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Correlates of autonomic nervous system function in a general population with special reference to HbA_{1c}: The Nagahama study

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ABSTRACT

Aims: As the glucose tolerance of patients with diabetes worsens, autonomic nervous system (ANS) function decreases. Only a few studies, using plasma glucose, have reported on this relationship in large general populations that include people with wide range of glycemia. This study aimed to examine correlates of ANS function with special reference to HbA_{1c} which is more stable than plasma glucose among community residents.

Methods: Spectral analysis was performed to assess heart rate variability (HRV) using 1-minute electrocardiogram RR interval data recordings from 7690 residents aged 35–79 years in Nagahama City, Japan. HRV parameters were log-transformed. Multiple regression analysis was performed using potential correlates.

Results: lnLF decreased with age (regression coefficient, −0.025; $P < 0.001$), BMI (−0.010; $P = 0.035$), and HbA_{1c} (−0.068; $P = 0.036$). lnHF decreased with age (−0.029; $P < 0.001$), BMI (−0.032; $P < 0.001$), and HbA_{1c} (−0.173; $P < 0.001$). lnLF/HF increased with age (0.003; $P = 0.002$), BMI (0.023; $P < 0.001$), and HbA_{1c} (0.105; $P < 0.001$). Women showed lower lnLF and lnLF/HF than men. Sleep quality assessed by the Pittsburgh Sleep Quality Index, smoking and drinking had almost no relation.

Conclusions: Although the associations were weak, age, BMI and HbA_{1c} were inversely correlated with parasympathetic activity, while positively correlated with sympathetic activity among general residents.

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1. Introduction

Diabetes mellitus is one of important risk factors for the development of cardiovascular diseases [1]. In patients with diabetes, the frequency of ischemic heart disease increases by 2- to 4-fold compared with non-diabetic patients [2–4]. As diabetes mellitus progresses, diabetic autonomic neuropathy tends to occur. Manifestations of diabetic autonomic neuropathy are diverse and involve the cardiovascular, gastrointestinal, and neuroendocrine systems. Heart rate variability (HRV) is commonly used to assess autonomic nervous system (ANS) function, as HRV spectral analysis allows for the separate evaluation of sympathetic and parasympathetic functions. Previous studies have shown that patients with diabetes have increased sympathetic and decreased parasympathetic cardiac activity [5,6].

Several large cohort studies have investigated the relationship between glucose tolerance and ANS function in diabetic and non-diabetic groups [7–11]. ANS function reportedly decreases with decreasing glucose tolerance in patients with severe diabetes [7,8], and patients with diabetes as well as those with impaired fasting glucose levels have reduced HRV. Some studies have also reported that a decrease in ANS function becomes a risk factor for the development of new diabetes mellitus afterwards [9–11].

Only a few studies targeting the general population have examined the relationship between glycemia and ANS function in healthy people. Most reports have examined the association of ANS function with plasma glucose levels, and that with HbA_{1c} has not been fully explored [7,8]. HbA_{1c}, a form of hemoglobin that is bound to glucose, reflects mean blood glucose over the previous 1–3 months, and is useful for clinical assessment [12,13]. HbA_{1c} reliably measures chronic hyperglycemia even without fasting and correlates well with the risk of long-term diabetes mellitus complications as well [13]. Moreover, the HbA_{1c} is reported to have greater preanalytical stability and less day-to-day perturbations during periods of stress and illness than plasma glucose [12].

The present study aimed to shed light on correlates of ANS function with special reference to HbA_{1c} among general people with wide range of glycemia.

2. Material and methods

2.1. Study design and study population

A cross-sectional study was conducted using survey data obtained between 2012 and 2015 from the Nagahama Prospective Genome Cohort for Comprehensive Human Bioscience (the Nagahama Study [14]). This cohort comprised healthy community residents of Nagahama City (population of 125000) in Shiga Prefecture, which is located in central Japan. We recruited participants aged 30–74 years from 2008 to 2010, yielding a cohort of 9804 participants. Of these, 8289 participated in the second phase survey (2012–2015). We excluded certain individuals due to the presence of arrhythmia and missing data (RR intervals of electrocardiograms, biochemical data, and required questionnaire items) (Fig. 1). The study protocol was approved by Kyoto University Graduate School and Faculty of Medicine Ethics Committee (E2048 and G278).

