Decreased Vagal Activity and Deviation in Sympathetic Activity Precedes Development of Diabetes

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OBJECTIVE

The objective of this study was to examine whether altered heart rate variability (HRV) could predict the risk of diabetes in Asians.

RESEARCH DESIGN AND METHODS

A cohort study was conducted in 54,075 adults without diabetes who underwent 3-min HRV measurement during health checkups between 2011 and 2014 at Kangbuk Samsung Hospital. We analyzed the time domain (SD of the normal-to-normal interval [SDNN] and root mean square differences of successive normal-to-normal intervals [RMSSD]) and the frequency domain (total power, normalized low-frequency power [LF], and normalized high-frequency power [HF] and LF/HF ratio). We compared the risk of diabetes until 2017 according to tertiles of heart rate and HRV variables, with tertile 1 serving as the reference group.

RESULTS

During 243,758.2 person-years, 1,369 subjects were diagnosed with diabetes. Both time and frequency domain variables were lower in the group with diabetes, with the exception of those with normalized LF and LF/HF ratio. In Cox analysis, as SDNN, RMSSD, and normalized HF tertiles increased, the risk of diabetes decreased (hazard ratios [95% CIs] of tertile 3: 0.81 [0.70–0.95], 0.76 [0.65–0.90], and 0.78 [0.67–0.91], respectively), whereas the risk of diabetes increased in the case of heart rate, normalized LF, and LF/HF ratio (hazard ratios [95% CIs] of tertile 3: 1.41 [1.21–1.65], 1.32 [1.13–1.53], and 1.31 [1.13–1.53], respectively) after adjusting for age, sex, BMI, smoking, drinking, systolic blood pressure, lipid level, CRP, and HOMA of insulin resistance.

CONCLUSIONS

Abnormal HRV, especially decreased vagal activity and deviation in sympathovagal imbalance to sympathetic activity, might precede incident diabetes.

Cardiac autonomic function is regulated by the dynamic equilibrium between sympathetic and parasympathetic branches (1). Recently, the role of the cardiac autonomic nervous system (ANS) in a wide range of diseases has attracted strong attention. Based on this perspective, growing evidence suggests that autonomic imbalance, in which the sympathetic branch is hyperactive while the parasympathetic branch is hypoactive, is implicated in a wide range of diseases (2).

Heart rate variability (HRV) is a noninvasive marker of autonomic imbalance and vagal activity (3). Increased sympathetic tone decreases HRV, whereas increased parasympathetic tone increases HRV. In 1996, the European Society of Cardiology and

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the North American Society of Pacing and Electrophysiology organized a task force to develop standards for HRV measurement (3). Although the gold-standard protocol for HRV estimation was 24-h measurement (3), short-term HRV recordings have been widely used. They appear to be the most commonly studied source of HRV examination, potentially in part because of the associated ease of recording (4).

Over the years, HRV abnormality has been found in various cardiometabolic diseases (5). In addition, it has been suggested that decreased HRV might precede the development of cardiovascular disease or diabetes (6–9). Although several studies have shown an association between diabetes and autonomic dysfunction (6–12), epidemiological studies investigating diabetes risk stratification based on HRV measurement predominantly included Caucasians or blacks (6,7,9,10).

Meanwhile, in the Asian population, Chang et al. (13) have investigated changes in cardiac autonomic function and insulin resistance in 1,298 Chinese subjects and suggested that ANS modifications might precede insulin resistance. In addition, sympathetic hyperactivity estimated using plasma norepinephrine level has been found to precede hyperinsulinemia in young and nonobese Japanese subjects (14). However, few longitudinal studies have analyzed the predictive value of HRV in incident diabetes among Asians.

Therefore, the objectives of the current study were to investigate the relationship between HRV measurement and the risk of diabetes and to elucidate whether HRV abnormality could predict the development of diabetes in an Asian population. A causal diagram describing the hypothesis of this study is shown in Supplementary Fig. 1 reproduced from Williams et al. (15).

RESEARCH DESIGN AND METHODS

Selection of Study Subjects

Study subjects consisted of a subset of the Kangbuk Samsung Health Study (KSHS) participants aged 20 years or older who underwent health-screening exams including HRV measurement between April 2011 and June 2014 (n = 70,915). The KSHS is a Korean cohort study including individuals aged 18 years or older who have participated in a comprehensive health-screening examination annually or biennially at Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, Republic of Korea (16). More than 80% of participants were employees of various companies or their family members. In South Korea, the Industrial Safety and Health Act requires health exams for all employees. These exams are offered free of charge to enhance the health status of employees via regular health exams and to promote early detection of diseases. The remaining participants voluntarily paid a screening fee.

