Heart rate variability predicts 8-year risk of cardiovascular disease: The Taiwan Bus Driver Cohort Study (TBDCS)

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Original investigation

Keywords: Early monitoring, Heart rate variability, Cardiovascular diseases, Professional bus driver, Cohort study

Posted Date: June 22nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-35202/v1>

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Abstract

Background: Characteristics of professional drivers like irregular work shifts, long hours of driving, sedentary restricted postures, long-term sleep deficiency, increase the probability of developing cardiovascular disease (CVD). Therefore, early monitoring CVD risk is important to device preventive measures in the workplace.

Objective: This cohort study used to evaluate the effectiveness of noninvasive heart rate variability (HRV) analysis to assess the 8-year risk of CVD events.

Methods: Personal and working characteristics were collected before biochemistry examinations and 5-min HRV tests from Taiwan Bus Driver Cohort Study (TBDCS) in 2005. Then, this cohort was linked to Taiwan's National Health Insurance Research Database (NHIRD) to obtain subjects' medical information. This study eventually identified 161 drivers with CVD and 627 without from 2005 to 2012. Cox proportional hazards model were performed to estimate the hazard ratio for CVD.

Results: Subjects with overall CVD had lower the standard deviation of NN intervals (SDNN) than their counterparts. Even after adjusting for risk factors, SDNN index have a strong association with overall CVD. Using median split for SDNN, hazard ratio of overall CVD was 1.83 (95% CI 1.10–3.04) in model 1 and 1.87 (95% CI 1.11–3.13) in model 2. Furthermore, Low frequency (LF) index associated with risk of overall CVD in the continuous approach. For hypertensive disease, the SDNN index was associated with increased risks in both the continuous and dichotomized approaches. When Root Mean Square of the Successive Differences (RMSSD), high frequency (HF), and LF as a continuous variable, the significant association with hypertensive disease were observed.

Conclusions: This cohort study suggests that SDNN and LF levels are useful for predicting 8-year CVD risk, especially for hypertensive disease. Further research is required to determine preventive measures for modifying HRV dysfunction as well as to investigate whether these interventions could reduce CVD risk in professional drivers.

Background

Cardiovascular disease (CVD) is not only the number one cause of death worldwide, but it is also one of the compensable work-related diseases [1, 2]. Research into occupational health of bus drivers has been conducted since the 1950s.^[3] Male bus drivers have an increased risk of and mortality from myocardial infarction (MI), ischemic heart disease (IHD), coronary heart disease (CHD),^[4–6] stroke,^[7] and arteriosclerosis based on brachial-ankle pulse wave velocity.^[8] Some studies have indicated that bus drivers have a high risk of developing CVD because of a high workload and psychosocial work environment, including a highly demanding job, overtime work, irregular shifts, and limited time for meals and rest.^[6, 9, 10] Therefore, early monitoring CVD risk is important to device preventive measures and thus limiting further health damage.

Examination of heart rate variability (HRV) is a simple, noninvasive, and relatively inexpensive method for an epidemiological study with a large sample size.^[11–17] HRV measures specifically reflect vagal activity and have been recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). The cardiovascular system is controlled by the nervous system, specifically the autonomic nervous system (ANS).^[17–19] Table S1 (available as online-appendix) presents the definitions of HRV measures applied in our research.^[20, 21]

Reduced HRV as a marker of autonomic dysfunction has been shown to be associated with a poor prognosis of CVD as well as with MI incidence, CVD mortality, and death from other causes in the general population.^[22–29] Furthermore, decreased HRV at rest is associated with a poor prognosis of CVD,^[30] and reduced resting HRV is considered a risk marker for future cardiovascular and other stress-related disease.^[31]

However, several problems were shown in this research field, including an incomplete CVD data collection, small sample sizes, and poor control for confounding factors, which limited the assessment of an independent predicted role for HRV, and did not show clear causal association. Thus, we performed a perspective cohort study to evaluate the effectiveness of noninvasive HRV analysis to measure professional drivers' autonomic function and then investigated the relationship between HRV and the 8-year risk of CVDs.