2.2. Electrocardiogram and spectral analysis of HRV

Electrocardiograms were recorded in the supine position with a blood pressure pulse wave inspection apparatus (VS-1500E, Fukuda Denshi, Tokyo, Japan) during the second phase survey of the Nagahama Study. We took a 10-second ECG recording with 12 leads as part of Japan's routine health checkup, and then performed 1-minute RR interval recordings with two leads (right wrist and left ankle) for the spectral analysis of HRV. The RR interval is the time elapsed between two successive R-waves of the QRS signal on the electrocardiogram.

Spectral analysis of HRV is used to evaluate sympathetic and parasympathetic activity based on the fact that HRV of specific frequency bands reflects these functions [15,16]. The high-frequency (HF) component (0.15–0.4 Hz) is an index of parasympathetic function. The low-frequency (LF) component (0.04–0.15 Hz) is influenced by both parasympathetic and sympathetic functions, and thus the ratio of LF to HF (LF/HF) is indicative of sympathovagal balance [16,17]. The ECG data length required in the frequency band can be calculated with the formula: 1/frequency (seconds). Minimum data lengths required for the analysis of HF and LF components are 6.7 and 25 s, respectively. Fast Fourier Transform (FFT) [18,19], autoregressive model (AR model) [19,20], and Maximum Entropy Method (MEM) [19] are examples of methods that can be used for the spectral analysis of HRV. The MemCalc method combines the maximum entropy method for spectral analysis with the non-linear least squares method for fitting analysis [20–22]. We adopted the MemCalc method for spectral analysis of HRV with 1-minute RR interval data in this study. MemCalc/Win (Suwa Trust, Tokyo, Japan) software was used.

Inappropriate arrhythmia types for spectral analysis were determined according to the Minnesota code [23] through discussion among co-authors (NT, registered nurse; AK & TN, general physician; KU, cardiologist), using 10-second ECG recordings.

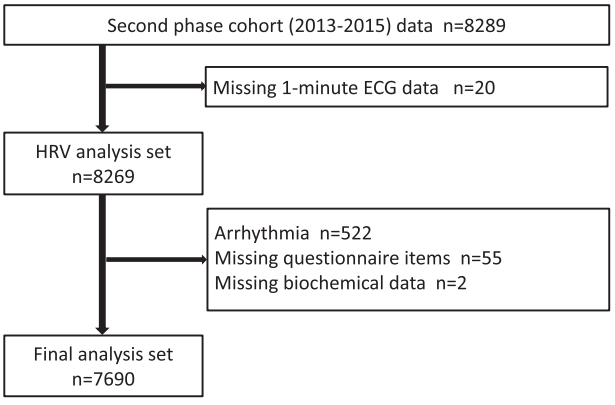

Fig. 1 – Flowchart of participant selection.

2.3. Measurements

We obtained information regarding the following: age, sex, height, weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), brain natriuretic peptide (BNP), HbA_{1c}, blood glucose, and insulin. Smoking and drinking habits, as well as sleep quality, were assessed with a questionnaire. Since sex-based differences in HRV have been reported [24], data for men and women were compared.

Recent studies have reported reduced sleep quality among diabetic patients [25,26]. Lack of sleep can cause sympathetic dominance during the daytime and affect the relationship between sleep and ANS function. To evaluate sleep quality, we used the Japanese version of the Pittsburgh Sleep Quality Index (PSQI) [27–29] which is widely used to evaluate sleep disorders. PSQI evaluates the quality of sleep using 18 items that cover sleep habits, difficulty of sleep, and daytime sleepiness. For studies in both Japan and the United States, $\geq$6 points is a common cut-off, with higher scores reflecting a higher degree of sleep obstruction [27,28].