To minimize the influence of several chronic diseases and medication on HRV, as shown in Fig. 1, we excluded 16,783 participants who had any of the following conditions at baseline: older than 65 years of age (n = 62), abnormal thyroid function at baseline (n = 6,424), history of thyroid disease (n = 5,537), thyroid hormone or antithyroidal drug use (n = 1,192), anemia (n = 3,520), estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (n = 107), serum CRP level >1.0 mg/dL (n = 5), history of diabetes or presence of diabetes at baseline (n = 2,039), malignancy (n = 1,330), heart disease (n = 341), chronic obstructive pulmonary disease (n = 318), and/or bronchial asthma (n = 754). Previous histories of diseases and medication were assessed using a self-reported questionnaire including the routine health-screening examination. The presence of heart disease was defined as angina, myocardial infarction, or arrhythmia that needed to be treated.

In addition, because the 75-g oral glucose tolerance test was not performed, we excluded 57 subjects with a follow-up duration of <1 year to avoid the inclusion of patients with undiagnosed diabetes. Finally, 54,075 participants were included in the analysis.

All subjects provided written informed consent for the use of their health-screening data in this study. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (KBSMC 2019–01–040; Seoul, Republic of South Korea). It was conducted in accordance with the tenets of the 1975 Declaration of Helsinki.

Study Outcome

Study outcome was the first diagnosis of diabetes until 31 December 2017 defined as fasting plasma glucose (FPG) level ≥126 mg/dL, glycated hemoglobin (HbA_{1c}) level ≥6.5%, and/or current use of antihyperglycemic medications based on the American Diabetes Association criteria (17).

Anthropometric and Laboratory Measurements

At the first visit, study subjects were required to complete a structured questionnaire involving a survey of demographic and lifestyle characteristics such as smoking status, alcohol consumption, and regular exercise. The questionnaire was based on the fourth Korea National

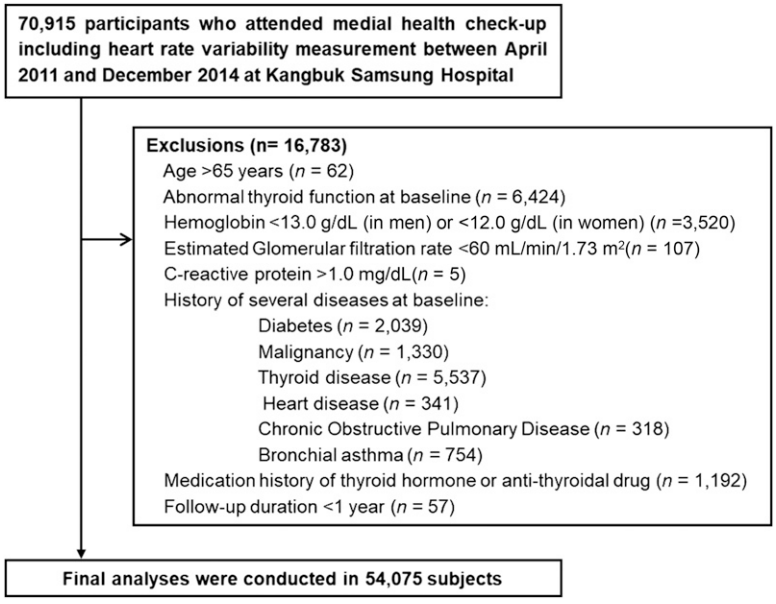

Figure 1—Selection of study subjects.

Health and Nutritional Examination Survey (18,19), the Korean Genome and Epidemiology Study (20), the Korean version of the International Physical Activity Questionnaire short form (21), and the Korean version of the Alcohol Use Disorders Identification Test (22). Alcohol consumption was categorized into none, moderate ($\leq$20 g/day), and high ($>$20 g/day).

Body weight was measured with the subject in light clothing without shoes using a digital scale. BMI was calculated as body weight in kilograms divided by the square of height in meters. Waist circumference was measured in the standing position at the midpoint between the anterior iliac crest and the lower border of the rib by a single examiner. Segmental bioelectric impedance with eight tactile electrodes (InBody 3.0; BioSpace, Seoul, Republic of Korea) was used to determine body composition measurements. Blood pressure (BP) was measured by trained nurses using a standardized mercury sphygmomanometer following 5 min of rest. Hypertension was defined as systolic BP $\geq$140 mmHg, diastolic BP $\geq$90 mmHg, or current use of antihypertensive medications (23).