Materials/subjects And Methods

Study population

A Taiwan Bus Drivers Cohort (TBDC) was established previously^[32] for a longitudinal follow-up study. We linked this cohort to Taiwan's National Health Insurance Research Database (NHIRD) to obtain the medical information of these subjects. The Institutional Review Board of the National Health Research Institutes, Taiwan, approved this study (NIRB File Number: EC1060516-E). The constitution and operation of review board are formulated according to the guidelines of ICH-GCP. Authors confirm that all experiments were performed in accordance with relevant guidelines and regulations. Informed consent was obtained from all participants. A questionnaire was used to collect basic information and working patterns, including demographic characteristics, work conditions (year of first employment and bus driving experience), lifestyle habits, and job stress assessment.

Figure 1 illustrates the procedures used in this study. The TBDC includes 1650 professional drivers from the largest transportation company in Taiwan since 2006. We used a Driving Hours Dataset from 2005 to 2007 to exclude subjects with a driving duration of fewer than 100 days ($n = 613$). Then, personal and working characteristics were collected before biochemistry examinations and HRV tests were performed from 2007 to 2008. We excluded individuals with incomplete questionnaires or laboratory data ($n = 249$). Subsequently, we linked the remaining 788 drivers to the ambulatory care expenditures-by-visits and inpatient expenditures-by-admissions data from the NHIRD from 2005 to 2012. The criteria for defining CVD cases was that study subjects had at least five recorded clinical visits because of CVD within a year or at least one inpatient record because of CVD for the first-listed diagnosis code. The strict criteria can

increase sensitivity and decreased specificity for CVD disease confirm. We identified 161 drivers with CVD (ICD-9-CM: 390–459) and 627 drivers without CVD from 2005 to 2012. Among the 161 drivers with CVD, 84 had CVD history before 2006. Finally, 77 incident CVD cases were defined. Meanwhile, CVD (not including hypertensive disease) (ICD-9-CM: 391, 392.0, 393–398, 410–414, 416, 420–429), IHD (ICD-9-CM: 410–414), cerebrovascular disease (ICD-9-CM: 430–438), and congestive heart failure (CHF) (ICD-9-CM: 398.91, 422, 425, 428, 402.x1, 404.x1, 404.x3) were solely investigated.

HRV and Biochemical Measurements

Each participant underwent a blood biochemistry test and noninvasive HRV examination in resting conditions by using an ANS Analyzer (Medicore SA-3000P, Jamsil-dong, Songpa-gu, *Seoul, Korea*). The change in heart rate during a short term (5 minutes) is analyzed by the method of time domain and frequency domain. This provides the degree of balance and activity of the ANS. The standard deviation of the Normal-to-Normal beats interval (SDNN) and the square root of the mean squared differences of successive N-N intervals (RMSSD), were used to compare the time domain indexes. Frequency domain methods, including very low frequency (VLF, 0.0033–0.04 Hz), low frequency (LF, 0.04–0.15 Hz), high frequency (HF, 0.15–0.4 Hz), and total power (TP), were used to determine the sympathetic and parasympathetic heartbeat rate modulations at rest. Physical stress index (PSI) reflected the load and pressure to the heart based on SDNN at the same time.

Biochemical analysis of fasting blood glucose (FG) was conducted using Hexokinase method on an AU640 analyzer (Beckman Coulter Ltd., High Wycombe, UK). For the determination of total cholesterol, the assay employed the Cholesterol Oxidase method on an AU640 analyzer (Beckman Coulter Ltd., High Wycombe, UK). Triglycerides (TG) concentration was determined using an enzymatic method on an on an AU640 analyzer (Beckman Coulter Ltd., High Wycombe, UK). High-density lipoprotein cholesterol (HDL-C) level was determined using the immunoinhibition method on an on an AU640 analyzer (Beckman Coulter Ltd., High Wycombe, UK).

Statistical analysis

Analyses were performed using SAS (Version 9.3 for Windows; SAS Institute Inc., Cary, NC, USA). Means and standard deviations were used to describe the distributions of continuous variables. Logarithmical transformation was performed to approximate the normal distribution. This study also used a Cox proportional hazards model to assess the effect of HRV parameters on the risk of CVD (hazard ratios (HRs) and 95% confidence intervals [CIs]) and to adjust for confounding variables. Standard median splits is used on HRV parameters (the continuous variables) to turn them into dichotomous variables. We adjusted for age at first employment (≥ 45 vs. < 45 years), body mass index (BMI; > 30 vs. ≤ 30), education, drinking, smoking, exercise, time since first employment (years), and shift work in model 1. Next, we adjusted for clinical conditions, including the systolic blood pressure, LnCHOL, LnTG, LnHDL, and Ln (fasting glucose) in model 2.