2.4. Statistical analysis

Descriptive statistics were used to assess participant characteristics. The normality of crude values of LF and HF components was examined by histograms, box plots, normal probability plots, and the Shapiro-Wilk test. After relationships between HRV parameters (LF, HF, and LF/HF) and HbA_{1c} were examined, multivariate analysis was performed. In order to examine the effect of HbA_{1c} on LF and HF component values and the LF/HF, three multiple regression models were created, with (1) log-transformed LF component values, (2) log-transformed HF component values, and (3) log-transformed LF/HF as response variables. Age, sex, BMI, HbA_{1c}, PSQI score, smoking habit, and drinking habit were used as explanatory variables. Statistical analyses were performed with Stata SE Ver.14.2 (College Station, TX, USA). All tests were two-sided, with $P < 0.05$ considered significant.

3. Results

3.1. Participant characteristics

Of the 8289 participants, we excluded 599 due to presence of arrhythmia (n = 522), missing of RR data (n = 20), response to a necessary questionnaire item (n = 55), and biochemical data (n = 2) (Fig. 1). Table 1 summarizes the characteristics and results of the HRV analysis of the final study population (n = 7690).

Mean ages were 60.2 and 57.3 years for men and women, respectively. Both mean HbA_{1c} and blood glucose were higher in men than in women (5.65% (38.3 mmol/mol) vs 5.54%

Table 1 – Participant characteristics and heart rate variability based on 1-minute ECG data.

		Men (n= 2394)	Women (n=5296)	Total (n=7690)	P-value
Age group	35–39	237(10%)	629(12%)	866(11%)	
	40–49	404(17%)	1047(20%)	1451(19%)	
	50–59	274(11%)	963(18%)	1237(16%)	<0.001
	60–69	750(31%)	1624(31%)	2374(31%)	
	70–79	724(30%)	1028(19%)	1752(23%)	
	80–85	5(0.2%)	5(0.1%)	10(0.1%)	
Age (years)		60.2±13.2	57.3±12.7	58.2±12.9	<0.001
Height (cm)		168.1±6.6	155.8±6.1	159.6±8.5	<0.001
Weight (kg)		65.8±10.5	52.7±8.3	56.8±10.9	<0.001
BMI (kg/m^2)		23.2±3.1	21.7±3.2	22.2±3.3	<0.001
Blood Pressure (mmHg)	SBP	131.9±17.6	123.4±19.0	126.0±19.0	<0.001
	DBP	76.3±10.9	70.4±10.7	72.2±11.1	<0.001
BNP (pg/ml)		13.8 [7.9, 23.4]	16.4 [10.4, 26.7]	15.6 [9.7, 25.8]	<0.001
HbA_{1c} (%)		5.65±0.58	5.54±0.43	5.58±0.49	<0.001
HbA_{1c} (mmol/mol)		38.3±6.34	37.1±4.75	37.4±5.33	<0.001
Glucose (mg/dl)		93.0±18.2	85.7±11.5	88.0±14.3	<0.001
Insulin (μU/ml)		3.20 [2.11, 5.01]	2.86 [2.03, 4.16]	2.95 [2.05, 4.39]	<0.001
Heart Rate (beats/min)		61 [55, 67]	63 [58, 69]	62 [57, 68]	<0.001
R-R (ms)		993.2±147.1	954.8±126.1	966.8±134.2	<0.001
lnLF		5.16±1.43	4.96±1.27	5.02±1.33	<0.001
lnLF, logarithmic inverse		174.2±4.18	142.6±3.56	151.4±3.78	
lnHF		4.98±1.50	5.08±1.38	5.05±1.42	<0.001
lnHF, logarithmic inverse		145.5±4.48	160.8±3.97	156.0±4.14	
lnLF/HF ratio		0.18±1.16	−0.11±1.13	−0.02±1.15	<0.001
lnLF/HF, logarithmic inverse		1.20±3.19	0.90±3.10	0.98±3.16	

SBP: systolic blood pressure, DBP: diastolic blood pressure, BNP: brain natriuretic peptide,
R-R: mean variation in R-R interval, lnHF: log-transformed HF component values, lnLF/HF: log-transformed LF/HF ratios.
Age, Height, Weight, BMI, Blood pressure, HbA_{1c}, Glucose, R-R, lnLF, lnHF, and lnLF/HF are presented as mean±SD.
BNP, Insulin, Heart rate are presented as median [first quartile, third quartile].
P-value for age group: chi-square test.
P-value for mean: t test.
P-value for median: Wilcoxon rank sum test.

