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Clinical Research Article

Heart Rate Variability and Incident Type 2 Diabetes in General Population

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Abstract

Context: Hyperglycemia and autonomic dysfunction are bidirectionally related.

Objective: We investigated the association of longitudinal evolution of heart rate variability (HRV) with incident type 2 diabetes (T2D) among the general population.

Methods: We included 7630 participants (mean age 63.7 years, 58% women) from the population-based Rotterdam Study who had no history of T2D and atrial fibrillation at baseline and had repeated HRV assessments at baseline and during follow-up. We used joint models to assess the association between longitudinal evolution of heart rate and different HRV metrics (including the heart rate–corrected SD of the normal-to-normal RR intervals [SDNNc], and root mean square of successive RR-interval differences [RMSSDc]) with incident T2D. Models were adjusted for cardiovascular risk factors. Bidirectional Mendelian randomization (MR) using summary-level data was also performed.

Results: During a median follow-up of 8.6 years, 871 individuals developed incident T2D. One SD increase in heart rate (hazard ratio [HR] 1.20; 95% CI, 1.09-1.33), and log(RMSSDc) (HR 1.16; 95% CI, 1.01-1.33) were independently associated with incident T2D. The HRs were 1.54 (95% CI, 1.08-2.06) for participants younger than 62 years and 1.15 (95% CI, 1.01-1.31) for those older than 62 years for heart rate (*P* for interaction <.001). Results from bidirectional MR analyses suggested that HRV and T2D were not significantly related to each other.

Conclusion: Autonomic dysfunction precedes development of T2D, especially among younger individuals, while MR analysis suggests no causal relationship. More studies are needed to further validate our findings.

Key Words: heart rate, heart rate variability, type 2 diabetes, joint model, Mendelian randomization

Abbreviations: BMI, body mass index; ECG, electrocardiogram; GWAS, genome-wide association study; HOMA-β, homeostatic model assessment for beta-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; HRV, heart rate variability; IQR, interquartile range; MR, Mendelian randomization; RMSSDc, heart rate–corrected root mean square of successive RR-interval differences; RS, Rotterdam Study; SDNNc, heart rate–corrected SD of the normal-to-normal RR intervals; SNP, single nucleotide polymorphism; T2D, type 2 diabetes mellitus.

Cardiac autonomic dysfunction due to hyperglycemia has been suggested as a mechanism of cardiovascular complications in type 2 diabetes mellitus (T2D) (1). Major organs responsible for insulin secretion and sensitivity, glucose production, and metabolism, including the pancreas, liver, and skeletal muscle, are innervated by the autonomic nervous system (2). Yet, there are numerous pathways whereby autonomic dysfunction could, in turn, affect glucose metabolism. Notably, an autonomic imbalance was found to be already present in persons with prediabetes (3) and was associated with incident diabetes (4). Autonomic dysfunction has also been related to reduced insulin sensitivity and beta-cell function in people without diabetes (5, 6).

Heart rate variability (HRV) is a marker of cardiac autonomic dysfunction, and a single assessment of HRV has been associated with changes in fasting glucose level (7) and incident T2D (8). Taken together, alterations in autonomic function may contribute to the pathogenesis of T2D. However, HRV has a strong and inverse relationship with heart rate, so HRV parameters should be corrected for heart rate during analysis. Therefore, the results from previous studies using uncorrected HRV might be confounded. In addition, given the considerable impact of age on HRV (9) and the possible bidirectional association between hyperglycemia and autonomic dysfunction (3, 4), studies using only single HRV measurements, cross-sectional designs, and short follow-up periods are all prone to confounding and reverse causation. Joint modeling is a novel method that can perform simultaneous analyses of repeated exposure measurements and survival data, and its principal advantage is the proper treatment of noisy and incompletely observed time-varying exposure information. Thus, this approach is appropriate to

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estimate the hazard of incident T2D for the HRV metrics as time-varying covariates, which enables unbiased estimation of the relationship between the exposure and the outcome.

