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The Association of Measures of Cardiovascular Autonomic Function, Heart Rate, and Orthostatic Hypotension With Incident Glucose Disorders: The Cardiovascular Health Study

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OBJECTIVE

The autonomic nervous system (ANS) innervates pancreatic endocrine cells, muscle, and liver, all of which participate in glucose metabolism. We tested whether measures of cardiovascular ANS function are independently associated with incident diabetes and annual change in fasting glucose (FG) levels as well as with insulin secretion and insulin sensitivity in older adults without diabetes.

RESEARCH DESIGN AND METHODS

Heart rate (HR) and measures of HR variability (HRV) were derived from 24-h electrocardiographic monitoring. Blood pressure, seated and standing, was measured. Cox proportional hazards models and linear mixed models were used to analyze the associations between HRV, HR, and orthostatic hypotension (SBP >20 mmHg decline) and incident diabetes or longitudinal FG change.

RESULTS

The mean annual unadjusted FG change was 1 mg/dL. Higher detrended fluctuation analyses (DFA) values, averaged over 4–11 (DFA1) or 12–20 beats (DFA2)—reflecting greater versus less organization of beat-to-beat intervals—were associated with less FG increase over time (per 1-SD increment: DFA1: −0.49 mg/dL/year [−0.96, −0.03]; DFA2: −0.55 mg/dL/year [−1.02, −0.09]). In mutually adjusted analyses, higher SD of the N-N interval (SDNN) was associated with less FG increase over time (per 1-SD increment: SDNN: −0.62 mg/dL/year [−1.22, −0.03]). Higher values of DFA1, DFA2, and SDNN were each associated with greater insulin secretion and insulin sensitivity but not with incident diabetes. We observed no association of HR or orthostatic hypotension with diabetes or FG change.

CONCLUSIONS

Specific measures of cardiac autonomic function are prospectively related to FG level changes and insulin secretion and action.

Strong physiological connections link the autonomic nervous system (ANS) with glucose metabolism. Pancreatic islet cells and their blood vessel supply are surrounded by a network of autonomic nerve fibers (1). In healthy individuals, parasympathetic nerve signaling (PNS) triggers early release of insulin from the pancreatic β-cells

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(e.g., first-phase insulin release) in response to sensory signals (e.g., aroma) to prepare the gastrointestinal tract for the processing of ingested foods (2). PNS also stimulates β-cell proliferation in rodent models (3). Sympathetic nerve signaling (SNS) regulates glucagon secretion by islet α-cells and inhibits insulin secretion in response to hypoglycemia (4). These two SNS effects are achieved by β-adrenoceptors expressed in α-cells and by α2-adrenoceptors expressed in β-cells. Liver, adipose tissue, and smooth muscle tissue, whose effects on glucose metabolism are related to insulin sensitivity, are also innervated by the ANS (5–7).

We previously showed that cardiovascular autonomic neuropathy can be present prior to the onset of diabetes (8). Metabolic syndrome without diabetes is associated with cardiovascular autonomic neuropathy (9). Likewise, autonomic dysfunction can be associated with reduced peripheral insulin sensitivity (10). Taken together, these studies suggest that ANS dysfunction could play a role in the pathogenesis of glucose dysregulation.

Here we explore whether markers of ANS function are prospectively associated with new-onset diabetes and/or longitudinal changes of fasting glucose (FG) levels in a sample of older individuals without diabetes. We examine markers of heart rate (HR) variability (HRV), a direct measure of ANS function, and HR and orthostatic hypotension (OH) as indirect measures of ANS function. We further examine whether markers of ANS function are associated with insulin sensitivity and/or insulin secretion.

RESEARCH DESIGN AND METHODS

The Cardiovascular Health Study (CHS) is a longitudinal study of community-dwelling adults, aged ≥65 years, from four U.S. communities drawn from Medicare lists (11). In 1989–1990, 5,201 participants were recruited, followed by an additional 687 predominantly African American participants in 1992–1993. All participants gave informed consent upon study entry. Institutional Review Board approval was received at all clinical sites. From 1989–1990 to 1998–1999, participants were seen in the clinic annually and had telephone contact midway between clinic visits. Following the 1998–1999 visit, participants continued to be contacted biennially by phone, except for an additional clinic visit in 2005–2006.

