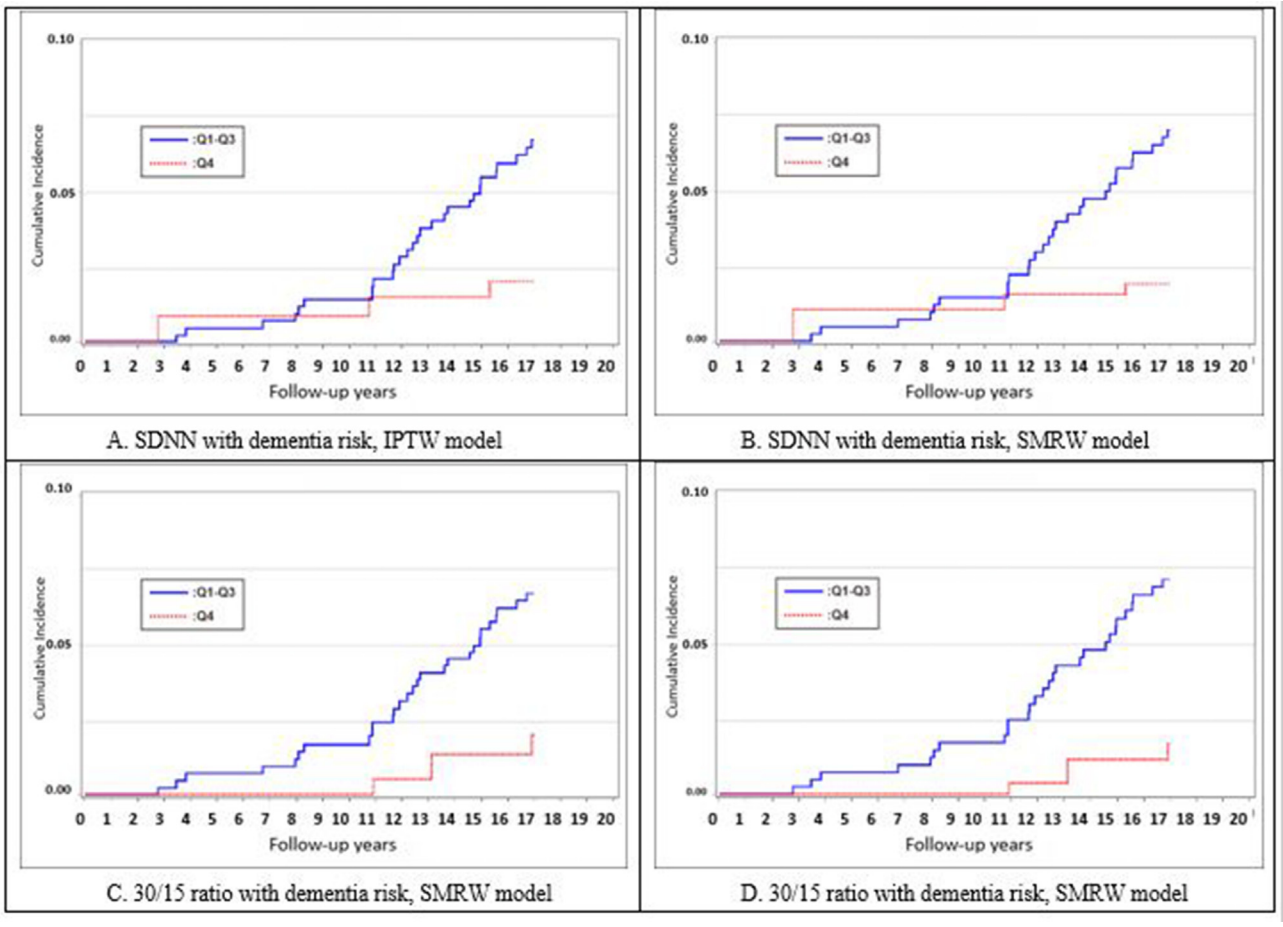

Fig. 1 **Cumulative incidence curves of parasympathetic activity indices with dementia by propensity score analysis. (A)** SDNN with dementia risk in IPTW model, Q1-Q3 (in blue) vs Q4 (in red), **(B)** SDNN with dementia risk in SMRW model, Q1-Q3 (in blue) vs Q4 (in red), **(C)** 30/15 ratio with dementia risk in IPTW model, Q1-Q3 (in blue) vs Q4 (in red) **(D)** 30/15 ratio with dementia risk in IPTW model, Q1-Q3 (in blue) vs Q4 (in red); SDNN: standard deviation of normal-to-normal R–R intervals, IPTW: stabilized inverse probability of treatment weighting, SMRW: standardized mortality ratio weighting, 30/15 ratio: the ratio between the 30th and 15th R–R interval after standing up from the supine position.

quartiles (HR: 3.52, 95%CI: 1.67–7.42, and HR: 4.43, 95% CI: 1.78–10.99, respectively). However, other parameters of parasympathetic activity, such as resting heart rate, HF, and E/I ratio did not show an increase in the dementia risk under cox proportional hazard regression, IPTW and SMRW models. [Fig. 1] presents the cumulative incidence curves for risk estimation of dementia for SDNN and 30/15 ratio subgroup analyses. The cumulative incidence curves for the rest of the parasympathetic parameters including resting heart rate, HF, and E/I ratio are presented in [Supplementary Fig. 2].