In the large prospective population-based Rotterdam Study with repeated measurements of HRV, we investigated the prospective association of evolution of HRV, as a proxy for autonomic function, with the incidence of T2D. In addition, we conducted a bidirectional Mendelian randomization (MR) analysis using summary-level data to explore the causality of the association between HRV and T2D.

Methods

Study Design and Population

This study was embedded within the Rotterdam Study (RS), a prospective cohort study of community-dwelling persons in Ommoord, Rotterdam, The Netherlands. The detailed study design has been described elsewhere (10). Briefly, the baseline examination of the first cohort was completed between 1990 and 1993 (RS-I, n = 7983) with participants aged 55 years or older. The study was extended in 2000, with the second cohort of individuals who had reached 55 years or moved into the study area after 1990 (RS-II, n = 3011). In 2006, a third cohort was enrolled, including inhabitants aged 45 years and older (RS-III, n = 3932). The overall response rate for the Rotterdam Study was 72%. There were no eligibility criteria to enter the Rotterdam Study apart from the minimum age and residential area based on postal codes. Participants attended follow-up examinations every 3 to 5 years.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study entered into the Netherlands National Trial Register (NTR; https://onderzoekmetmensen.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under the shared catalog number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from their treating physicians.

The current study was based on the third visit of RS-I (RS-I-3) and the first visit of RS-II (RS-II-1) and RS-III (RS-III-1). Participants with no informed consent for follow-up data collection (n = 137), prevalent T2D (n = 2133), or prevalent atrial fibrillation (n = 344) at baseline, or no available electrocardiogram (ECG) measurements (n = 1496) were excluded. Therefore, 7630 participants were included in the study (Supplementary Figure S1 (11)).

Assessment of Heart Rate Variability

A standard 10-s, 12-lead resting ECG was recorded during each follow-up examination with an ACTA Gnosis electrocardiograph (Esaote Biomedica, Italy) at a sampling frequency of 500 Hz and stored digitally. The ECGs were processed by the Modular ECG Analysis System (MEANS), an ECG computer program that has been validated extensively (12, 13). The HRV was calculated based on RR intervals between normal heartbeats; RR intervals were excluded if they immediately preceded or followed premature atrial complexes or premature ventricular complexes. The following HRV indices were used for the analyses: the heart rate–corrected standard deviation of the normal-to-normal RR intervals (SDNNc) and the heart rate–corrected root mean square of successive RR-interval differences (RMSSDc) (9).

Assessment of Cardiovascular Risk Factors

Information on covariates was collected at baseline using a structured questionnaire. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Fasting blood glucose and insulin levels, and total and high-density lipoprotein cholesterol were measured using standard laboratory techniques. Homeostatic model assessment of insulin resistance (HOMA-IR) and beta-cell function (HOMA-β) were calculated based on fasting blood glucose and serum insulin concentration to assess insulin resistance and β-cell function separately. Smoking status was categorized into never, former, and current smoking. Blood pressure was measured in the right upper arm with the participant in a sitting position, of which the mean of 2 consecutive measurements was used. Physical activity levels were assessed using validated questionnaires (the Zutphen Physical Activity Questionnaire for RS-I and RS-II (14), the LASA Physical Activity Questionnaire for RS-III (15)) and further quantified into metabolic equivalent task (MET) values per week doing moderate and vigorous-intensity activities classified according to the 2017 Dutch Physical Activity Guideline (16). Medication use (blood pressure– and lipid-lowering drugs) was derived from baseline questionnaires and pharmacy data and was categorized and defined according to the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) classifications. Specifically, antihypertensive medication, use of beta blockers, use of calcium blockers, and lipid-lowering medication were defined according to the WHO ATC categories c02, c07, c08, and c10, respectively. In addition, information about prevalent cardiovascular disease (including coronary heart disease, heart failure, and stroke) was also collected at baseline.