Analytic Samples

We constructed two CHS analytic samples for these analyses, based on the marker of ANS function included as the exposure measure. For OH (the larger sample), 5,265 participants attended the 1992–1993 visit, 4,578 participants were from the original cohort (1989–1990), and 687 were from the new (1992–1993) cohort (Supplementary Fig. 1). Of these, OH was not measured in 520. Another 1,030 were excluded on account of prevalent diabetes or missing information on diabetes status at baseline or on follow-up. This left 3,715 participants for incident diabetes analysis. Of these, another 24 were excluded on account of not having FG levels on follow-up, leaving 3,691 participants for longitudinal glucose analyses. Due to missing model 2 covariates, model 2 had fewer participants than model 1.

The 1994–1995 visit was used as the baseline for the HRV analysis (Supplementary Fig. 2). Of the 4,842 participants who attended the visit, 1,184 underwent 24-h electrocardiographic (i.e., Holter) monitoring. This included 816 participants from the original cohort (1989–1990) who had been randomly selected to undergo Holter monitoring at baseline and returned to the 1994–1995 visit. They were performing a second Holter examination. A random sample of 368 participants from the new (1992–1993) cohort had an initial Holter examination in 1994–1995. Of the 1,184 Holter monitorings, we excluded 127 who were not in predominantly sinus rhythm and 250 who had prevalent diabetes or incomplete diabetes follow-up. This left 807 participants available for incident diabetes analysis. Of these 807 participants, 78 had missing FG values over follow-up, leaving 729 participants for longitudinal glucose analyses. Of the 807 participants in the incident diabetes analyses, 210 participants were missing Matsuda or Stumvoll indices from the oral glucose tolerance test performed in 1996–1997, leaving 597 participants available for analysis of Matsuda or Stumvoll indices. Depending on the HRV measure analyzed, different numbers of participants were excluded due to missing the specific HRV measure or missing model 2 covariates. Also, analyses involving Stumvoll had fewer observations than those only involving Matsuda.

Outcomes

There were two outcomes for these analyses:

1. Incident diabetes through 1998–1999: FG ≥126 mg/dL on follow-up, a random glucose ≥200 mg/dL, or use of insulin or oral hypoglycemic medication were used as diagnostic criteria for incident diabetes. FG levels were available at years 1992–1993, 1994–1995, 1996–1997, and 1998–1999. Information on medications was available annually. In addition, Centers for Medicare & Medicaid Services claims were used to ascertain diabetes. Individuals were considered to have diabetes if they had an ICD-9-CM Medicare claim code for diabetes at two or more inpatient, three or more outpatient, or one or more inpatient and one or more outpatient visits over a 2-year period.
2. The trajectory of FG level change: Participants had one to four longitudinal measures of FG between 1992–1993 and 1998–1999. We used these to evaluate longitudinal change in FG (i.e., the association of time with FG). To account for participants who initiated diabetes medication use after the analysis baseline, we imputed a 35 mg/dL increase among those taking hypoglycemic agents (12). The maximum number of observations that were imputed was 70 for the OH analysis and 16 for the HRV analysis.

Measures of Autonomic Function

1. Average and SD of N-N intervals (SDNN) as a proxy for HR: The average and SDNN time derived from the 24-h Holter recording was calculated (13). HR can be derived by dividing 60,000 by the N-N interval. Additional details appear in Supplemental List 1.
2. Other measures of autonomic function: Details of the Holter monitoring data collection and analysis have been previously reported (13). Measures of HRV were derived from the Holter recordings. Details about time and frequency domain HRV variables, detrended fluctuation analyses (DFA) 1 and DFA2 (measures of the structure of the HR time series), and HR

turbulence (the autonomic response to a premature ventricular beat) appear in Supplemental List 1.

3. OH: OH was defined as a decrease of ≥20 mmHg in systolic BP and/or of ≥10 mmHg in diastolic BP after changing from a seated to a standing position (14).