(37.1 mmol/mol); 93.0 mg/dl vs 85.7 mg/dl, respectively. Measurement unit was transformed according to a conversion formula [30]. As LF and HF component values were not normally distributed, the values were log transformed. The mean log-transformed LF component (lnLF) value and mean log-transformed ratio of LF to HF (lnLF/HF) for men were higher than those for women (lnLF: 5.16 vs. 4.96; lnLF/HF: 0.18 vs. − 0.11, respectively). The mean lnHF value for women was higher than that for men (5.08 vs. 4.98).

3.2. *Correlation between HRV parameters (LF, HF, and LF/HF) and HbA_{1c}*

Fig. 2 shows scatter plots with Pearson correlation coefficients between HbA_{1c} and lnLF, LnHF, and lnLF/HF for men (−0.09, −0.12, 0.04) and women (−0.12, −0.19, 0.10). All correlation coefficients between HRV parameters and HbA_{1c} were higher in women than in men.

3.3. *Age-adjusted means of HRV parameters by HbA_{1c} category and sex*

Fig. 3 shows age-adjusted means of lnLF, LnHF, and lnLF/HF with 95% confidence intervals (CIs) by HbA_{1c} category and sex. As HbA_{1c} increased, adjusted means of lnLF and lnHF decreased, and adjusted means of lnLF/HF increased, for both sexes. Especially among women with $HbA_{1c} \geq 8.5$, the adjusted mean was significantly lower for lnHF and higher for lnLF/HF.

3.4. *Factors associated with HRV parameters*

Table 2 shows results of multiple regression analysis. lnLF decreased with age (regression coefficient, −0.025; P < 0.001), BMI (−0.010; P = 0.035), and HbA_{1c} (−0.068; P = 0.036). lnHF decreased with age (−0.029; P < 0.001), BMI (−0.032; P < 0.001), and HbA_{1c} (−0.173; P < 0.001). lnLF/HF increased