Assessment of Type 2 Diabetes

Participants were followed up from the date of attending the baseline visit onward. At baseline and during follow-up, cases of T2D were ascertained by the use of general practitioners records, hospital discharge letters, and serum glucose measurements collected from center visits, which took place roughly every 4 years. T2D was defined as a fasting blood glucose concentration equal to or above 7.0 mmol/L, a nonfasting blood glucose concentration of 11.1 mmol/L or higher (when fasting samples were unavailable), or the use of blood glucose-lowering medications. Information about blood glucose-lowering medications was obtained from both structured home interviews and pharmacy dispensing records. Two study physicians independently adjudicated all potential events of T2D. In the case of disagreement, a consensus was sought from a diabetologist. Participants were followed until incident T2D, death, or the end of the study period (January 1, 2015).

Statistical Analyses

Descriptive statistics were performed by reporting mean (SD) or median (interquartile range, IQR) for continuous variables and number (percentages) for categorical variables. Two HRV

metrics (SDNNc and RMSSDc) were log-transformed to fulfill the normality assumption. Heart rate and log-transformed HRV metrics were further standardized to allow for direct comparisons of effect sizes, per 1-SD increase. Linearity was explored with restricted cubic splines for each exposure, with no evidence of deviation from linearity (*P* for nonlinear:.479 for heart rate;.865 for log[SDNNc]; and.286 for log[RMSSDc]).

For the longitudinal analysis, joint models for longitudinal and time-to-event data were performed (17). The joint model estimates continuous profiles of each HRV metric based on the repeated measured data collected during the whole follow-up period for each individual; therefore, it would consider individual variations and reduce the bias associated with missing data. In addition, joint models are more appropriate for estimating the hazard of incident T2D for the HRV metrics as time-varying covariates because they account for their endogenous nature. For the HRV metrics, we used linear mixed-effect models. When appropriate and judged by residuals plots, transformed HRV metrics were used as dependent variables. We included age (the time scale variable) and sex in the fixed-effects, with both the intercept and the slope fitted as random effects. Next, a joint model was implemented by combining the joint distribution of HRV metrics in the linear mixed-effects model with the Cox model. For the crude model, we included baseline age, sex, and cohort in the survival part of the models. The full model was fitted by further adjusting for BMI, smoking status, systolic blood pressure, total and high-density lipoprotein cholesterol, use of blood pressure–lowering or lipid-lowering medication, and prevalent cardiovascular disease. We also used Spearmen correlation to examine the cross-sectional associations between heart rate and different HRV metrics and glycemic traits (fasting blood glucose and insulin levels, HOMA-IR, and HOMA-β) at baseline.

To check for any possible effect modification by age, sex, BMI, or use of blood pressure–lowering medication, we separately added an interaction term between each variable; (age [continuous], sex [dichotomous], BMI [continuous], use of blood pressure–lowering medication [dichotomous]), and HRV metrics to the joint model and then further explored these by stratification. To ensure a sufficient sample size for subgroup analyses, age stratification was based on the median age (62 years), and BMI stratification was based on the cutoff point for overweight (25.0 kg/m^2). To test the robustness of the longitudinal findings, we performed the following sensitivity analyses: (1-3) excluded participants who had prediabetes (defined as a fasting blood glucose concentration >6.0 mmol/L and <7.0 mmol/L), had prevalent cardiovascular disease, or were underweight (BMI ≤18.5 kg/m^2) at baseline; (4) further adjusted the model for fasting blood glucose and physical activity; (5) excluded participants used beta blockers or calcium blockers at baseline or during follow-up; (6) conducted a complete case analysis.

Additionally, we conducted two-sample bidirectional MR analyses to examine the association between heart rate–uncorrected HRV (SDNN and RMSSD) and T2D. The inverse variance weighted (IVW) method was the main method used in our analyses. MR estimates were presented as odds ratios (ORs) with corresponding 95% CIs. More details on the rationale, assumptions, and sensitivity analyses of the MR analyses are shown in the Supplementary Methods S1 (11).