Venous blood samples were collected between 8:00 A.M. and 9:00 A.M. after an overnight fast of $>$12 h. The hexokinase method was used to determine FPG concentrations (Hitachi Modular D2400; Roche, Tokyo, Japan). An enzymatic calorimetric test was used to measure total cholesterol and triglyceride (TG) concentrations. The selective inhibition method was used to measure HDL cholesterol level, while a homogeneous enzymatic calorimetric test was used to measure LDL cholesterol (LDL-C) level. HbA_{1c} was measured with an immunoturbidimetric assay using a COBAS Integra 800 automatic analyzer (Roche Diagnostics, Basel, Switzerland) with a reference value of 4.4–6.4%. This methodology was aligned with the Diabetes Control and Complications Trial and National Glycohemoglobin Standardization Program standards (24). The intra-assay coefficient of variation (CV) was 2.3%, and the interassay CV was 2.4%. Both values were within acceptable limits of the National Glycohemoglobin Standardization Program. Serum hs-CRP concentration was measured using a nephelometric assay and a BN II nephelometer (Dade Behring, Deerfield, IL). Serum insulin level was determined with an immunoradiometric assay using a DIAsource Kit (DIAsource ImmunoAssays SA, Louvain-la-Neuve, Belgium). Serum hs-CRP level was analyzed via nephelometry using a BN II nephelometer (Dade Behring). Serum thyroid-stimulating hormone (TSH) and free thyroxin (T4) levels were measured using commercially available radioimmunoassay kits (RIA-gnosthTSH, free T4; Schering-CIS Bio International, Gif-sur-Yvette, France) with lower detection limits of 0.025 μIU/mL and 0.06 ng/dL, respectively. Notably, the normal range was 0.25–5.0 μIU/mL for TSH and 0.9–1.8 ng/dL for free T4. Intra- and interassay CVs for quality control specimens were 1.2–5.7% and 2.4–5.4%, respectively, for TSH. These values were 2.3–4.4% and 2.1–5.7%, respectively, for free T4. Serum free triiodothyronine (T3) was measured with a radioimmunoassay kit (RIA-mat; Byk-Sangtec Diagnostica, Dietzenbach, Germany) at a lower detection limit of 0.6 pg/mL and a normal range of 2.0–4.25 pg/mL. Intra- and interassay CVs for free T3 were 5.0–6.8% and 5.0–7.6%, respectively. We calculated eGFR using the Chronic Kidney Disease-Epidemiology Collaboration equation (25). Serum creatinine was measured with the kinetic alkaline picrate (Jaffe) method. Within-batch and total CVs for creatinine determinations ranged from 1.4 to 3.9% for the duration of the study. Hemoglobin level was detected with cyanide-free sodium lauryl sulfate using an XE-2100 analyzer (Sysmex, Kobe, Japan).

HRV Measurement

To assess levels of stress coping ability and physical fitness and to find early signs of the development of pathological processes or the presence of a functional disorder, HRV measurement was included in the KSHS. HRV measurement was conducted via 3-min recordings while sitting in a quiet room using an SA-3000P analyzer (Medicore Co., Ltd., Seoul, Korea) as a component of the health-screening exam. Prior to HRV measurement, study subjects were instructed about the measurement process. They were asked to stay still with eyes open, to remain silent, and to breathe normally during the procedure. All abnormal beats not generated by sinus node depolarization were eliminated from the HRV analysis. When a heart rate $>$200 beats per minute was detected, measurement was repeated, and lower results were recorded.

We analyzed HRV in both time and frequency domains according to methodological standards recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology for HRV (3). Time domain measurements included SD of the normal-to-normal interval (SDNN; in milliseconds) and root mean square differences of successive normal-to-normal intervals (RMSSD; in milliseconds). SDNN is considered as a marker of overall autonomic modulation, while RMSSD reflects the cardiac parasympathetic drive (26). Fast Fourier transformation was used to calculate the power spectral density curve (3). For frequency domain measurements, total (TP; 0–0.4 Hz; ms^2), low-frequency (LF; 0.04–0.15 Hz; ms^2), and high-frequency power (HF; 0.15–0.4 Hz; ms^2) and LF/HF ratios were assessed. Normalized low-frequency (LF norm) and normalized high-frequency (HF norm) were calculated as LF/(LF+HF) and HF/(LF+HF), respectively. LF and HF norms calculated in percentile units emphasize changes in sympathetic and parasympathetic (vagal) regulation, respectively. The LF/HF ratio is regarded as a measure of sympathovagal balance (3).

Statistical Analysis

Data are presented as mean $\pm$ SD or number (percentage). Because distributions of TG level and HRV measurement were right-skewed, they were transformed with natural log to obtain a normal distribution. Baseline characteristics were compared between the group with diabetes and the control group (with no diabetes) using t tests for continuous variables and χ^2 test for categorical variables. Subsequently, we divided subjects into tertiles of heart rate, SDNN, RMSSD, TP, LF norm, HF norm, and LF/HF ratio.

To estimate hazard ratios (HRs) and 95% CIs for the development of diabetes, Cox proportional hazards models were used according to tertiles, with tertile 1 representing the reference group. In addition to the age- and sex-adjusted model, two models were used per tertile. Model 1 was adjusted for age and sex, BMI, LDL-C, hs-CRP, current smoking, and alcohol intake $\geq$20 g/day. Model 2 was the same as model 1, except that it also included an adjustment for systolic BP and HOMA of insulin resistance (HOMA-IR) levels.