Covariates

Multivariate analyses were adjusted for factors that could impact autonomic function and glucose levels. Primary covariates used in model 1 included age, clinic site, and the interaction of sex and race. This interaction was modeled to account for the possibility of differential effects by sex-race categories. Additional covariates used in model 2 included technician-measured waist circumference, self-reported blocks walked per week, alcoholic drinks/week, score on the Centers for Epidemiologic Studies-Depression scale, hypertension, prevalent coronary heart disease (CHD), log-transformed hs-CRP, and estimated glomerular filtration rate (eGFR) as estimated by cystatin C. Self-identified race was collected at enrollment, and waist circumference, hs-CRP, and eGFR by cystatin C were measured at the 1992–1993 visit. All other covariates were measured at the analysis baseline (1992–1993 for the OH analysis and 1994–1995 for the HRV analysis).

Statistical Analyses

Cox proportional hazards regression models were used to analyze the adjusted associations between ANS measures and incident diabetes. Hazard ratios (HRs), 95% CIs, and Wald *P* values were calculated. For models with trajectory of FG level change as the outcome, mixed-effects models with random intercepts were used, and the time-by-exposure interaction was the primary measure of association. Regression coefficients (β), 95% CIs, and Wald *P* values were calculated. No adjustments for multiple comparisons were made. Due to the lack of adjustment for multiple comparisons, conclusions drawn from these regression models should be replicated to ensure their validity.

For ANS measures with statistically significant associations with incident diabetes or FG trajectory, we examined associations with insulin sensitivity (the Matsuda index [15]) and insulin secretion using a β-cell function index (Stumvoll equation [16]). Both formulas use glucose and insulin levels from times 0 and 120 min of an oral glucose tolerance test administered in 1996–1997. To account for increases in insulin secretion due to insulin resistance, we fit models with Matsuda or Stumvoll as outcomes adjusted for covariates only or adjusted for covariates and for the other index.

Analyses were performed using the R statistical package 2019 (17).

Data and Resource Availability

Data for this article are available upon request.

RESULTS

Autonomic Variables

Baseline characteristics according to median of the SDNN intervals are presented in Supplementary Table 2. The total sample was a mean age of 75.3 years, 30% were African American, and 38% were men.

During a median of 4 years of follow-up, we identified 32 cases of diabetes among the 807 participants included in the HRV analysis. The individual associations of autonomic function measures with incident diabetes are provided in Table 1. In model 1, 1-SD higher SDNN

Table 1—Individual and conjoint associations of cardiovascular autonomic measures with incident diabetes

		Individual associations of autonomic measures with incident diabetes				Conjoint associations of autonomic measures with incident diabetes			
Model	Exposure	Incident diabetes, *n*/*N* (%)	Median follow-up (years)	HR (95% CI)	*P* value	Incident diabetes, *n*/*N* (%)	Median follow-up (years)	HR (95% CI)	*P* value
Model 1	Mean N-N interval*	32/768 (4)	4	0.78 (0.53, 1.15)	0.21	32/708 (5)	4	0.86 (0.53, 1.39)	0.53
	SDNN interval*	32/768 (4)	4	0.67 (0.45, 1.00)	**0.05**			0.66 (0.37, 1.18)	0.16
	VLF power**	32/715 (4)	4	0.77 (0.55, 1.08)	0.13			0.85 (0.31, 2.34)	0.76
	Mean DFA1*	32/715 (4)	4	0.80 (0.57, 1.14)	0.21			1.09 (0.54, 2.23)	0.81
	Mean DFA2*	32/715 (4)	4	0.88 (0.64, 1.22)	0.46			0.93 (0.45, 1.90)	0.84
	Abnormal HR turbulence								
	Onset	38/797 (5)	4	1.06 (0.44, 2.55)	0.9			0.48 (0.14, 1.66)	0.25
	Slope	38/797 (5)	4	1.25 (0.61, 2.55)	0.54			1.46 (0.62, 3.43)	0.38
	rMSSD**	32/768 (4)	4	0.98 (0.69, 1.40)	0.92			1.38 (0.41, 4.63)	0.6
Model 2	Mean N-N interval*	32/735 (4)	4	0.75 (0.50, 1.11)	0.15	32/677 (5)	4	0.79 (0.47, 1.30)	0.35
	SDNN interval*	32/735 (4)	4	0.68 (0.45, 1.02)	0.06			0.68 (0.37, 1.24)	0.21
	VLF power**	32/684 (5)	4	0.77 (0.55, 1.09)	0.14			0.92 (0.34, 2.51)	0.8
	Mean DFA1*	32/684 (5)	4	0.83 (0.57, 1.20)	0.32			1.08 (0.52, 2.23)	0.84
	Mean DFA2*	32/684 (5)	4	0.89 (0.64, 1.24)	0.48			0.88 (0.43, 1.81)	0.73
	Abnormal HR turbulence								
	Onset	38/763 (5)	4	1.05 (0.43, 2.56)	0.91			0.48 (0.14, 1.66)	0.24
	Slope	38/763 (5)	4	1.07 (0.52, 2.21)	0.86			1.18 (0.50, 2.82)	0.71
	rMSSD**	32/735 (4)	4	0.95 (0.67, 1.37)	0.79			1.28 (0.39, 4.21)	0.69