Information on covariables was missing for up to 2.5%. To deal with missing values, we used single imputation with the expectation-maximization method. Data were handled and analyzed with SPSS Statistics version 25.0.0.1 (IBM Corp., Armonk, NY, USA) and R, CRAN version 4.0.5, with packages "JMbayes2" and "TwoSampleMR." All analyses were performed at the significance level of.05 (2-tailed).

Table 1. Baseline characteristics of the total study population

	Total study population (n = 7630)
Age, years	63.7 (9.5)
Women, n (%)	4444 (58%)
Education, n (%)	
Primary	859 (11%)
Lower/intermediate general or lower vocational	2989 (40%)
Intermediate vocational or higher general	2252 (30%)
Higher vocational or university	1466 (19%)
Height, cm	168.4 (9.5)
Weight, kg	76.7 (14.0)
Body mass index, kg/m^2	27.0 (4.1)
Smoking status, n (%)	
Current	1529 (20%)
Former	3590 (47%)
Never	2511 (33%)
Systolic blood pressure, mmHg	138.0 (20.6)
Use of blood pressure–lowering medication, n (%)	2183 (29%)
Total cholesterol, mmol/L	5.8 (1.0)
High-density lipoprotein, mmol/L	1.4 (0.4)
Use of lipid-lowering agents, n (%)	1359 (18%)
Fasting blood glucose, mmol/L	5.4 (0.6)
Fasting insulin level, mmol/L	71.0 (50.0, 99.0)
HOMA-IR	2.8 (1.9, 4.0)
HOMA-β	126.2 (89.6, 175.3)
History of cardiovascular disease, n (%)	639 (8%)
Metrics of heart rate variability	
Heart rate	67.7 (61.2, 74.9)
SDNNc	26.1 (16.4, 43.5)
RMSSDc	32.1 (19.8, 53.6)

Values are mean (SD) or median (interquartile range) for continuous variables and number (percentages) for categorical variables.
Abbreviations: HOMA-β, homeostatic model assessment of beta-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; RMSSDc, heart rate–corrected root mean square of successive RR-interval differences; SDNNc, heart rate–corrected standard deviation of normal-to-normal RR intervals.
HOMA-IR = (fasting blood insulin × fasting blood glucose)/22.5.
HOMA-β = (20 × fasting blood insulin)/(fasting blood glucose − 3.5).

Results

Among 7630 included participants, the median age was 62.1 (IQR, 45.5 to 98.0) years, and 4444 (58%) were women (Table 1). During a median follow-up time of 8.6 years (IQR, 7.1 to 14.1), 871 individuals developed T2D (incidence rate: 11.4 cases per 1000 person-years).

In the joint model analysis, heart rate and HRV metrics were positively associated with incident T2D (Table 2). For heart

Table 2. Joint model results for the association between longitudinal measures of heart rate and heart rate variability with incident type 2 diabetes

Model	Number of participants	Number of events	HR (95% CI)	*P*
Heart rate				
Model 1	7630	871	1.18 (1.07, 1.31)	.0018
Model 2	7630	871	1.20 (1.09, 1.33)	.0004
Log(SDNNc)				
Model 1	7630	871	1.05 (0.89, 1.21)	.5538
Model 2	7630	871	1.10 (0.94, 1.29)	.2256
Log(RMSSDc)				
Model 1	7630	871	1.16 (1.02, 1.30)	.0227
Model 2	7630	871	1.16 (1.01, 1.33)	.0438

Model 1 was adjusted for baseline age, sex, and cohort for relative risk model. Model 2 was further adjusted for body mass index, smoking status, systolic blood pressure, use of blood pressure–lowering medications, total cholesterol, high-density lipoprotein, use of lipid-lowering medications, and history of cardiovascular disease (coronary heart disease, heart failure, and stroke) at baseline. The hazard ratio for incident diabetes was calculated per 1-SD increase in heart rate or the log of HRV indices (SDNNc and RMSSDc). Abbreviations: HR, hazard ratio; RMSSDc, heart rate–corrected root mean square of successive RR-interval differences; SDNNc, heart rate–corrected standard deviation of normal-to-normal RR intervals.