Results

Demographic characteristics of the study population were presented in table 1. A total of 788 drivers and 5334.2 person-years was accumulated in this cohort. Almost half of the cohort subjects were older than 40 years old at the time of their first employment (43.3%), more than half of the cohort (51.5%) had >5 years of driving experience, and almost half of the subjects worked irregular shifts (47%). About 16% of the cohort subjects were obese (body mass index [BMI] ≥ 30 kg/m²), 21.7% of subjects had a drinking habit, and more than half of the subjects had a smoking habit (57.5%).

Comparison of HRV parameters between different cardiovascular diagnostic categories was shown in table S2 (available as *online appendix*). The cohort of 788 subjects included 49 people with CVD (not including hypertensive disease), 128 people with hypertensive disease, 35 people with IHD, 14 people with cerebrovascular disease, 8 people with disease of arteries, arterioles, and capillaries as well as other diseases of the circulatory system, and 15 people with CHF.

HRV indices and 8-year CVD risks

Table 2 lists Hazard Ratio for CVD per single unit increment of HRV parameters (as continuous variables) as well as for dichotomized HRV parameters. For the 788 drivers with known CVD history, an increased SDNN level had a negative association with the risk of CVD in the continuous approach in both models. The SDNN had a significant hazard ratio (per single unit increment) of 0.67 to 0.70. Regarding the dichotomized approach by a median split, a low SDNN level was associated with CVD (hazard ratio = 1.47; 95% CI 1.04–2.07) in model 1 and (1.44; 95% CI 1.01–2.05) in model 2.

Similar to the aforementioned findings, among the 704 drivers without known CVD history at baseline, SDNN index continued to have a statistically significant association with the risk of CVD. In model 2, a single unit increment in Ln SDNN was associated with a decrease of 44% in the hazard for CVD, with adjustments for demographics, working characteristics, and clinical risk factors (95% CI 0.34–0.95, $p = 0.031$). Regarding the dichotomized approach by a median split, a low SDNN was associated with a hazard ratio of 1.83 (95% CI 1.10–3.04) in model 1 and 1.87 (95% CI 1.11–3.13) in model 2. Furthermore, LF index exhibited associations with the risk of CVD in the continuous approach in both models.

HRV indices and 8-year cardiovascular diagnostic categories risks

Tables 3 and table S3 list the hazard ratio of HRV indices for cardiovascular diagnostic categories among the different driver groups with or without known CVD history at baseline. After we excluded 84 cases of prevalent CVD before 2006 (table 3), we found that the SDNN index was associated with increased risks of hypertensive disease in both the continuous and dichotomized approaches. A single unit increment in Ln SDNN was associated with a decrease of 65% in hypertensive disease in both models (model 1: 95% CI: 0.19–0.66, $p = 0.001$; and model 2: 95% CI = 0.19–0.67; $p = 0.002$). Low levels of SDNN (0–30) were associated with increased risks of hypertensive disease in both models (model 1: hazard ratio = 1.99; 95% CI = 1.03–3.84; $p = 0.039$; and model 2: hazard ratio = 2.02; 95% CI = 1.03–3.96; $p = 0.041$).

Meanwhile, a single unit increment in Ln RMSSD was associated with a decrease of 45%–46% in hypertensive disease in two models (model 1: hazard ratio = 0.54; 95 % CI: 0.31–0.92, $p = 0.024$; and model 2: hazard ratio = 0.55; 95% CI = 0.31–0.96; $p = 0.035$).

A single unit increment in Ln HF was associated with a decrease of 26–27% in hypertensive disease in two models (model 1: hazard ratio = 0.73; 95 % CI: 0.57–0.94, $p = 0.015$; and model 2: hazard ratio = 0.74; 95% CI = 0.57–0.96; $p = 0.026$). Ln LF had a significant hazard ratio of 0.76 for hypertensive disease in model 1 (95% CI = 0.59–0.97; $p = 0.027$), which became nonsignificant in model 2.

For congestive heart failure, Ln RMSSD only had a significant hazard ratio of 3.51 for CHF in model 2 (95% CI = 1.03–12.0; $p = 0.046$).

Discussion

This is the first prospective professional cohort study to investigate the association between HRV and the risk of CVD in professional drivers without known CVD. The major finding of this study was that the SDNN and LF levels are useful for predicting the 8-year CVD risk even when adjusting for CVD risk factors. Furthermore, the SDNN and LF levels had an increase of HR for other CVD events such as hypertensive disease.