After further stratifying subjects according to sex and FPG cutoff of 100 mg/dL, we performed subgroup analyses. In addition, we conducted two sensitivity analyses. First, we performed the above-mentioned Cox analysis for subgroups whose HbA_{1c} levels were <6.0%. Second, we extracted the data of 17,408 subjects who repeated the HRV test within 2 years. Subjects were divided based on the median of each HRV variable. They were then stratified into four groups based on results from repeated tests within 2 years.

To compare the predictive value for incident diabetes among HRV variables, we calculated areas under the receiver operating characteristics curves (AUCs) and 95% CIs. In addition to the univariate model of each HRV variable, fasting glucose, HbA_{1c}, HOMA-IR, and the self-assessment score for diabetes risk developed for Koreans (27), we estimated AUC values when they were combined with fasting glucose, HbA_{1c}, HOMA-IR, or Korean diabetes prediction value.

We assessed proportional hazards using graphs of estimated log (−log) survival and Schoenfeld residuals. Stata version 14.0 (StataCorp LP, College Station, TX) was used for all statistical analyses. A P value <0.05 was considered statistically significant. Bonferroni correction was applied for multiple comparisons.

RESULTS

During 243,758.2 person-years of follow-up (median [interquartile range] follow-up period: 4.5 [3.8–5.6] years), a total of 1,369 subjects were diagnosed with diabetes. As shown in Table 1, patients with diabetes had poorer metabolic parameters (such as obesity and lipid profile) and a higher proportion of current smokers. In the case of HRV variables, SDNN, RMSSD, TP, and HF norm were lower and LF norm and LF/HF were higher in the group with diabetes.

In Cox analysis, as continuous variables, natural logarithmic values (ln) of SDNN and RMSSD showed negative correlations with incident diabetes, whereas heart rate, LF norm, and LF/HF ratios showed positive relationships with incident diabetes (Supplementary Table 1).

When we assessed the risk of diabetes according to tertiles of each variable, fully adjusted HRs in model 2 decreased as SDNN, RMSSD, and HF norm tertiles increased (Table 2 and Supplementary Fig. 2) (HRs [95% CIs] of tertile 3: 0.81 [0.70–0.95], 0.76 [0.65–0.90], and 0.78 [0.67–0.91], respectively). For heart rate, LF norm, and LF/HF tertiles, a positive relationship was found between each tertile and the risk of incident diabetes (all P for trend <0.001; HRs [95% CIs] of tertile 3: 1.41 [1.21–1.65], 1.32 [1.13–1.53], and 1.31 [1.13–1.53], respectively).

When we divided subjects according to sex, significant findings were observed only in males (Supplementary Table 2). In females, most significances disappeared in model 2. There was a significant interaction between sex and the risk of diabetes according to heart rate, RMSSD, LF norm, HF norm, and LF/HF ratio.

When we stratified subjects according to FPG cutoff of 100 mg/dL, significant correlations of heart rate and HRV variables with the risk of diabetes were found in subjects with FPG ≥100 mg/dL, whereas significant association of LF/HF ratio was found in those with FPG levels <100 mg/dL (Supplementary Table 3). In subjects whose HbA_{1c} levels were <6.0%, significant findings were observed in heart rate, RMSSD, and LF/HF ratio (Supplementary Table 4).

In the analysis conducted in subjects who underwent follow-up HRV exams within 2 years, those with sustained elevated heart rate, SDNN, RMSSD, and HF norm had significantly lower risk for diabetes compared with those with sustained decreased levels, whereas individuals with continuously increased LF norm and LF/HF ratio exhibited higher risk (Table 3).

As shown in Supplementary Table 5, AUCs of HRV measurement were <0.600. However, when each HRV variable was added into the multivariate model, AUCs showed significant increases. This increase was the most pronounced in RMSSD. The cutoff value of RMSSD for predicting incident diabetes was 29.6 (sensitivity: 44.9 [95% CI 42.3–47.6]; and specificity: 32.6 [95% CI 32.2–33.0]).