rate, a 1-SD increment was associated with the risk of developing T2D in the crude model (hazard ratio [HR], 1.18; 95% CI, 1.07 to 1.31). After adjustments, the association remained significant (HR 1.20; 95% CI, 1.09 to 1.33). For HRV, both metrics showed positive associations with T2D development with statistically significant associations only found for RMSSDc. The HRs (95% CIs) of incident T2D per SD increment of log(RMSSDc) were 1.16 (1.02, 1.30) in the crude model and 1.16 (1.01, 1.33) in the fully adjusted model. The association of SDNNc with incident T2D was not statistically significant (HR 1.10 [0.94, 1.29]) in the full model.

We observed a significant interaction between age (continuous) and heart rate (*P* for interaction <.001). We stratified participants based on the median age (62 years) and found that the association between heart rate and incident T2D was relatively stronger among younger participants (Fig. 1; Supplementary Table S1 (11)). Although significant associations were restricted to men (Fig. 1; Supplementary Table S1 (11)), the interaction term for sex was not statistically significant. The HRs (95% CIs) of incident T2D per SD increment were 1.25 (1.09, 1.43) for men and 1.16 (0.99, 1.35) for women for heart rate, 1.23 (1.01, 1.51) for men and 0.97 (0.78, 1.20) for women for log(SDNNc), and 1.23 (1.04, 1.46) for men and 1.08 (0.89, 1.30) for women for log(RMSSDc). We also did not find a significant interaction for BMI or use of blood pressure–lowering medication (Supplementary Table S1 (11)), although statistically significant associations were restricted to participants who were overweight or without use of blood pressure–lowering drugs, respectively.

In sensitivity analyses, similar associations between heart rate and different HRV metrics with incident T2D were observed after excluding participants who had prediabetes (n = 1029) or prevalent cardiovascular disease (n = 639) at baseline and also after excluding participants who were underweight (n = 48) or used beta blockers or calcium blockers during follow-up (n = 1236). In further analyses with additional adjustments for baseline measurement of fasting blood glucose and physical activity and in a complete case analysis, results remained consistent with our main results (Supplementary Table S2 (11)).

The Spearmen correlation analyses indicated that heart rate was significantly associated with all glycemic traits, including fasting blood glucose, insulin, HOMA-IR, and HOMA-β, while RMSSDc was only related to fasting blood glucose (Fig. 2). After excluding individuals with baseline prediabetes, the associations between HRV metrics and glycemic traits were not statistically significant (Supplementary Figure S2 (11)).

A total of 9 single nucleotide polymorphisms (SNPs) for SDNN and 9 SNPs for RMSSD were available in the T2D genome-wide association study (GWAS) and were used for the MR analyses after removal of potential outliers (Supplementary Table S3 (11)). As presented in Supplementary Table S4 (11), the results from the MR analyses suggested no causal association between HRV and incident T2D (OR [95% CI] 0.94 [0.75, 1.18] per one unit log increment for SDNN and 1.04 [0.82, 1.32] per one unit log increment for RMSSD). In addition, 156 SNPs for T2D were available in the HRV GWAS (Supplementary Table S5 (11)), and the results from the MR analyses showed that genetically predicted T2D was not significantly associated with log(SDNN) or log(RMSSD) (Supplementary Table S6 (11)). The WME and MR-Egger slope estimates were also insignificant, consistent with the inverse variance weighted method after correcting for outliers using MR-PRESSO during the bidirectional MR analysis, and we found no evidence for violation of the MR assumptions.

Discussion

In this large prospective population-based cohort study, longitudinal evolutions of both heart rate and different HRV metrics were significantly associated with new-onset T2D, independent of a vast number of other contributing factors. However, the effects were largely restricted to younger individuals. MR analyses suggested no causal association between HRV and incident T2D.