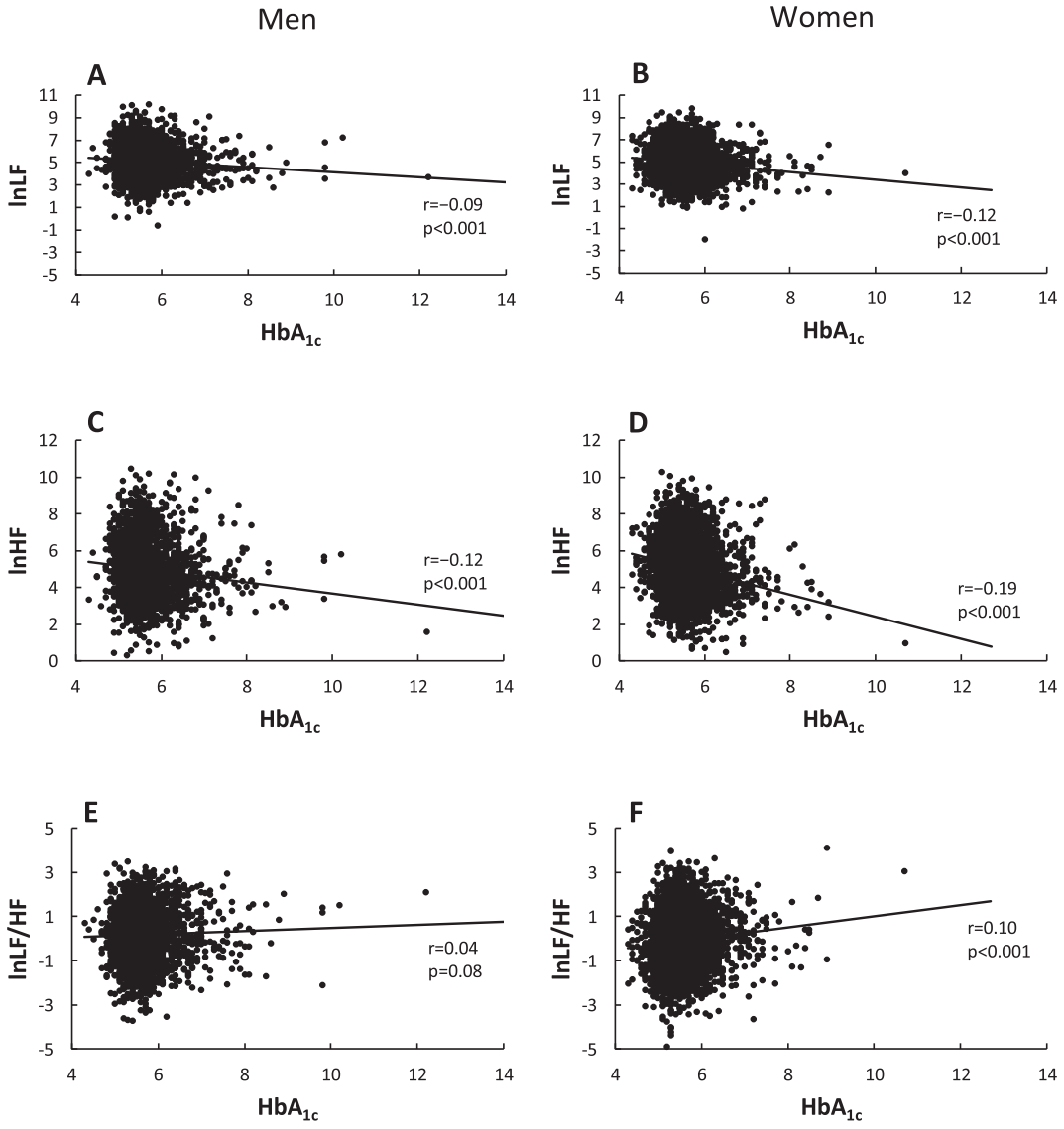

Fig. 2 – Scatter plots for log-transformed LF values and HbA_{1c}, log-transformed HF values and HbA_{1c}, and log-transformed LF/HF and HbA_{1c}. A: lnLF vs. HbA_{1c} (men), B: lnLF vs. HbA_{1c} (women), C: lnHF vs. HbA_{1c} (men), D: lnHF vs. HbA_{1c} (women), E: lnLF/HF ratio vs. HbA_{1c} (men), F: lnLF/HF vs. HbA_{1c} (women) lnHF: log-transformed HF component values, lnLF/HF: log-transformed LF/HF.

