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Association of heart rate variability with progression of retinopathy among adults with type 2 diabetes

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Abstract

Aim: We evaluated the associations of heart rate variability (HRV) with incident vision-threatening retinopathy and retinopathy progression among adults with type 2 diabetes.

Methods: Participants recruited to the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study with HRV measures at baseline were analysed. HRV measures included standard deviation of all normal-to-normal intervals (SDNN) and root mean square of successive differences between normal-to-normal intervals (rMSSD). Low SDNN was defined as SDNN <8.2 ms; low rMSSD as rMSSD <8.0 ms. We used multivariable adjusted Cox proportional hazards and modified Poisson regression models to generate risk estimates for incident vision-threatening retinopathy and retinopathy progression, respectively.

Results: A total of 5810 participants without incident vision-threatening retinopathy at baseline (mean age 62 years, 40.5% women, 63.5% White) were included. Over a median of 4.7 years, 280 incident vision-threatening retinopathy cases requiring treatment occurred. Low HRV (vs. normal HRV) was associated with higher risk of incident vision-threatening retinopathy (adjusted hazard ratio 1.32 [95%CI 1.03–1.71] and 1.14 [95%CI 1.01–1.28] for low SDNN and rMSSD, respectively). In the subset of 2184 participants with complete eye examinations at baseline and 4 years, 191 experienced retinopathy progression, and low HRV (vs. normal HRV) was associated with a higher risk of retinopathy progression (adjusted relative risks 1.36 [95%CI 1.01–1.83] and 1.36 [95%CI 1.01–1.84] for low SDNN and rMSSD, respectively).

Conclusions: Cardiac autonomic neuropathy, as assessed by low HRV, was independently associated with increased risks of incident vision-threatening retinopathy and overall retinopathy progression in a large cohort of adults with type 2 diabetes.

KEYWORDS

autonomic dysfunction, diabetes, heart rate variability, retinopathy, type 2

1 | INTRODUCTION

Diabetic retinopathy is the leading cause of blindness among working-age adults in the United States.[1] It significantly affects health-related quality of life and healthcare costs. Although medical and surgical interventions exist for proliferative diabetic retinopathy, which has a high risk of blindness if left untreated, by this stage some degree of irreversible visual loss has often already occurred. The ability to better identify patients at risk for the development and progression of diabetic retinopathy may result in improved visual outcomes and major cost savings, especially in the context of high diabetes mellitus prevalence. Extant evidence suggests that the degree of glycaemic control as measured by haemoglobin A_{1C} (HbA_{1C}) and diabetes duration only account for ~11% of the diabetic retinopathy risk, suggesting that 89% of the risk may be explained by other factors.[2] The possible role of autonomic nervous dysfunction on the risk of diabetic retinopathy has not received enough attention. Although a few small studies have suggested a possible link between cardiovascular autonomic dysfunction and diabetic retinopathy severity or progression to proliferative diabetic retinopathy,[3-5] the impact of autonomic dysfunction on the incidence or progression of diabetic retinopathy has seldom been assessed in large-scale epidemiological studies.

We evaluated the associations of autonomic dysfunction, as assessed by heart rate variability (HRV) measures, with the incidence and progression of retinopathy, among adults with type 2 diabetes.

What is new?

What is already known?

- Low heart rate variability (HRV) is linked to higher risks of adverse cardiovascular and renal outcomes.
- Whether HRV measures predict higher risks of retinopathy among adults with type 2 diabetes is unclear.

What this study has found?

- Low HRV was associated with higher risk of incident vision-threatening retinopathy.
- The 4-year risk of retinopathy progression was higher among those with low HRV.

What are the clinical implications of the study?

- Our findings indicate the potential utility of cardiac autonomic neuropathy in estimating the risks of vision-threatening retinopathy and progression of retinopathy among patients with type 2 diabetes.