At first sight, our findings suggest an association between elevated heart rate and increased risk of developing T2D, consistent with previous studies (18, 19). However, the effects were restricted to younger individuals. As a surrogate marker for autonomic activity, a high heart rate usually indicates increased sympathetic activity, potentially inducing insulin resistance. On the one hand, a more straightforward relationship between a fast heart rate and sympathetic predominance at a young age may explain the relatively strong association among the young participants (18, 19). On the other hand, older participants tend to have worse health status and use more medications such as beta blockers that reduce heart rate (20) and hyperglycemia (21). Hence, the associations might be diluted at old age.

Although diabetes is the leading cause of primary autonomic dysfunction, limited evidence exists regarding the relationship between autonomic dysfunction and incident diabetes (22). Prior studies assessing the risk of developing T2D associated with HRV have mostly shown an association of autonomic dysfunction with incident T2D. However, the direction between various HRV metrics and glycemic traits is still inconsistent (3-5, 8). For example, the Atherosclerosis Risk In Communities (ARIC) study found no significant association between SDNN and incident T2D (8), while the Kangbuk Samsung Health Cohort reported that as SDNN and RMSSD tertiles increased, the risk of diabetes decreased

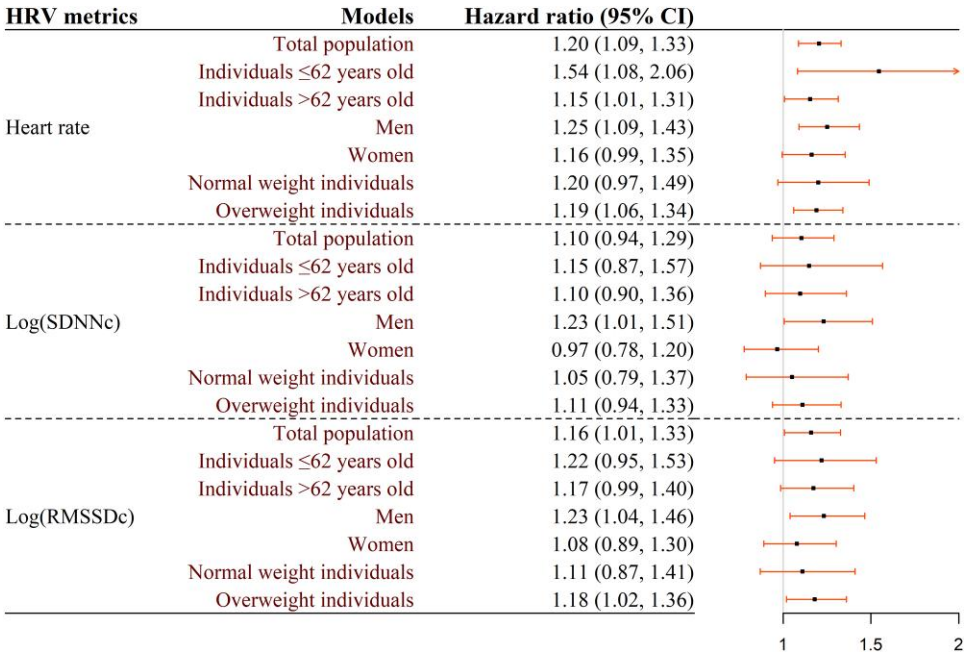

Figure 1. Forest plot summarizing the joint model results for the associations of heart rate and heart rate variability with incident type 2 diabetes. Plot is based on the results of the model adjusted for baseline age, sex, cohort, body mass index, smoking status, systolic blood pressure, use of blood pressure–lowering medications, total cholesterol, high-density lipoprotein, use of lipid-lowering medications, and history of cardiovascular disease (coronary heart disease, heart failure, and stroke) at baseline for relative risk model. The hazard ratio for incident diabetes was calculated per 1-SD increase in heart rate or in the log of HRV indices (SDNNc and RMSSDc). Abbreviations: RMSSDc, heart rate–corrected root mean square of successive RR-interval differences; SDNNc, heart rate–corrected standard deviation of normal-to-normal RR intervals.