[Table 3] shows the impact of sympathetic-vagal imbalance and predominantly sympathetic activity on dementia risk. The IPTW of the cox model showed that the highest quartile of LF/HF ratio was significantly associated with risk of dementia (HR: 2.05, 95% CI: 1.12–3.72). Furthermore, the cox proportional hazard regression and SMRW model of the cox regression also demonstrated a trend of higher dementia risk among those with the highest quartile of LF/HF ratio (HR: 2.38, 95% CI: 0.83–6.80, and HR: 1.73, 95% CI: 0.90–3.33, respectively). However, the relationship between LF, the sympathetic parameter, and the development of dementia was insignificant in the cox proportional hazard regression, IPTW and SMRW by COX regression models [Table 3]. The cumulative incidence curves for dementia in both LF/HF and LF subgroups are presented in [Fig. 2].

Discussion

Principal findings

This is the first population-based cohort study with 17-year follow-up data to evaluate autonomic modulation in a middle-aged population in association with the development of dementia. We found the risk of dementia was significantly increased in subjects with lower parasympathetic activity, measured by SDNN and 30/15 ratio. Moreover, the risk of dementia was increased in subjects with higher sympathetic-vagal imbalance, measured by low-frequency/high frequency ratio. On top of traditional risk factors such as hypertension, diabetes, and dyslipidemia, we found autonomic modulation, as measured by heart rate variability in middle age, could be a predictor for the incidence of dementia.

Parasympathetic activity and sympathetic-vagal indices

Previous cross-sectional studies have demonstrated that lower parasympathetic activity or higher sympathetic-vagal imbalance were associated with higher risk of dementia, Alzheimer's disease or cognitive decline in elderly adults [31,35,36,55–58]. A few longitudinal studies have also demonstrated that autonomic dysfunction such as decreased parasympathetic tone may be associated with dementia or poor cognitive performance in the elderly [32,35,36]. Some studies have provided indirect evidence of mid-life HRV playing a role in the prediction of dementia risk in later life. Some cross-sectional studies have demonstrated that HRV parameters (e.g., SDNN and LF/HF ratio) are significantly related to cognitive performance in middle-aged adults [51,59,60]. A longitudinal study has shown that high SDNN is associated with better cognitive performance evaluated in the future [35].Extending this knowledge, our result was consistent in that autonomic dysfunction in middle-age was associated with the development of dementia [61]. The mechanisms surrounding autonomic modulation (e.g., decreased parasympathetic tone and sympathetic-vagal imbalance) and damage to the central nervous system remain unclear. One possible path may be that reduced parasympathetic tone may result in chronic vasoconstriction and impaired cerebral blood flow regulation [62], which may relate to neurodegeneration. Although vascular dementia and neurodegeneration differs somewhat in their disease characteristics, they may share similar risk factors in their pathophysiology [2,63]. For example, reduced parasympathetic tone and sympathetic-vagal imbalance are related to orthostatic hypotension [64–67], which might be a culprit for transient cerebral hypoperfusion and subsequent brain damage and subsequent development of both vascular dementia and Alzheimer's disease [61,63]. In addition, accumulated evidence has indicated that impaired autonomic activity is related to elevated blood pressure, including both pre-hypertension and hypertensive status [68–71], which has been shown to have a dose–response effect on risk of both vascular dementia and neurodegeneration at midlife [72,73]. Furthermore, autonomic dysregulation increases insulin resistance and dysglycemia [46,74], and diabetic neuropathy also exacerbates autonomic dysfunction [24]. This bidirectional interaction might be

Table 3 Association of sympathetic activity and sympathetic-vagal imbalance with dementia risk.

Variables	N	Event	Follow year	Incidence rate (1000 person-years)	Overall		IPTW with PS		SMRW with PS	
					HR	95% CI	HR	95% CI	HR	95% CI
Sympathetic-vagal imbalance										
LF/HF ratio										
Q2-Q4	424	27	6611.49	4.08	2.38	0.83–6.80	2.05	1.12–3.72	1.73	0.90–3.33
Q1	141	4	2285.05	1.75	1.00	reference	1.00	reference	1.00	reference
Sympathetic activity										
Low frequency										
Q2-Q4	423	23	6616.51	3.48	1.00	0.45–2.24	0.97	0.59–1.60	0.93	0.53–1.64
Q1	142	8	2280.03	3.50	1.00	reference	1.00	reference	1.00	reference

Abbreviations; LF: low frequency; HF: high frequency; IPTW: inverse probability of treatment weighting, SMRW: standardized mortality ratio weighting, PS: propensity score, HR: hazard ratio, 95% CI: 95% confidence interval.