CONCLUSIONS

This longitudinal study indicated that abnormal HRV, especially decreased vagal activity and deviation in sympathovagal imbalance to sympathetic activity, preceded incident diabetes in young Korean adults. Several cross-sectional (8,11,12) and longitudinal studies (6,7,9,10) have investigated the relationship between autonomic dysfunction and diabetes in Caucasian or black populations. In the Atherosclerosis Risk in Communities (ARIC) study, subjects in the group with incident diabetes showed decreased LF and SDNN at baseline (6). In addition, LF quartile 1 showed a 39% higher risk of diabetes compared with LF quartile 4 (6). Recently, a large Brazilian cohort study showed that decreased HRV indices (SDNN, RMSSD, LF, and HF) were independent predictors for incident diabetes (9). However, implications of these longitudinal studies mainly revolved around the impact of decreased overall autonomic modulation rather than the autonomic imbalance in predicting incident diabetes. In contrast, the current study suggested that a decrease in parasympathetic modulation and the imbalance between the two branches of ANS as well as diminished overall HRV activity might increase the risk of diabetes. Furthermore, this study showed that HRV, especially RMSSD, could enhance the predictability of classical risk factors for diabetes through receiver operating characteristic analysis. These findings were attributed to the possibility of altered ANS function as a mediator of insulin resistance (28,29). Parasympathetic activity stimulates insulin secretion by pancreatic β-cells, whereas sympathetic activation inhibits its release. Furthermore, sympathetic nerve fibers can decrease glucose uptake of skeletal muscle by increasing the distance of insulin to cell membranes or reducing the blood flow (7,28). They can also increase lipolysis in adipose tissue, which contributes to increased insulin resistance (30). Additionally, hyperinsulinemia and sympathetic activity reciprocally can reinforce each other (31). However, in the current study, after adjustment for HOMA-IR as a confounding factor, most significances persisted, suggesting the prognostic ability of abnormal HRV for incident diabetes beyond insulin resistance.

In subgroup analysis according to sex, men showed a stronger relationship between HRV and the risk of diabetes (Supplementary Table 2). Prior evidence has indicated a stronger correlation between HOMA-IR and HRV among men compared with that in women (32–34). In addition, sex differences in HRV among individuals with diabetic neuropathy have been observed (32). Men tend to present symptoms of diabetic neuropathy earlier than women (33). They might

Table 1—Baseline characteristics of study subjects according to development of diabetes

Variable	No diabetes (n = 52,706)	Diabetes (n = 1,369)	P value*
Age (years)	36.3 ± 5.9	39.2 ± 5.9	<0.001
Sex, male	31,839 (60.4)	1,114 (81.4)	<0.001
BMI (kg/m^2)	23.2 ± 3.2	26.5 ± 3.5	<0.001
WC (cm)	81.6 ± 9.4	91.0 ± 9.5	<0.001
Body fat mass (kg)	16.3 ± 5.7	21.3 ± 7.3	<0.001
Percent body fat (%)	24.6 ± 6.4	27.3 ± 6.5	<0.001
Systolic BP (mmHg)	109.4 ± 12.6	118.7 ± 13.3	<0.001
Fasting glucose (mg/dL)	94.0 ± 8.0	107.0 ± 9.7	<0.001
Hemoglobin A_{1c} (%)	5.6 ± 0.2	5.9 ± 0.3	<0.001
TC (mg/dL)	194.0 ± 33.4	211.3 ± 36.4	<0.001
TG (mg/dL)	113.1 ± 75.6	177.9 ± 103.2	<0.001
HDL-C (mg/dL)	57.6 ± 14.6	48.5 ± 11.6	<0.001
LDL-C (mg/dL)	119.2 ± 31.1	136.6 ± 33.1	<0.001
HOMA-IR score	1.4 ± 1.0	2.4 ± 1.5	<0.001
Hs-CRP (mg/mL)	0.1 ± 0.3	0.2 ± 0.3	<0.001
Hemoglobin (g/dL)	14.8 ± 1.4	15.6 ± 1.2	<0.001
TSH (μIU/mL)	2.1 ± 1.0	2.0 ± 1.0	0.161
Free T4 (ng/dL)	1.3 ± 0.2	1.3 ± 0.2	0.809
Free T3 (pg/mL)	3.2 ± 0.4	3.4 ± 0.4	<0.001
eGFR (mL/min/1.73 m^2)	101.2 ± 13.3	97.6 ± 12.9	<0.001
Current smoker	11,767 (25.0)	535 (43.6)	<0.001
Alcohol intake ≥20 g/day	10,802 (21.7)	462 (35.7)	<0.001
Vigorous exercise greater than or equal to five times per week	1,941 (3.8)	45 (3.4)	0.173
Antihypertensive drug	1,257 (2.39)	129 (9.42)	<0.001
Heart rate†	65.0 ± 8.6	67.8 ± 9.2	<0.001
SDNN (ms)‡	44.2 ± 16.5	39.2 ± 15.2	<0.001
RMSSD (ms)‡	39.6 ± 18.6	31.3 ± 16.7	<0.001
TP (ms^2)‡	1,551.7 ± 1,365.7	1,279.6 ± 1,154.0	<0.001
LF (ms^2)§	448.7 ± 1,033.4	374.7 ± 438.6	<0.001
HF (ms^2)‡	473.1 ± 480.4	322.9 ± 368.6	<0.001
LF norm (n.u.)§	46.6 ± 97.0	53.0 ± 20.3	<0.001
HF norm (n.u.)‡	53.1 ± 20.1	46.6 ± 20.2	<0.001
LF/HF ratio§	1.5 ± 4.1	1.9 ± 2.4	<0.001