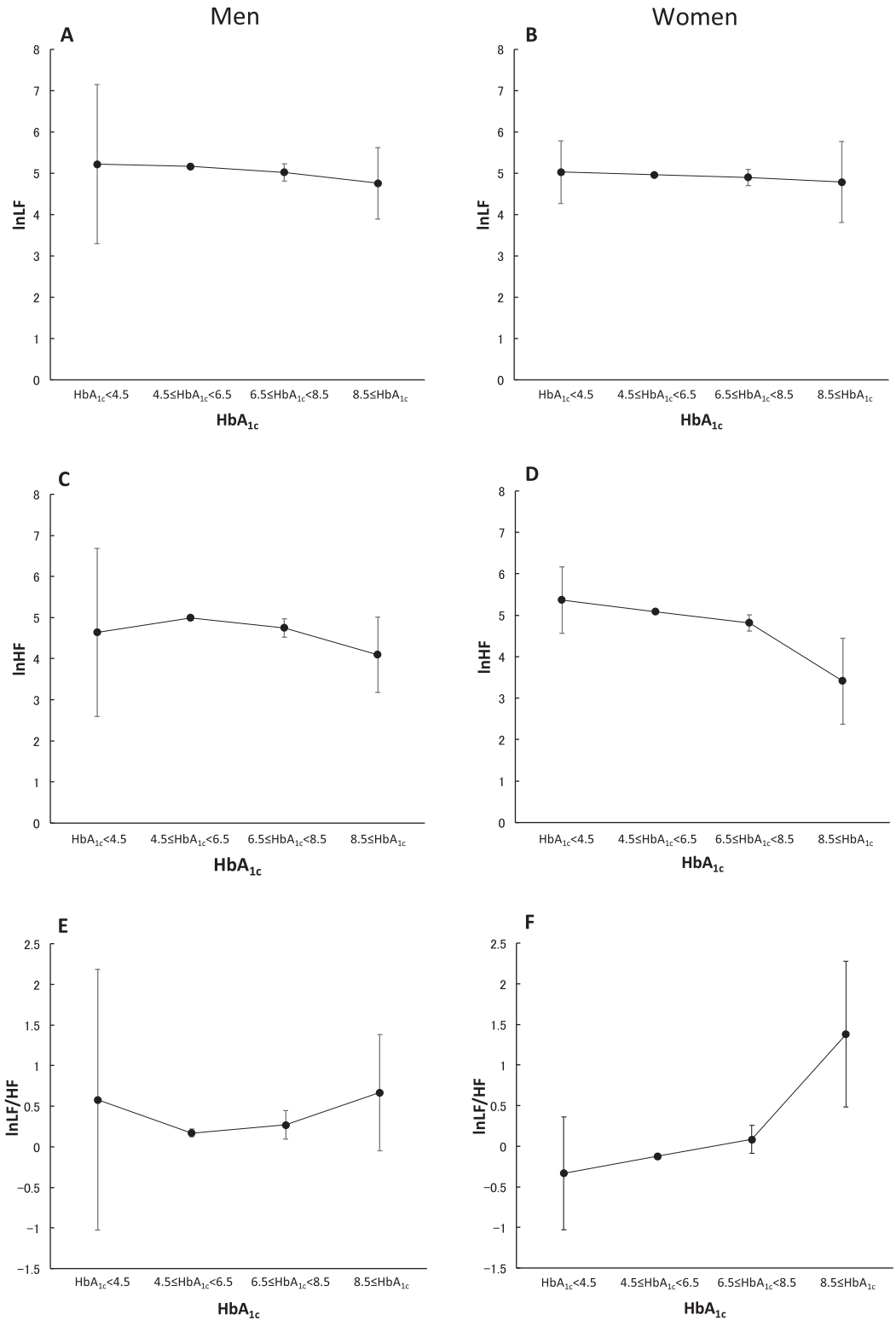

Fig. 3 – Adjusted means of log-transformed LF, HF, and LF/HF by HbA_{1c} category (age-adjusted) A: Adjusted mean of lnLF by HbA_{1c} (men) B: Adjusted mean of lnLF by HbA_{1c} (women) C: Adjusted mean of lnHF by HbA_{1c} (men) D: Adjusted mean of lnHF by HbA_{1c} (women) E: Adjusted mean of lnLF/HF by HbA_{1c} (men) F: Adjusted mean of lnLF/HF by HbA_{1c} (women) lnHF: log-transformed HF component values, lnLF/HF: log-transformed LF/HF ratios Error bar: 95% confidence interval $p < 0.001$ for all lnLF and lnHF adjusted means, and lnLF/HF adjusted means (men & women: $4.5 \leq HbA_{1c} < 6.5$) $p = 0.003$ for lnLF/HF adjusted means (men: $6.5 \leq HbA_{1c} < 8.5$ women: $HbA_{1c} < 4.5$, $8.5 \leq HbA_{1c}$) $p = 0.478$ (men: $HbA_{1c} < 4.5$) $p = 0.345$ (women: $HbA_{1c} < 4.5$, $6.5 \leq HbA_{1c} < 8.5$).