Each unit increment in Ln SDNN was associated with a decrease of 65% in hypertensive disease in model 2 (95% CI = 0.19–0.67, $p = 0.002$). Our results are consistent with a meta-analysis that indicated that the predicted risks of incident CVD of the 10th and 19th HRV (SDNN) percentiles compared with the 50th percentile were 1.50 (95% CI = 1.22, 1.83) and 0.67 (95% CI = 0.41, 1.09), respectively.^[33] In general, the SDNN is the gold standard for medical stratification of cardiac risk and predict both CVD morbidity and mortality. However, this only applies in recorded over a 24 h period. Our result prove that 5-min HRV test also can detect the cardiac risk during a 8-year follow-up period.

Furthermore, this study observed that LF index associated with risk of overall CVD and hypertensive disease in the continuous approach. While sitting upright during resting conditions, the LF reflects parasympathetic nervous system activity and baroreflex activity, not sympathetic nervous system activity and cardiac sympathetic innervation.^[20] Previous study presented more occupational workload was significantly associated with reduced LF power, which indicates that high workload is associated with attenuated cardiac autonomic modulation during sleep. In contrast, enhanced sympathetic-baroreceptor cardiac modulation during sleep among workers with higher levels of Leisure-time physical activity was observed.^[34] This is a possible pathway that bus drivers have high workload and less leisure-time activity and lead to developing CVDs; thus, low LF power reflect in advance.

Additionally, these drivers with low HRV may already suffer from silent CVD. It represents numerous overlapping risk factors exist for reduced HRV and CVD events.^[35] However, the causal relationship of risk factors with the development of CVD or reduced HRV is still not completely understood. Work stress is found to be associated with both CVD and reduced HRV;^[36] however, we do not yet know whether work stress affects the development of CVD more than it contributes to reduced HRV. Further investigating the association between psychosocial risk factors and HRV indices would be worthwhile.^[37, 38] Psychosocial conditions such as work stress, stressful life events, and mood disorders are emerging risk factors for CVD.^[39] Because risk factors are preceded by indicators of decreased vagal function, HRV is found to be a useful tool for studying work-related stress and the accompanying physiological effects. The SDNN is reported to be significantly lower among those categorized into a high-job-strain group than among those categorized into a low-job-strain group.^[40] Amelsvoort^[36] reported that a decreased SDNN level in shift workers indicates less favorable cardiovascular autonomic regulation. Moreover, numerous studies have indicated that chronic autonomic imbalance with sympathetic dominance may partially explain the effects of work stress on CVD events.^[19] Therefore, HRV could be used to screen workers at high risk of CVD, and preventive measures could be taken in advance.

The strengths of this study include the large cohort, prospective design, noninvasive marker of 5-min HRV measurement, confounders' adjustment, and systematic CVD data collection. Moreover, we fully acknowledge that the methodology of this investigation has some limitations. First, the inclusion of only male professional drivers restricts the generalization of the results to females. Second, HRV may be influenced by the severity of CVD, respiratory patterns, as well as by the use of β -blockers or antidepressants.^[41–43] Thus, analyses should be further stratified by the severity of diseases, such as MI or revascularization, as well as by ICD-10-PCS (Procedure Codes). In addition, a history of diabetes, cognitive disorders, severe lung diseases and the use of β -blockers and antidepressants must be considered. Third, the current study design could not clarify which risk factors contribute more to reduced HRV and CVD events so that preventive measures can be taken in advance. The small number of subjects in these sub-categories is a restriction of this study. It may be difficulty of generalizing enough statistic power to other subjects. Final, this study afraid that high false positive rate will cause incorrect results. Therefore, we used the strict criteria that CVD cases had at least five visits for the same diagnosis medical records within 1 year or inpatient with one or more admissions during the study period based on clinic physician's suggestion. It can increase sensitivity and decreased specificity for CVD disease confirm, but it could be underestimating the effect of our finding result.

Conclusion

This professional driver's cohort study concluded that the HRV parameters SDNN and LF are independent predictors of overall CVD and hypertensive disease, even after adjusting for risk factors. Further research is required to determine preventive measures for modifying HRV dysfunction as well as to investigate whether these interventions could reduce CVD risk in professional drivers.