Data are mean ± SD or n (%). HDL-C, HDL cholesterol; n.u., normalized units; TC, total cholesterol; WC, waist circumference. *Student t tests for continuous variables and χ^2 tests for categorical variables were used to compare the characteristics of the study subjects at baseline, and the right-skewed variables (TG, SDNN, RMSSD, TP, LF norm, HF norm, and LF/HF ratio) were log-transformed for Student t tests. †Data for heart rate were available in 54,069 subjects. ‡Lower is worse. §Higher is worse.

be more susceptible to autonomic failure (defined by low HRV, for instance) (34).

To the best of our knowledge, the present investigation is the first longitudinal study to investigate the relationship between HRV abnormality and the risk of incident diabetes in a large number of Asians. However, several limitations should be considered. First, we conducted 3-min HRV measurements, not the 5-min variation. In addition, we did not perform these measurements repeatedly due to the standardized short-term HRV measurement protocols (3). However, strong correlations between ultra-short-term and 5-min HRV measurement data were demonstrated. The minimal recording periods of HRV required to correlate with 5-min measurements were <3 min (35). Indeed, prior longitudinal studies for which the findings were consistent with ours were based on 2-min or 10-s HRV recordings (6,7). Regarding the issue of repeated implementation of HRV measurement, we showed consistent significance for individuals who had prospective follow-up HRV tests within 2 years (Table 3). Second, we cannot rule out possibilities of alcohol or caffeine consumption at 1 day before HRV examination. However, because HRV measurement was one of the components of health screening examinations including endoscopy and fasting venous sampling, all subjects were in a fasting state for at least 12 h. Third, given that the follow-up period was shorter than that in previous studies conducted in other populations (6,10), we could not sufficiently exclude possible effects of reverse causality. In addition, because the group with diabetes already had increased FPG levels within the prediabetes range at baseline, patients with undiagnosed diabetes might have been included in this study. In light of this finding, we not only excluded subjects with a follow-up duration of <1 year, but also conducted a subgroup analysis according to FPG level of 100 mg/dL and a sensitivity analysis for those whose HbA_{1c} levels were <6.0%,

Table 2—Risk of incident diabetes according to tertiles of HRV measurement

Variable	Person-years	Number of events	Incidence rate (1,000 person-years)	Age- and sex-adjusted HR (95% CI)*	Multivariate-adjusted HR (95% CI)*	
					Model 1	Model 2
Heart rate (bpm)†						
T1 (32–60)	75,280.3	295	3.92 (3.50–4.39)	1 (reference)	1 (reference)	1 (reference)
T2 (61–67)	82,305.8	413	5.02 (4.56–5.53)	1.39 (1.20–1.62)	1.31 (1.11–1.53)	1.18 (1.01–1.39)
T3 (≥68)	86,145.9	661	7.67 (7.11–8.28)	2.21 (1.92–2.53)	1.72 (1.48–2.00)	1.41 (1.21–1.65)
P for trend				<0.001	<0.001	<0.001
SDNN (ms)‡						
T1 (−1.0 to 35.4)	80,945.5	635	7.84 (7.26–8.48)	1 (reference)	1 (reference)	1 (reference)
T2 (35.5–48.3)	82,336.4	422	5.13 (4.66–5.64)	0.73 (0.64–0.82)	0.91 (0.80–1.04)	0.97 (0.85–1.11)
T3 (≥48.4)	80,476.4	312	3.88 (3.47–4.33)	0.60 (0.52–0.69)	0.75 (0.64–0.87)	0.81 (0.70–0.95)
P for trend				<0.001	<0.001	0.012
RMSSD (ms)‡						
T1 (−1.0 to 29.5)	81,508.3	754	9.25 (8.61–9.94)	1 (reference)	1 (reference)	1 (reference)
T2 (29.6–43.6)	81,786.7	355	4.34 (3.91–4.82)	0.54 (0.47–0.61)	0.70 (0.61–0.80)	0.76 (0.66–0.87)
T3 (≥43.7)	80,463.3	260	3.23 (2.86–3.65)	0.47 (0.40–0.54)	0.65 (0.55–0.76)	0.76 (0.65–0.90)
P for trend				<0.001	<0.001	<0.001
TP (ms^2)‡						
T1 (0–815.5)	81,219.3	594	7.31 (6.75–7.93)	1 (reference)	1 (reference)	1 (reference)
T2 (815.6–1,612.9)	81,573.1	431	5.28 (4.81–5.81)	0.80 (0.71–0.91)	0.95 (0.83–1.09)	0.98 (0.86–1.12)
T3 (≥1,613.0)	80,965.9	344	4.25 (3.82–4.72)	0.69 (0.60–0.79)	0.85 (0.73–0.98)	0.92 (0.80–1.07)
P for trend				<0.001	0.034	0.293
LF norm (n.u.)§						
T1 (0–35.2)	80,754.5	296	3.67 (3.27–4.11)	1 (reference)	1 (reference)	1 (reference)
T2 (35.3–56.1)	81,333.4	441	5.42 (4.94–5.95)	1.30 (1.12–1.51)	1.20 (1.02–1.41)	1.16 (0.99–1.37)
T3 (≥56.2)	81,670.4	632	7.74 (7.16–8.37)	1.67 (1.45–1.93)	1.40 (1.20–1.63)	1.32 (1.13–1.53)
P for trend				<0.001	<0.001	<0.001
HF norm (n.u.)‡						
T1 (0–43.2)	81,400.2	629	7.73 (7.15–8.36)	1 (reference)	1 (reference)	1 (reference)
T2 (43.3–64.2)	81,393.3	437	5.37 (4.89–5.90)	0.77 (0.68–0.87)	0.84 (0.74–0.96)	0.87 (0.76–0.99)
T3 (≥64.3)	80,964.7	303	3.74 (3.34–4.19)	0.61 (0.53–0.70)	0.73 (0.63–0.85)	0.78 (0.67–0.91)
P for trend				<0.001	<0.001	0.001
LF/HF ratio§						
T1 (0–0.5)	80,852.8	297	3.67 (3.28–4.12)	1 (reference)	1 (reference)	1 (reference)
T2 (0.6–1.2)	78,456.8	419	5.34 (4.85–5.88)	1.28 (1.10–1.49)	1.18 (1.00–1.39)	1.15 (0.97–1.35)
T3 (≥1.3)	84,448.7	653	7.73 (7.16–8.35)	1.67 (1.45–1.92)	1.40 (1.20–1.63)	1.31 (1.13–1.53)
P for trend				<0.001	<0.001	<0.001