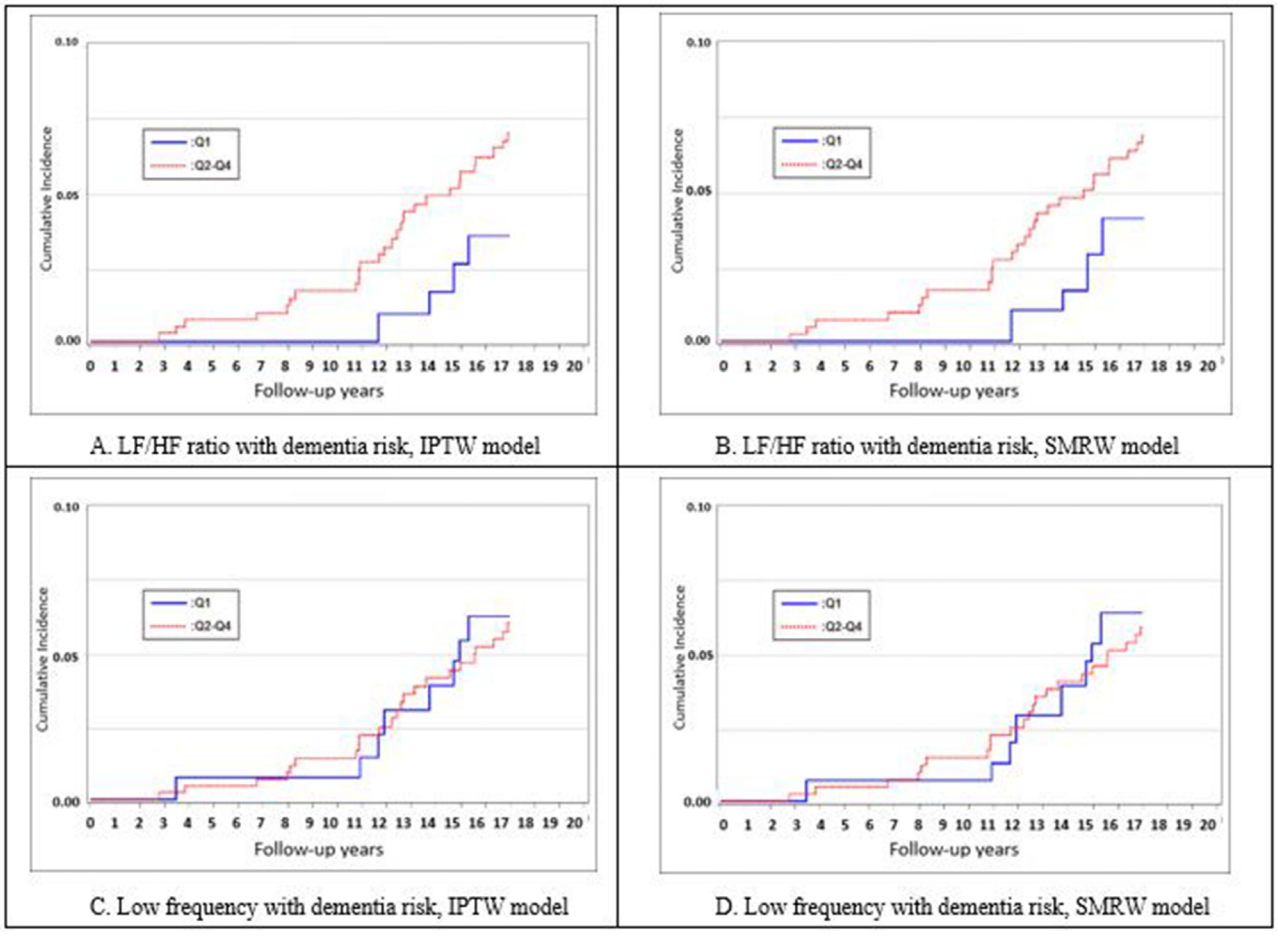

Fig. 2 **Cumulative incidence curves of sympathetic activity and sympathetic-vagal imbalance with dementia by propensity score analysis**. **(A)** LF/HF ratio with dementia risk in IPTW model, Q1 (in blue) vs Q2-Q4 (in red), **(B)** LF/HF ratio with dementia risk in SMRW model, Q1 (in blue) vs Q2-Q4 (in red), **(C)** Low frequency with dementia risk, IPTW model, Q1 (in blue) vs Q2-Q4 (in red) **(D)** Low frequency with dementia risk in SMRW model, Q1 (in blue) vs Q2-Q4 (in red); LF/HF ratio: The ratio between low frequency power and high frequency power, IPTW: stabilized inverse probability of treatment weighting, SMRW: standardized mortality ratio weighting.

associated with the process of cerebral neurodegeneration and vessel damage [75]. Thus, poor blood pressure and blood glucose control provide another possible explanation for the causal relationship between autonomic dysfunction and the development of dementia.