Tables

Table 1 Baseline characteristics of the study population

Variables	All drivers		Person-years	
	<i>N</i>	(%)	<i>sum</i>	(%)
Total subjects	788	100.0	5334.2	100.0
Non-CVD drivers	627	79.6	5014.3	94.0
CVD drivers ^{a.}	161	20.4	319.9	6.0
CVD history before 2006 ^{a. b.}	84	10.7	11.7	0.2
Age (years)				
<35	87	11.0	666.5	12.5
35-44	340	43.1	2417.4	45.3
45-49	199	25.3	1339.6	25.1
≥50	162	20.6	910.7	17.1
Age at first employment (years)				
≤32	175	22.2	1320.6	24.8
33-38	272	34.5	1872.6	35.1
≥39	341	43.3	2141.1	40.1
Time since first employment (years)				
≤2	150	19.0	1091.8	20.5
2.1-5	232	29.4	1647.2	30.9
5.1-8	164	20.8	1059.9	19.9
>8	242	30.7	1535.4	28.8
Shift work modes ^{c.}				
Day shifts only	338	42.9	2264.8	42.5
Irregular shift	370	47.0	2587.1	48.5
Evening and Night shift	80	10.2	482.4	9.0
BMI (kg/m ²)				
<25	299	37.9	2166.6	40.6
25-29.9	359	45.6	2361.8	44.3
≥30	130	16.5	805.9	15.1
Marital status				
Unmarried	124	15.7	919.8	17.2
Married	577	73.2	3841.7	72.0
Others	87	11.0	572.7	10.7
Education				
≤ Junior high school	235	29.8	1556.9	29.2
Senior high and vocational school	498	63.2	3396.2	63.7
University and College	55	7.0	381.1	7.1
Cigarette smoking				
Current smokers	276	35.0	1808.7	33.9
Ex-smokers	54	6.9	337.4	6.3
Never smokers	453	57.5	3148.1	59.0
Missing	5			
Alcohol use				
Yes	612	77.7	4240.5	79.5

No	171	21.7	1061.3	19.9
Missing	5			
Moderate exercise				
Yes	557	70.7	3857.0	72.3
No	221	28.0	1397.3	26.2
Missing	10			

^aThe selection criteria for CVD (ICD-9-CM: 390–459) were at least five clinical visit records within a year or at least one inpatient record.

^bDrivers who had CVD history before 2006.

^cBased on the Driving Hours Dataset from 2005 to 2007

Table 2 Hazard ratios and 95% confidence intervals for cardiovascular disease by HRV index in the study population

		All drivers (N = 788)							Drivers (N = 704) ^a								
		Model 1 ^b .			Model 2 ^c .				Model 1 ^b .			Model 2 ^c .					
	<i>Independent variables^d</i>	<i>HR</i>	<i>95%CI</i>		<i>p-value</i>	<i>HR</i>	<i>95%CI</i>		<i>p-value</i>	<i>HR</i>	<i>95%CI</i>		<i>p-value</i>	<i>HR</i>	<i>95%CI</i>		<i>p-value</i>
1	As a continuous (LnSDNN)	0.67	0.48	0.93	0.018	0.70	0.50	1.00	0.047	0.57	0.35	0.95	0.029	0.56	0.34	0.95	0.031
2	As a categorical variable: SDNN (≤30 vs. >30)	1.47	1.04	2.07	0.029	1.44	1.01	2.05	0.044	1.83	1.10	3.04	0.020	1.87	1.11	3.13	0.018
3	As a continuous (LnRMSSD)	0.83	0.62	1.10	0.185	0.85	0.64	1.13	0.264	0.83	0.54	1.28	0.397	0.81	0.52	1.26	0.348
4	As a categorical variable: RMSSD (≤20 vs. >20)	1.34	0.95	1.89	0.098	1.34	0.94	1.91	0.104	1.34	0.81	2.20	0.256	1.38	0.83	2.28	0.211
5	As a continuous (LnLF)	0.85	0.74	0.97	0.016	0.88	0.76	1.02	0.084	0.80	0.66	0.98	0.031	0.79	0.64	0.98	0.032
6	As a categorical variable: LF (≤380 vs. >380)	1.18	0.79	1.74	0.420	1.14	0.76	1.69	0.535	1.25	0.70	2.23	0.445	1.25	0.70	2.25	0.453
7	As a continuous (LnHF)	0.91	0.79	1.04	0.176	0.93	0.81	1.06	0.283	0.84	0.69	1.03	0.098	0.84	0.68	1.04	0.112
8	As a categorical variable: HF (≤168 vs. >168)	1.05	0.72	1.54	0.786	1.07	0.72	1.58	0.743	0.98	0.58	1.67	0.949	1.00	0.58	1.71	0.996
9	As a continuous (LnLF/HF)	0.90	0.76	1.06	0.212	0.94	0.80	1.11	0.486	0.93	0.73	1.18	0.541	0.93	0.72	1.19	0.544
10	As a categorical variable: LF/HF (≤3.5 vs. >3.5)	1.27	0.90	1.78	0.173	1.16	0.82	1.63	0.409	1.24	0.75	2.03	0.405	1.20	0.72	1.97	0.486