n.u., normalized units; T1, tertile 1; T2, tertile 2; T3, tertile 3. *Cox proportional hazards regression models were used to estimate HRs and 95% CIs. Right-skewed variables (i.e., SDNN, RMSSD, TP, LF norm, HF norm, and LF/HF ratio) were log-transformed for the analysis. Model 1 was adjusted for age, sex, BMI, LDL-C, hs-CRP, current smoking, and alcohol intake ≥20 g/day. Model 2 is the same as model 1 with an adjustment for systolic BP and HOMA-IR score. †Data for heart rate were available in 54,069 subjects. ‡Lower is worse. §Higher is worse.

resulting in similar findings (Supplementary Tables 3 and 4). Additionally, when we adjusted FPG level instead of HOMA-IR in Cox analysis, similar findings were observed (Supplementary Table 6). Because the association between FPG level in the nondiabetic range and HRV was inconsistent among studies, the exact cutoff points of glucose and insulin related to autonomic dysfunction were not determined in subjects with diabetes (36,37). Fourth, given that medication history was identified by self-report, unidentified medications such as diuretics or β-blockers could be relevant as confounders. However, because we excluded individuals who responded to take medications for heart disease or thyroid disease, a large number of individuals taking diuretics or β-blockers were excluded. When we conducted Cox analysis after excluding those who were taking antihypertensive medications during HRV examination, similar results were found (Supplementary Table 7). Finally, given that our study subjects mainly consisted of employees and their families, they were biased toward people with easy access to health care. Nevertheless, the current study provided a large number of HRV data from a single ethnicity with detailed biochemical and clinical assessments, allowing us to adjust various confounders.

In conclusion, alterations in HRV measurements are related to increased risk of incident diabetes. Decreased vagal activity and deviation in sympathetic activity represented by elevated LF norm and LF/HF ratio and suppressed HF norm can facilitate the development of diabetes in young Asian adults.

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Table 3—Risk of incident diabetes according to change of HRV measurement in the subjects who underwent follow-up HRV examination within 2 years