Low frequency activity and dementia

We did not find an association between LF and the development of dementia. This result was similar to a systematic review and meta-analysis wherein LF activity was not associated with Alzheimer's disease [55]. The biological mechanism for this result has not been well elucidated. Although LF has traditionally been used to evaluate sympathetic activity [29], some evidence suggests that LF represents not only sympathetic tone, but also modified parasympathetic activity [76,77], which makes LF a poor marker of pure sympathetic function [76,77]. Therefore, the controversial features of LF may limit its role in predicting the development of dementia.

Clinical implications

Dementia leads not only to detrimental impacts on patients and families, but also huge burdens on health care systems in modern society. Since the prevalence of dementia continues to rise rapidly worldwide, finding potential risk factors of dementia as early as possible is critical for prevention. This study assessed autonomic modulation evaluated by HRV in middle-aged subjects, and assessed the association with dementia risk. Because HRV is a well-established, non-invasive examination for evaluating autonomic dysregulations, it could be considered as a convenient, relatively low-cost tool with which to predict dementia risk. Future investigation evaluating the pattern of long-term, time-varying HRV and the

associated dementia may be helpful to obtain more information about the relationship between autonomic dysfunction and the development of dementia.

Strengths and limitations

This population-based study incorporated a long follow-up period with detailed information about standard HRV measurements including parasympathetic, predominantly sympathetic, and sympathetic-vagal imbalances. Our data containing comprehensive information about personal history, socio-economic status, lifestyles and laboratory data provides the evidence from the real-world practice [78]. However, there were some limitations to this study. First, the diagnosis of dementia was obtained from the NHID data set, which was based on ICD-9-CM and ICD-10 diagnostic coding. We defined the diagnosis of dementia based on previous studies [79–84]. However, these diagnose have not been validated in the NHID, leading to possible misclassification of study outcomes. We may have underestimated the effects on the development of dementia across various HRV groups. The database did not provide detailed information on the subtype or severity of dementia, or on the medication used for the dementia. Second, the HRV parameters were assessed cross-sectionally, leading to possible misclassification if the subjects' condition changed over time after the follow-up. Therefore, we may have underestimated the impact of autonomic modulation on the prediction of dementia (i.e., bias toward null due to misclassification). Third, some residual confounders should be acknowledged, including catecholamine activation, increased stress, sleep deprivation, and heart disease. Future studies taking these confounders into account may be warranted to confirm our findings. Fourth, we could not conduct response curve analysis or subgroup analysis due to the relatively small sample size and event numbers (A post-hoc analysis indicated only 5 cases of Alzheimer's disease and 26 cases of other subtypes of dementia). Fifth, orthostatic hypotension is also considered to be related to sympathetic dysfunction. However, our study lacked parameters that could properly reflect sympathetic activity. The only available parameter for sympathetic tone was LF, which was known to represent both sympathetic tone and modified parasympathetic activity [76,77]. Hence, sympathetic modulation was not thoroughly investigated in this study. Further study might be necessary to evaluate the role of sympathetic modulation in predicting dementia risk. Lastly, we classified patients based on HRV examinations performed in 1996, but the HRV may have changed over time due to aging, exercise, diseases or exposure to medications. These changes in HRV may have led to misclassification bias toward null in our results. Although the differences remained statistically significant among the HRV groups, we may have underestimated the actual effects from autonomic modulation.

Conclusion

We found that subjects with lower parasympathetic activity, measured by SDNN and 30/15 ratio, and subjects with higher sympathetic-vagal imbalance, measured by low-frequency/high frequency ratio had higher risk of dementia. On top of traditional risk factors such as hypertension, diabetes, and dyslipidemia, autonomic dysfunction, measured by HRV in middle age, could be a good predictor for dementia. This finding offers a foundation for further study regarding early identification of increased dementia risk and may lead to opportunities for early prevention and interventions. It also provides strong grounds for future large, prospective studies to confirm the association between autonomic dysfunction in middle age and long-term outcome of dementia.

Ethics approval and consent to participate

This study was approved by the research committee of National Cheng Kung University Hospital, Taiwan (IRB number: A-ER-108-025).

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Conflicts of Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bj.2022.12.004.

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