^aExcluded 84 drivers who had CVD history before 2006.

^bModel 1: Adjusted for age at first employment (≥ 45 vs. < 45 years), body mass index (> 30 vs. ≤ 30), education, drinking, smoking, exercise, time since first employment (years), and shift work.

^cModel 2: As Model 1 with additional adjustments for systolic blood pressure, LnCHOL, LnTG, LnHDL, and Ln(fasting sugar).

^dEach independent variable (1–20) was separately included in the models.

Table 3 Hazard ratios and 95% confidence intervals for cardiovascular events by HRV index in the study population (n = 704)^a

			Cardiovascular disease (not included Hypertensive disease)				Hypertensive disease				Ischemic heart disease				Congestive heart failure (CHF)			
		<i>Independent variables^d</i>	<i>HR</i>	<i>95%CI</i>		<i>p-value</i>	<i>HR</i>	<i>95%CI</i>		<i>p-value</i>	<i>HR</i>	<i>95%CI</i>		<i>p-value</i>	<i>HR</i>	<i>95%CI</i>		<i>p-value</i>
Model 1 ^b	1	As a continuous (LnSDNN)	1.44	0.59	3.55	0.423	0.35	0.19	0.66	0.001	1.12	0.35	3.54	0.851	2.46	0.64	9.42	0.1
	2	As a categorical variable: SDNN (≤ 30 vs. >30)	1.61	0.64	4.05	0.316	1.99	1.03	3.84	0.039	1.36	0.45	4.14	0.584	1.96	0.35	10.95	0.4
	3	As a continuous (LnRMSSD)	2.06	1.01	4.21	0.048	0.54	0.31	0.92	0.024	2.02	0.81	5.03	0.133	2.92	0.92	9.29	0.0
	4	As a categorical variable: RMSSD (≤ 20 vs. >20)	0.80	0.34	1.91	0.615	1.87	0.94	3.70	0.074	0.64	0.23	1.79	0.392	0.82	0.18	3.71	0.7
	5	As a continuous (LnLF)	1.05	0.73	1.51	0.783	0.76	0.59	0.97	0.027	0.96	0.61	1.50	0.855	1.30	0.64	2.66	0.4
	6	As a categorical variable: LF (≤ 380 vs. >380)	1.01	0.36	2.80	0.988	1.31	0.62	2.74	0.479	1.13	0.31	4.11	0.852	0.42	0.07	2.73	0.3
	7	As a continuous (LnHF)	0.99	0.69	1.42	0.971	0.73	0.57	0.94	0.015	1.15	0.73	1.80	0.543	0.90	0.45	1.80	0.7
	8	As a categorical variable: HF (≤ 168 vs. >168)	0.71	0.28	1.77	0.460	1.29	0.63	2.64	0.492	0.66	0.22	1.98	0.453	0.54	0.09	3.26	0.5
	9	As a continuous (LnLF/HF)	1.09	0.71	1.67	0.708	1.04	0.77	1.42	0.786	0.78	0.47	1.32	0.358	1.70	0.72	4.00	0.2
	10	As a categorical variable: LF/HF (≤ 3.5 vs. >3.5)	0.95	0.40	2.26	0.901	1.02	0.56	1.85	0.954	1.34	0.42	4.28	0.621	0.77	0.17	3.53	0.7
Model 2 ^c	11	As a continuous (LnSDNN)	1.70	0.64	4.52	0.290	0.35	0.19	0.67	0.002	1.04	0.30	3.66	0.947	3.18	0.75	13.47	0.1
	12	As a categorical variable: SDNN (≤ 30 vs. >30)	1.61	0.62	4.18	0.332	2.02	1.03	3.96	0.041	1.40	0.44	4.41	0.568	1.94	0.30	12.57	0.4
	13	As a continuous (LnRMSSD)	2.17	1.03	4.59	0.043	0.55	0.31	0.96	0.035	2.30	0.88	5.98	0.089	3.51	1.03	12.02	0.0
	14	As a categorical variable: RMSSD (≤ 20 vs. >20)	0.79	0.33	1.91	0.600	1.92	0.96	3.87	0.067	0.57	0.20	1.68	0.310	0.55	0.09	3.42	0.5
	15	As a continuous (LnLF)	1.02	0.68	1.51	0.936	0.77	0.59	1.01	0.057	0.90	0.55	1.47	0.674	1.35	0.59	3.10	0.4
	16	As a categorical	1.03	0.36	2.91	0.960	1.21	0.57	2.58	0.620	1.19	0.32	4.41	0.790	0.29	0.03	2.67	0.2