The bold *P* value is statistically significant. rMSSD, root mean square of successive differences. Model 1 adjusts for age, clinic site, and the interaction of sex and race. Model 2 adjusts for model 1 covariates, as well as waist circumference, blocks walked per week, hs-CRP, drinks/week, depression scale total, hypertension, prevalent CHD, and eGFR by cystatin C. *Estimates shown are for a 1-SD increase in the measure. **Estimates shown are for a 1-SD increase in the log(measure).

was associated with a lower risk of diabetes (HR 0.67 [95% CI 0.45, 1.00], $P = 0.05$). Further adjustment for covariates in model 2 did not meaningfully change the magnitude of this association (0.68 [0.45, 1.02], $P = 0.06$). Other HRV variables, such as very low frequency (VLF) power, mean DFA1, and mean DFA2, were not significantly associated with risk of diabetes. In a joint analysis, when all HRV measures were simultaneously adjusted for each other (Table 1), no significant associations with incident diabetes were found. The HR for SDNN, however, was similar to the estimate in its individual model.

The mean unadjusted change in FG levels was ~1 mg/dL/year from the 1994–1995 to the 1998–1999 visit among participants included in the HRV analysis. Higher DFA1 and DFA2 were each significantly associated with lower annualized increases in FG levels in the fully adjusted model (Table 2). When the HRV variables were simultaneously adjusted for each other (Table 2), a 1-SD higher SDNN value was associated with a statistically significant 0.62 mg/dL lower annualized increase in FG after adjusting for model 2 covariates (95% CI −1.22, −0.03; $P = 0.04$). Neither DFA1 nor DFA2 had significant associations with annualized change in FG levels in the simultaneously adjusted model.

Relationship of DFA1, DFA2, and SDNN with Insulin Sensitivity and Insulin Secretion

The associations of DFA1, DFA2, and SDNN with insulin sensitivity (Matsuda index) and insulin secretion (Stumvoll equation) are summarized in Table 3. Higher values for each of the three HRV measures were associated with higher insulin sensitivity and higher insulin secretion in fully adjusted models. Additional adjustment of insulin sensitivity for insulin secretion and insulin secretion for insulin sensitivity generally enhanced associations.

Average N-N Interval

The mean 24-h N-N interval ($n = 768$ participants) was not significantly associated with incident diabetes (Table 1). There were few changes in these estimates when models with average N-N intervals were adjusted for the association of other autonomic variables with incident diabetes (Table 1). The average N-N interval was not significantly associated with change in annual FG values, with or without adjustment for other autonomic variables (Table 2).

OH

There were 495 participants (13%) of the 3,715 participants from the 1992–1993 sample with OH. During a median follow-up of 6 years, we documented 40 incident cases of diabetes among the 495 participants with OH (8.1%) and 214 cases of incident diabetes among the 3,220 without OH (6.6%). The association between OH and incident diabetes was not statistically significant (Table 4). Likewise, there were no associations of OH with annual change in FG values.