(4). Our findings support an association between increased SDNNc and RMSSDc with incident T2D. Notably, these 2 heart rate–corrected HRV metrics have not been studied before concerning incident T2D, which limits the comparability with former studies. The participants in our study were also considerably older than Kangbuk Samsung Health study (4). Age has an impact on both SDNNc and RMSSDc. The upper limit of their normal values decreases until the age of 60 and increases markedly afterward (9). Besides the autonomic nervous system dysfunction, increased HRV may also be affected by the sinus node dysfunction (23). With growing age, pathologic changes occur in the sinoatrial node, including increasing collagen and elastic fibers (24). Intrinsic sinus node function tends to deteriorate with age, resulting in prolonged RR intervals and increased, irregular HRV (25), which was also found in our study (26). Therefore, the association between increased HRV and incident T2D could, at least partly, be explained by sinus node dysfunction.

Unlike results from our longitudinal analyses, only heart rate and not HRV metrics was associated with different glycemic traits at the baseline of our study. The HRV effect could be difficult to observe due to compensatory mechanisms preserving glucose homeostasis among a substantial number of nondiabetic participants. In line, we found that the effect of HRV disappeared after excluding persons with prediabetes. A prior study also reported that only heart rate, not HRV, is associated with changes in insulin sensitivity. This could imply that pathways other than autonomic dysfunction mediate the associations with diabetes or that heart rate is just a marker of other mechanisms (5). These results regarding the correlations with glycemic traits should, however, be interpreted with caution since they were based on cross-sectional analyses and cannot address the temporal relationship of heart rate and HRV with glycemic traits. More studies are needed to further delineate the underlying mechanisms.

However, inconsistent with the longitudinal findings, our bidirectional MR analysis showed no causal association between HRV and T2D. This may be due to limited power since only a few instrumental variables for SDNN and RMSSD were available to be used for the MR analyses. Furthermore, unlike longitudinal analysis using these novel heart rate–corrected HRV parameters (SDNNc and RMSSDc), the MR analysis could only use heart rate–uncorrected HRV (SDNN and RMSSD) due to the lack of available SNPs, which may partly explain the heterogeneity we observed. A previous study reported substantial overlap of loci between HRV and heart rate, with SNPs in 5 of the 21 heart rate loci being associated with HRV at genome-wide significance level and 6 more attaining nominal significance (27). This suggests that part of the HRV SNPs exert their effect on heart rate through oscillatory modulation of pacemaker activity by the vagal nerves. Therefore, the insignificant association between RMSSD and T2D in our MR analysis might be biased by heart rate. Future GWAS with a larger sample size and individual-level data could identify more genetic variants that could be used to assess the association between the heart rate–corrected HRV and T2D.

The strengths of this population-based study include the prospective cohort design, long follow-up time, and meticulous assessment of incident T2D. We also had detailed information regarding possible confounders. Another strength is using joint models, which enables the analysis of individual heart rate and HRV values, including those with missing data. It generates the most likely continuous exposure profile for each individual while simultaneously accounting for exposure and survival processes. Also, we are the first study to report the health effect of heart rate–corrected HRV metrics, which are more appropriate to allow meaningful comparison of different HRV measurements and their association with adverse outcomes. However, our study mainly included older