Table 2 – Multiple regression model for lnLF, lnHF, and lnLF/HF for HbA_{1c}.

	lnLF	lnHF	lnLF/HF
Age	−0.025 [−0.028 – −0.023] P<0.001	−0.029 [−0.031 – −0.026] P<0.001	0.003 [0.001 – 0.006] P=0.002
Women	−0.280 [−0.361 – −0.198] P<0.001	−0.004 [−0.090 – 0.083] P= 0.929	−0.275 [−0.348 – −0.203] P<0.001
BMI	−0.010 [−0.019 – 0.001] P= 0.035	−0.032 [−0.042 – −0.023] P<0.001	0.023 [0.014 – 0.031] P<0.001
HbA_{1c}	−0.068 [−0.132 – −0.004] P=0.036	−0.173 [−0.240 – −0.105] P<0.001	0.105 [0.048 – 0.161] P<0.001
PSQI≥6	−0.005 [−0.065 – 0.056] P= 0.875	−0.053 [−0.116 – 0.011] P=0.106	0.048 [−0.006 – 0.101] P= 0.080
Smoking	0.011 [−0.067 – 0.089] P= 0.780	0.061[−0.022 – 0.144] P=0.147	−0.050[−0.119 – 0.019] P=0.157
Drinking	0.012 [−0.050 – 0.074] P= 0.701	0.032[−0.034 – 0.098] P=0.341	−0.020[−0.075 – 0.035] P=0.482

Regression coefficient [95% confidence interval].
lnLF: log-transformed LF component values, lnHF: log-transformed HF component values, lnLF/HF: log-transformed LF/HF ratios.

with age (0.003; P = 0.002), BMI (0.023; P < 0.001), and HbA_{1c} (0.105; P < 0.001). Women showed lower lnLF and lnLF/HF than men. PSQI score, smoking and drinking had almost no relation with lnLF, lnHF, and lnLF/HF. No issues with multicollinearity were noted based on variance inflation factors (VIFs) (i.e., VIF < 2 in all models). However, the proportion of variance in the dependent variable explained by the variance in the independent variables was not high in each model (adjusted R Square: lnLF, 0.07; lnHF, 0.10; lnLF/HF, 0.02).

4. Discussion

The present study, which targeted a large general Japanese population, found that both lnLF and lnHF decreased with age, BMI and HbA_{1c}, meaning decreased parasympathetic function. On the other hand, lnLF/HF increased with age, BMI and HbA_{1c}, meaning increased parasympathetic function. However, these associations were weak. Women showed lower lnLF and lnLF/HF than men. Sleep quality, smoking and drinking had almost no relation.

ANS function was assessed using 1-minute ECG data and found to be reliable for the spectral analysis of HRV, which we previously validated [31]. In HRV analysis using short-time ECG data, 5-minute data are typically used [16]. When HRV is measured to evaluate ANS function, strict experimental settings, e.g., measurement after the rest in the supine position for 15 min or more, are required, and taking alcohol or caffeine for 24 h before measurements is prohibited [16,17]. Therefore, the burden on examinees is large and thus conventional 5-minute ECG may not be suitable for examining large populations. While there are some community-based cohort studies in Japan [32,33], no other studies have used HRV analysis on a population of nearly 8000 people. The feasibility of HRV analysis using 1-minute RR data in the present study suggests that short-time ECG may be suitable to assess ANS function in large populations.

According to the Framingham Heart study and ARIC study that focused on plasma glucose levels, ANS function declines as glucose tolerance decreases [7,8]. We found that ANS function slightly declined when HbA_{1c} levels were high. It is well known that diabetic neuropathy manifests as diabetes mellitus progresses, but diabetic autonomic neuropathy is one of them. Short-time ECG may easily detect autonomic neuropathy in outpatients. We found that parasympathetic function tends to decrease, and sympathetic function tends to increase, as HbA_{1c} levels increase in women. For example, the $HbA_{1c} \geq 8.5$ group showed sympathetic hyperactivity in women. In men, sympathetic hyperactivity was observed in both the low HbA1c group ($HbA_{1c} < 4.5$) and high HbA_{1c} group ($HbA_{1c} \geq 8.5$).