CONCLUSIONS

In this exploratory analysis of the association of measures of dysautonomia, as characterized by HRV, HR, and OH, with incident glucose disorders in a sample of older adults without diabetes, there were two salient outcomes. First, in individual analyses, we observed a borderline statistically significant association of a higher SDNN value with lower diabetes risk. Higher DFA1 and DFA2 were each significantly associated with lower annualized FG level trajectories. A higher SDNN value was significantly associated

Table 2—Association of cardiovascular autonomic measures with annualized change in fasting glucose in separate and combined mixed-effects models with random intercepts

		Annualized change in fasting glucose levels in separate mixed-effects models			Annualized change in fasting glucose levels in combined mixed-effects models		
Model	Exposure with time (years) interaction	*N*	β (95% CI)	*P* value	*N*	β (95% CI)	*P* value
Model 1	Mean N-N interval*	697	−0.18 (−0.61, 0.25)	0.42	646	−0.27 (−0.84, 0.30)	0.35
	SDNN interval*	697	−0.28 (−0.69, 0.14)	0.19		−0.59 (−1.17, −0.01)	**0.04**
	VLF power**	652	−0.03 (−0.50, 0.43)	0.88		0.62 (−0.61, 1.86)	0.32
	Mean DFA1*	652	−0.43 (−0.88, 0.02)	0.06		−0.18 (−1.07, 0.70)	0.69
	Mean DFA2*	652	−0.53 (−0.97, −0.09)	**0.02**		−0.73 (−1.63, 0.17)	0.11
	Abnormal HR turbulence onset	721	0.37 (−0.81, 1.56)	0.54		0.20 (−1.11, 1.50)	0.77
	Abnormal HR turbulence slope	721	0.08 (−0.91, 1.07)	0.88		0.53 (−0.60, 1.65)	0.36
	rMSSD**	697	0.33 (−0.08, 0.75)	0.12		−0.20 (−1.72, 1.32)	0.8
Model 2	Mean N-N interval*	667	−0.20 (−0.64, 0.24)	0.37	618	−0.28 (−0.87, 0.30)	0.34
	SDNN interval*	667	−0.28 (−0.70, 0.14)	0.2		−0.62 (−1.22, −0.03)	**0.04**
	VLF power**	624	−0.05 (−0.52, 0.43)	0.85		0.75 (−0.52, 2.01)	0.25
	Mean DFA1*	624	−0.49 (−0.96, −0.03)	**0.04**		−0.31 (−1.23, 0.61)	0.51
	Mean DFA2*	624	−0.55 (−1.02, −0.09)	**0.02**		−0.78 (−1.72, 0.16)	0.1
	Abnormal HR turbulence onset	690	0.40 (−0.82, 1.62)	0.52		0.16 (−1.18, 1.50)	0.81
	Abnormal HR turbulence slope	690	0.23 (−0.78, 1.25)	0.65		0.70 (−0.46, 1.85)	0.24
	rMSSD**	667	0.34 (−0.09, 0.77)	0.12		−0.31 (−1.87, 1.25)	0.7

The bold *P* values are statistically significant. rMSSD, root mean square of the successive differences. Model 1 adjusts for age, clinic site, and the interaction of sex and race. Model 2 adjusts for model 1 covariates, as well as waist circumference, blocks walked per week, hs-CRP, drinks/week, depression scale total, hypertension, prevalent CHD, and eGFR by cystatin C. The β-coefficients estimate the difference in annual change in glucose associated with a 1-unit increment in the HRV measure. Significant negative coefficients mean that higher values of the HRV measure are associated with less increase in fasting glucose. *Estimates shown are for a 1-SD increase in the measure. **Estimates shown are for a 1-SD increase in the log(measure) effects models with random intercepts.

Table 3—Association of autonomic measures with insulin sensitivity (Matsuda) and insulin secretion (Stumvoll) indices, determined through linear regression models