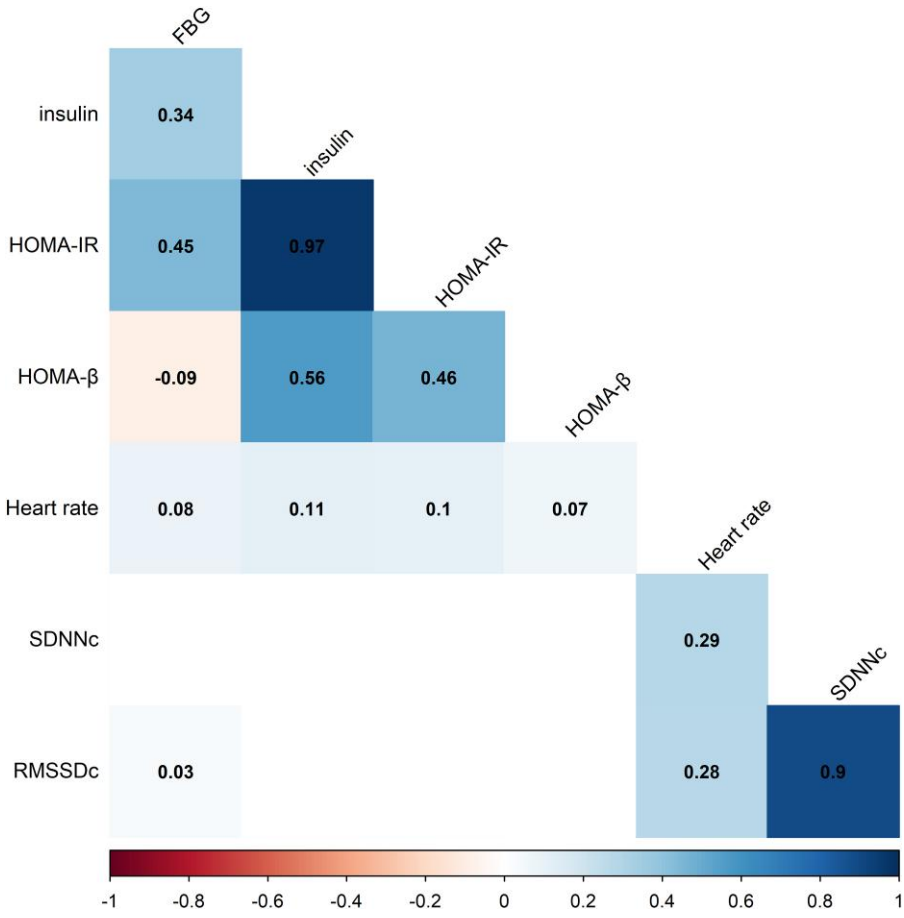

Figure 2. Correlation plot between heart rate and heart rate variability and glycemic traits. Abbreviations: FBG, fasting blood glucose; HOMA-β, homeostatic model assessment of beta-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; RMSSDc, heart rate–corrected root mean square of successive RR-interval differences; SDNNc, heart rate–corrected standard deviation of normal-to-normal RR intervals.

individuals of European ancestry, limiting our findings generalizability to younger populations and other ethnicities. In addition, although the moderately nonlinear change of HRV was reported by former studies, we found no evidence of deviation from linearity, which might be due to the different outcomes we used. The additional MR analysis we used also assumes linearity. Given that the more novel MR approaches can check the potential nonlinear association between exposure and outcomes using individual-level data, future studies with more detailed data and using comprehensive methods are needed to validate our findings.

Conclusion

Our results suggest that high heart rate and HRV were significantly associated with an increased risk of developing T2D, especially among younger individuals. To our knowledge, this is the only prospective investigation using repeated measurements of heart rate and HRV to investigate the role of autonomic dysfunction in the development of T2D. More studies are needed to validate our findings and to elucidate further the underlying mechanisms.

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Author Contributions

M.K. is responsible for the study concept and design; K.W. and S.G. composed the statistical dataset and performed the statistical analyses; K.W. wrote the manuscript; F.A., S.G., B.A., J.A.K., D.R., E.S., M.A.I., and M.K. revised/edited the manuscript for intellectual content.

Disclosures

The authors report no potential conflicts of interest.

Data Availability

Data generated by the authors or analyzed during the study are available upon request. Requests should be directed toward the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

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