		variable: LF (≤380 vs. >380)																
	17	As a continuous (LnHF)	1.03	0.70	1.53	0.880	0.74	0.57	0.96	0.026	1.19	0.73	1.93	0.482	0.89	0.41	1.95	0.7
	18	As a categorical variable: HF (≤168 vs. >168)	0.62	0.24	1.61	0.330	1.28	0.61	2.66	0.517	0.62	0.19	1.96	0.412	0.46	0.06	3.35	0.4
	19	As a continuous (LnLF/HF)	0.98	0.62	1.56	0.932	1.08	0.79	1.48	0.617	0.70	0.40	1.22	0.207	1.72	0.67	4.43	0.2
	20	As a categorical variable: LF/HF (≤3.5 vs. >3.5)	0.95	0.39	2.31	0.901	0.91	0.50	1.67	0.762	1.44	0.45	4.63	0.543	0.79	0.15	4.09	0.7

^aExcluded 84 drivers who had CVD history before 2006.

^bModel 1: Adjusted for age at first employment (≥ 45 vs. < 45 years), body mass index (> 30 vs. ≤ 30), education, drinking, smoking, exercise, time since first employment (years), and shift work.

^cModel 2: As Model 1 with additional adjustments for systolic blood pressure, LnCHOL, LnTG, LnHDL, and LnAC.

^dEach independent variable (1–20) was separately included in the models.

Abbreviations

- CVD: cardiovascular disease
- HRV: Heart rate variability
- (TBDCS)Taiwan Bus Driver Cohort Study
- (NHIRD)Taiwan's National Health Insurance Research Database
- RMSSD: The Root Mean Square of the Successive Differences
- SDNN: The standard deviation of NN intervals
- LF: Low frequency
- HF: High frequency
- ANS: Autonomic nervous system
- MI: Myocardial infarction
- IHD: Ischemic heart disease
- CHD: Coronary heart disease
- CHF: Congestive heart failure
- FG: Fasting blood glucose
- HDL-C: High-density lipoprotein cholesterol
- TG: Triglycerides

Declarations

Ethics approval and consent to participate

The Institutional Review Board of the National Health Research Institutes, Taiwan, approved this study (NIRB File Number: EC1060516-E). The constitution and operation of review board are formulated according to the guidelines of ICH-GCP. Authors confirm that all experiments were performed in accordance with relevant guidelines and regulations. Informed consent was obtained from each of the participants after a detailed explanation of the content.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available due the current analysis was based on data provided by the Health and Welfare Data Science Center, Ministry of Health and Welfare, Executive Yuan, Taiwan, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This study was supported by the National Health Research Institutes of Taiwan (grants 98-EO-PP01, 99-EO-PP01, and 00-EO-PP01) as well as by the Institute of Occupational Safety and Health (grants IOSH96-M102 and IOSH97-M102), Taiwan. The funder had no role in the study design, data collection and analysis, preparation of the manuscript, and decision about publication.

Authors' contributions

YCW designed the study, collected data, analysis, engaged in drafting the manuscript and revising it critically. WTW and BLC carried out acquisition of data, analysis, interpretation of data, and helped to draft the manuscript and revising it critically. CCW participated in data analysis, involved in drafting the manuscript. WTW conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We gratefully acknowledge the contribution of the late Prof. Saou-Hsing Liou to this article. We thank the administrators and drivers at the bus company for their participation and cooperation.

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Figures

Figure 1

Study flow diagram in Taiwan Bus Driver Cohort Study

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