2 | MATERIALS AND METHODS

2.1 | Study design

The participants were individuals recruited to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which was a randomized clinical trial that enrolled 10,251 adults with type 2 diabetes from 77 US and Canadian centres, from January 2001 to October 2005.[6] Participants were assigned to either an intensive glucose-lowering arm with a goal of a glycated haemoglobin (HbA_{1C}) <6% or a standard treatment arm with an HbA_{1C} goal of 7.0%–7.9%, as well specific blood pressure and lipid intervention arms. The design and methods of the ACCORD study have been published previously.[6]

After the relevant exclusions, 5810 participants were included in our main analyses (Figure S1). For the retinopathy progression outcome, we analysed a subset of participants ($n = 2184$) from the ACCORD Eye study who had eye examinations (including seven-field stereoscopic colour fundus photographs) conducted at baseline and 4-year follow-up visits.[7]

The study protocol was approved by the Institutional Review Board or ethics committee at each participating location and each participant provided an informed consent.[7]

2.2 | Assessment of heart rate variability

HRV was assessed at baseline using 12-lead digitalized electrocardiograms (ECGs) recorded over 10 s at 10 mm/mV calibration and a speed of 25 mm/s with the patient resting supine after an overnight fast (GE MAC 1200 electrocardiograph system, GE, Milwaukee, Wisconsin).[8] ECGs were transferred via phone line to the reading centre where they were analysed and reviewed to ensure technical quality before being automatically processed using GE 12-SL Marquette Version 2001 (GE, Milwaukee, Wisconsin). ECG reading was performed centrally at the Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston Salem, North Carolina. Two HRV time-domain indices were derived: standard deviation of all normal-to-normal R-Rs intervals (SDNN) and root mean square of successive differences between normal-to-normal R-R intervals (rMSSD). We used SDNN and rMSSD to define HRV as these indices are

accepted measures of HRV and their use has been recommended by a joint task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[9] These indices have been used in epidemiological studies evaluating the associations between HRV and various cardiovascular and mortality outcomes both in the general population as well as individuals with diabetes mellitus.[10-13] We defined low HRV using cut-off values recently derived using reference ranges established in healthy US populations: low SDNN defined as SDNN <8.2 ms and low rMSSD as rMSSD <8.0 ms.[14] These cut-off points have been have used to define low HRV in prior studies of individuals with type 2 diabetes.[10,15]

2.3 | Ascertainment of incident vision-threatening retinopathy and retinopathy progression

A diagnosis of vision-threatening retinopathy was ascertained at yearly clinic visits whereby participants were queried about hospitalizations and procedures including retinal laser photocoagulation or vitrectomy performed to treat diabetic retinopathy since the prior visit. If participants missed a clinic visit, they were contacted by clinic staff to perform the ascertainment over the telephone. Incident vision-threatening retinopathy was defined as the use of retinal photocoagulation or vitrectomy to treat diabetic retinopathy during follow-up. Retinopathy progression was assessed in a subset of participants who had two standardized eye examinations performed by an ophthalmologist or optometrist along with fundus photography of seven standard stereoscopic fields at baseline and year 4. The fundus photographs were evaluated by trained graders at the Fundus Photograph Reading Center (University of Wisconsin, Madison), and graded according to a modified version of the Early Treatment Diabetic Retinopathy Study (ETDRS) scale.[16] Retinopathy progression was defined as the composite of either progression of diabetic retinopathy by at least three steps on the ETDRS severity scale or progression to proliferative diabetic retinopathy requiring photocoagulation and/or vitrectomy. The outcome adjudication process has been previously described.[7]

2.4 | Covariates

The covariates were selected a priori based on prior knowledge, clinical relevance and their known pathophysiological link with HRV and diabetic retinopathy. These included the following measures collected at baseline. These included age, sex, race/ethnicity, treatment arm, cigarette smoking, alcohol consumption, body mass index, glycosylated haemoglobin (HbA_{1C}), use of insulin, duration of diabetes, systolic blood pressure (BP), use of antihypertensive medications, total cholesterol, high-density lipoprotein (HDL) cholesterol, estimated glomerular filtration rate (eGFR) and prevalent cardiovascular disease.