	Visit 1 exam	Visit 2 exam	Number of subjects	Age- and sex-adjusted HR (95% CI)*	Multivariate-adjusted HR (95% CI)*	
					Model 1	Model 2
Heart rate (bpm)	V1 < 32	V2 < 33	8,299	1 (reference)	1 (reference)	1 (reference)
	V1 < 32	V2 ≥ 65	2,519	1.42 (1.07–1.89)	1.35 (0.99–1.84)	1.29 (0.95–1.76)
	V1 ≥ 32	V2 < 33	3,525	1.24 (0.94–1.62)	1.24 (0.93–1.65)	1.10 (0.82–1.48)
	V1 ≥ 32	V2 ≥ 65	9,408	2.25 (1.87–2.70)	1.96 (1.60–2.40)	1.69 (1.38–2.08)
SDNN (ms)‡	V1 < 40.3	V2 < 39.5	6,198	1 (reference)	1 (reference)	1 (reference)
	V1 < 40.3	V2 ≥ 39.5	2,840	0.67 (0.52–0.86)	0.81 (0.62–1.06)	0.85 (0.65–1.11)
	V1 ≥ 40.3	V2 < 39.5	2,462	0.91 (0.72–1.16)	1.08 (0.84–1.40)	1.16 (0.90–1.51)
	V1 ≥ 40.3	V2 ≥ 39.5	5,908	0.56 (0.46–0.70)	0.66 (0.52–0.83)	0.71 (0.56–0.90)
RMSSD (ms)‡	V1 < 34.3	V2 < 33.3	6,714	1 (reference)	1 (reference)	1 (reference)
	V1 < 34.3	V2 ≥ 33.3	2,308	0.54 (0.41–0.72)	0.65 (0.48–0.88)	0.64 (0.47–0.87)
	V1 ≥ 34.3	V2 < 33.3	1,973	0.70 (0.53–0.92)	0.80 (0.59–1.07)	0.87 (0.65–1.18)
	V1 ≥ 34.3	V2 ≥ 33.3	6,413	0.47 (0.38–0.58)	0.57 (0.46–0.72)	0.64 (0.51–0.80)
TP (ms^2)‡	V1 < 1,076.3	V2 < 1,020.8	5,882	1 (reference)	1 (reference)	1 (reference)
	V1 < 1,076.3	V2 ≥ 1,020.8	3,079	0.72 (0.57–0.92)	0.86 (0.66–1.10)	0.92 (0.71–1.18)
	V1 ≥ 1,076.3	V2 < 1,020.8	2,820	0.84 (0.66–1.06)	0.99 (0.76–1.27)	1.04 (0.80–1.34)
	V1 ≥ 1,076.3	V2 ≥ 1,020.8	5,627	0.63 (0.51–0.77)	0.74 (0.58–0.93)	0.79 (0.62–1.00)
LF norm (n.u.)§	V1 < 46.5	V2 < 46.9	5,618	1 (reference)	1 (reference)	1 (reference)
	V1 < 46.5	V2 ≥ 46.9	3,071	1.24 (0.95–1.63)	1.17 (0.87–1.56)	1.20 (0.90–1.61)
	V1 ≥ 46.5	V2 < 46.9	3,077	1.37 (1.05–1.79)	1.21 (0.90–1.62)	1.18 (0.88–1.58)
	V1 ≥ 46.5	V2 ≥ 46.9	5,642	1.76 (1.41–2.20)	1.43 (1.13–1.81)	1.39 (1.09–1.76)
HF norm (n.u.)‡	V1 < 53	V2 < 52.7	5,624	1 (reference)	1 (reference)	1 (reference)
	V1 < 53	V2 ≥ 52.7	3,057	0.81 (0.64–1.02)	0.89 (0.69–1.14)	0.89 (0.69–1.15)
	V1 ≥ 53	V2 < 52.7	3,073	0.71 (0.56–0.91)	0.81 (0.63–1.05)	0.86 (0.66–1.11)
	V1 ≥ 53	V2 ≥ 52.7	5,654	0.58 (0.47–0.73)	0.72 (0.57–0.92)	0.75 (0.59–0.95)
LF/HF ratio§	V1 < 0.9	V2 < 0.9	5,386	1 (reference)	1 (reference)	1 (reference)
	V1 < 0.9	V2 ≥ 0.9	3,127	1.16 (0.88–1.53)	1.10 (0.82–1.49)	1.15 (0.85–1.55)
	V1 ≥ 0.9	V2 < 0.9	3,014	1.29 (0.98–1.69)	1.13 (0.84–1.53)	1.10 (0.82–1.49)
	V1 ≥ 0.9	V2 ≥ 0.9	5,881	1.76 (1.41–2.20)	1.44 (1.14–1.83)	1.40 (1.10–1.78)

n.u., normalized units; V1, visit 1; V2, visit 2. *Cox proportional hazards regression models were used to estimate HRs and 95% CIs. Right-skewed variables (i.e., SDNN, RMSSD, TP, LF norm, HF norm, and LF/HF ratio) were log-transformed for the analysis. Model 1 was adjusted for age, sex, BMI, LDL cholesterol, hs-CRP, current smoking, and alcohol intake ≥20 g/day. Model 2 is the same as model 1 with an adjustment for systolic BP and HOMA-IR score. ‡Lower is worse. §Higher is worse.

reviewed and edited the manuscript. C.-Y.P. and K.-W.O. contributed to the discussion. M.Y.L., S.-W.P., and S.R. assisted in the analysis and interpretation of the data. S.E.P. conceptualized and designed the study, reviewed and edited the manuscript, and supervised the study. S.E.P. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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