	Exposure	Outcome	Covariates	*N*	β (95% CI)	*P* value
Model 1	SDNN interval*	Matsuda	Model	568	3.11 (0.06, 6.16)	0.05
			Model + Stumvoll	558	5.11 (2.04, 8.17)	<0.005
		Stumvoll	Model	558	640 (401, 879)	<0.005
			Model + Matsuda	558	699 (468, 931)	<0.005
	Mean DFA1*	Matsuda	Model	532	2.78 (−0.86, 6.41)	0.14
			Model + Stumvoll	522	5.03 (1.37, 8.69)	0.01
		Stumvoll	Model	522	688 (410, 965)	<0.005
			Model + Matsuda	522	739 (469, 1009)	<0.005
	Mean DFA2*	Matsuda	Model	532	2.97 (−0.68, 6.62)	0.11
			Model + Stumvoll	522	5.35 (1.67, 9.03)	<0.005
		Stumvoll	Model	522	746 (468, 1023)	<0.005
			Model + Matsuda	522	799 (529, 1069)	<0.005
Model 2	SDNN interval*	Matsuda	Model	543	9.84 (5.93, 13.76)	<0.005
			Model + Stumvoll	540	10.65 (6.77, 14.52)	<0.005
		Stumvoll	Model	540	355 (45, 665)	0.03
			Model + Matsuda	540	511 (200, 821)	<0.005
	Mean DFA1*	Matsuda	Model	509	10.55 (6.16, 14.94)	<0.005
			Model + Stumvoll	506	11.33 (6.97, 15.68)	<0.005
		Stumvoll	Model	506	362 (23, 700)	0.04
			Model + Matsuda	506	506 (166, 847)	<0.005
	Mean DFA2*	Matsuda	Model	509	10.23 (5.78, 14.68)	<0.005
			Model + Stumvoll	506	11.18 (6.76, 15.60)	<0.005
		Stumvoll	Model	506	441 (99, 782)	0.01
			Model + Matsuda	506	580 (237, 923)	<0.005

Model 1 adjusts for age, clinic site, and the interaction of sex and race. Model 2 adjusts for Model 1 covariates, as well as waist circumference, blocks walked/week, hs-CRP, drinks/week, depression scale total, hypertension, prevalent CHD, and eGFR by cystatin C. *Estimates shown are for a 1-SD increase in the measure.

with lower annualized FG level trajectories in joint analyses. Second, OH and average N-N interval (i.e., HR) were not statistically significantly associated with increased risks of diabetes or with the trajectory of annualized FG change.

Regarding the latter point, OH is heterogeneous; in many instances, it is not related to autonomic dysfunction. Common forms of OH are related to medication use (hypertension or psychiatric medications), dehydration, and to cardiac and metabolic disorders. It is therefore not surprising that there was no significant association with changes in glucose metabolism. Average N-N intervals were not significantly associated with incident diabetes or FG changes, although the risk of incident diabetes and the FG trajectory tended to be lower with higher average N-N intervals (i.e., slower HR). It is possible that the small number of participants and diabetes cases limited our ability to detect any associations. The lack of association of average N-N interval (or its inverse, HR) with diabetes or annualized FG changes stands in contrast to studies reporting an association of high HR with incident glucose disorders (18–25). These studies had more participants than our study and, in most cases, longer duration of follow-up. All of them examined populations 10–30 years younger than our sample. The individuals in such samples would likely have fewer chronic illnesses, better conditioning, less obesity, and different balances of parasympathetic and sympathetic activity. Parasympathetic activity predominates in younger individuals; loss of parasympathetic activity is associated with greater sympathetic activation in older age (26,27). Several studies used resting HR, measured over seconds to minutes, while we used average HR derived from 24-h monitoring. Finally, in other studies, a significant association of HR with incident glucose disorders was present only in subgroups (e.g., the nonobese or those of younger age), but not in all

Table 4—Association of OH with incident diabetes and annualized change in fasting glucose

Incident diabetes

Model	Exposure	Incident diabetes, *n*/*N* (%)	Median follow-up (years)	HR (95% CI)	*P* value
Model 1	OH	254/3,715 (7)	6	1.27 (0.91, 1.79)	0.16
Model 2	OH	244/3,603 (7)	6	1.31 (0.93, 1.85)	0.13

Annualized change in fasting glucose

Model	Exposure with time (years) interaction	*N*	β (95% CI)	*P* value
Model 1	OH	3,691	−0.01 (−0.27, 0.25)	0.93
Model 2	OH	3,580	0.00 (−0.27, 0.27)	0.99

Model 1 adjusts for age, clinic site, and the interaction of sex and race. Model 2 adjusts for Model 1 covariates, as well as waist circumference, blocks walked/week, hs-CRP, drinks/week, depression scale total, hypertension, prevalent CHD, and eGFR by cystatin C. Note: Those taking diabetes drugs have recorded fasting glucose measures increased by 35 mg/dL.

participants (22,23). In others (28,29), no independent associations between HR and new onset glucose disorders were documented.