Some clinical studies have reported a relationship between diabetes mellitus and sleep quality. For example, Yoda et al. reported that poor glycemic control in patients with type 2 diabetes is associated with impaired sleep quality, as reflected by decreased REM sleep latency [26]. Skomro et al. reported that adult type 2 diabetics have higher rates of insomnia, excessive somnolence, and hypnotics use than controls [25]. However, in the present study, no significant difference was observed in PSQI score, suggesting that the influence of sleep quality on autonomic nervous function could be limited in healthy community residents setting. It is possible that the influence of sleep quality on blood glucose control may differ between healthy participants and patients with diseases. Thus, studies comparing a healthy group and patient group will be necessary to address this issue.

There are concerns regarding the potential harmful effects of unnecessary sympathetic dominance on the body such as the severity of hypertension, abnormal diurnal blood pressure variation, hypertensive organ disorder, and abnormal metabolism [34]. In general, HbA_{1c} should be controlled to 6.5 or less of the reference value. One study found that the risk of ischemic heart disease increased with high HbA_{1c}, whereas the risk of cerebral infarction and cerebral hemorrhage increased in low and high HbA_{1c} groups [35]. A pooled analysis of about 300,000 people also found that there was an approximately J-shaped association between HbA_{1c} values and cardiovascular disease (ischemic heart disease and stroke) risk in analyses adjusted for several conventional cardiovascular risk factors [36], although the mechanism remains unclear. Considering these previous studies and our

findings, low levels of HbA_{1c} may increase the risk of sympathetic hyperactivity in a sex-specific manner. Further studies are needed in order to clarify association of low levels of HbA_{1c} with Sympathetic hyperactivity and cardiovascular disease risk.

We found that ANS function slightly decreased as HbA_{1c} increased within the normal HbA_{1c} range. Given that diabetic neuropathy is a common complication of diabetes mellitus, our findings may be clinically relevant in that they suggest the possibility of suppressing the onset and progression of diabetic autonomic neuropathy if a decline in ANS function could be detected during the early prediabetic stage. It would be prudent of us to recommend modification of clinical practices for patients with diabetes or preventive measures among general residents, because the associations we uncovered between HbA_{1c} and ANS function were not strong. Our findings may have potential implications for clinical or preventive actions, but further examination of heart rate variability is necessary in order to make appropriate clinical recommendations.

Our study has some limitations. First, we could not determine causality between ANS function and HbA_{1c} because of cross-sectional nature. Second, as our participants were aged 35–80 years, our findings cannot be generalized to younger age groups. Third, since we targeted general community-dwelling residents, there were not many people in the low HbA_{1c} group ($HbA_{1c} < 4.5$) and high HbA_{1c} group ($HbA_{1c} \geq 8.5$). Therefore, additional studies that include more participants in these groups are warranted. Finally, we did not obtain the names of the medications, thus, we could not consider their influence.

In conclusions, based on spectral analysis of HRV using 1-minute RR data in a general community-dwelling adult population in Japan, parasympathetic activity was found to decrease (i.e., HF component values decreased) and sympathetic activity increase (i.e., LF/HF increased) slightly as HbA_{1c} levels increased.

Authors contributions

N.T., study design, data analysis, data interpretation, and manuscript writing; Yo.T., data collection, data interpretation, and manuscript writing; Ya.T., T.M., T.K., K.C., data collection, data interpretation; A.K., K.U., study design and data interpretation; F.M., cohort design and data collection; T.N., supervised the cohort study, cohort design, data collection, study design, data interpretation, and manuscript writing. All authors revised the manuscript critically for important intellectual content and approved the version to be published.

Declaration of Competing Interest

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Research data

This study was conducted by analyzing a dataset of the Nagahama Prospective Cohort for Comprehensive Human Bioscience (the Nagahama Study), and the data are available upon request because we did not obtain consent from each participant for publication of individual data in public domains. Data from the Nagahama Study are available upon request to the Nagahama office (nagahama-office@genome.med.kyoto-u.ac.jp).

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