Regarding the HRV findings, SDNN had the most consistent association with incident glucose disorders. After adjusting for model 2 covariates, 1-SD higher SDNN had a borderline association with a 32% lower risk of diabetes in its individual analysis and a statistically significant −0.62 mg/dL lower FG level increase per year. SDNN reflects many of the cyclic and diurnal components that make up HRV but is dominated by the circadian rhythm. The main inputs are the SNS and PNS, baroreflexes, thermoregulation, hormones, sleep-wake cycle, meals, physical activity, and stress. Healthy individuals who exercise (and have low HRV during exercise) and who sleep deeply without interruption (with lower HR and high HRV) have a wide distribution of HRV. Stressed individuals, those with obstructive sleep apnea and/or chronic pain, have disturbed sleep and elevated HRs and reduced SDNN. It may then be that SDNN is a marker of good health. Participants with SDNN values above the median compared with those with values below the median had a smaller waist circumference, walked more blocks per week, had lower hs-CRP values, and had less hypertension (Supplementary Table 2). We also found that a 1-SD higher DFA1 and DFA2 level had significant individual associations with annual FG level decline, although not in the joint analysis. DFA1 reflects the predictability of HR patterns on a scale of 4–11 beats. Values vary from 0.5 to 1.5, with 0.5 associated with totally random HR patterns (rhythm fragmentation) and 1.5 associated with total predictability. The same is true for DFA2, except the scale is 12–20 beats. Healthy values are in between, and an increase in the random component over time (e.g., a decrease in their values) is a marker for adverse changes in cardiovascular regulation (30).

As an explanation for the associations of those HRV variables with lower risk of diabetes or FG change over time, we found that they were related to insulin sensitivity, which is a measure of peripheral glucose disposal, and to insulin secretion, which is a measure of β-cell function. This suggests that higher HRV and an organized HR are both associated with better metabolic health. These findings are consistent with the Whitehall Study (29). It reported that a majority of HRV indices exhibited a trend in which higher values were associated with lower insulin levels and higher insulin sensitivity. Other studies have shown that an increased ratio of sympathetic to parasympathetic markers is related to insulin resistance (4,24,25,31,32). Further evidence for our results comes from a study of older men in which impaired rest-activity rhythm (a measure of circadian rhythm) was associated with the development of impaired glucose metabolism (33).

Advantages of this study are the relatively large number of individuals with Holter monitoring and HRV measurements. Holter scans were read to research standards and were calculated over 24 h. Many measures of cardiovascular autonomic neuropathy were calculated, giving a broad view of autonomic function with incident metabolic changes. Most prior studies rely on resting rhythm strips of a few minutes' duration and do not reflect the changes in autonomic measures during a 24-h period. Also, two measures of glucose change were examined, incident diabetes and the annual trajectory of FG. Measures of insulin sensitivity and secretion were derived from oral glucose tolerance tests.

Limitations of the study include a small number of incident diabetes cases, making it difficult to attain statistical significance, although the incidence rate of diabetes was within expectation for a population of this age (34). The study is observational, and unmeasured factors could have influenced our findings. Results did not account for multiple comparisons and should be replicated to ensure accuracy. Also, we used measures of cardiovascular autonomic function, and not direct measures of ANS effect on pancreatic endocrine cells, liver, or muscle. We assumed that the cardiovascular dysautonomia captured in HRV and OH analyses reflected the effects of the ANS on organs related to glucose metabolism.

In conclusion, higher levels of specific cardiovascular autonomic variables associated with better cardiovascular health are prospectively associated with a borderline lower risk of incident diabetes in individual analyses and with significantly lower FG level increases over time in individual and joint analyses. These findings support the hypothesis that ANS function plays a role in metabolic homeostasis.

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Author Contributions. J.I.B. and K.J.M. conceived and planned the paper, wrote the paper, and analyzed the data. W.T and M.L.B. performed the analyses and reviewed the paper for intellectual content. P.K.S. oversaw the Holter monitoring in CHS, interpreted Holter data, and reviewed the paper for intellectual content. J.R.K. has obtained funding for CHS, participates in the diabetes and heart working groups in CHS, and reviewed the paper for intellectual content. S.G.S. and Y.B.-A. are members of the CHS diabetes working group, reviewed the paper for intellectual content, and contributed to the formulation of the article. K.J.M. is the guarantor of this work and, as such, had full access to all 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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