2.5 | Statistical analyses

We compared the baseline characteristics of participants by HRV metrics using the *t*-test (for continuous variables with a normal distribution), Kruskal–Wallis test (for continuous variables with a skewed distribution) or χ^2 test (for categorical variables). We assessed the time-to-event distributions for incident vision-threatening retinopathy using the Kaplan–Meier curve and compared the groups with low and higher HRV using the log-rank test.

We used Cox proportional hazards regression models to generate hazard ratios (HR) and 95% confidence intervals (CI) for incident vision-threatening proliferative retinopathy and modified Poisson regression with robust variance estimation to estimate the relative risk (RR) of retinopathy progression at 4 years. For all regression models, the person-years were estimated from the baseline visit to the earliest date of the incident retinopathy outcome, date of death or trial termination. HRV measures were assessed as categorical (low vs. normal) and continuous (per 1-standard deviation [SD] decrease in each HRV metric) variables. We built sequential regression models. Model 1 adjusted for age, sex, race/ethnicity and treatment arm; model 2 included model 1 variables plus cigarette smoking, alcohol intake, HbA_{1C}, use of insulin, duration of diabetes, body mass index, systolic BP, use of antihypertensive medication, total/high-density cholesterol ratio and eGFR; model 3 included variables in model 2 plus additional adjustment for history of CVD. We tested for statistical interaction of HRV measures by glycaemic treatment arm.

All analyses were conducted using STATA 14.2 (Stata, Inc, College Station, TX). A $p < 0.05$ was deemed statistically significant.

3 | RESULTS

3.1 | Baseline characteristics by heart rate variability measures

The baseline characteristics of study participants by HRV status are displayed in Table 1. A total of 5810 participants were included (mean age 62.0 [SD: 6.4] years, 41% women, 63% White) in the main analysis. Of the entire sample, 26% had low SDNN ($n = 1503$); 23%, low rMSSD ($n = 1351$).

Participants with low HRV had higher BMI, HbA_{1C}, duration of diabetes, lower eGFR and were more likely to be current smokers or insulin users and to have CVD. A similar pattern of the baseline characteristics was observed in the subset of participants who had complete eye examinations conducted at the baseline and 4-year follow-up visits (Table S1).

3.2 | Heart rate variability and incident vision-threatening retinopathy

Over median follow-up of 4.7 years (interquartile range: 4.0–5.4), 280 participants had incident vision-threatening retinopathy. Participants with low HRV measures (both SDNN and rMSSD) had higher cumulative incidence of vision-threatening retinopathy (Figure 1, all $p < 0.01$).

After multivariable adjustment for covariates, low HRV (compared with normal HRV) was associated with a higher risk of incident retinopathy, with HR of 1.32 (95% CI 1.03–1.71) and 1.33 (95% CI 1.02–1.73) for low SDNN and low rMSSD, respectively (Table 2). The HRs per 1-SD decrease in HRV metric were 1.09 (95% CI 0.97–1.23) and 1.14 (95% CI 1.01–1.28) for SDNN and rMSSD, respectively.

3.3 | Heart rate variability and retinopathy progression

In the subset of 2184 participants with complete eye examinations at baseline and 4 years (38% of the overall study sample), 191 experienced progression of any retinopathy over 4 years. The risk of retinopathy progression was higher among participants with low HRV compared

TABLE 1 Baseline characteristics of participants by heart rate variability status

		Low SDNN			Low rMSSD		
Variable	**Total**	**No**	**Yes**	**P**	**No**	**Yes**	**P**
N	5810	4307	1503	...	4459	1351	...
Age, years	62 (6)	62 (6)	62 (7)	0.019	62 (7)	62 (6)	0.430
Women, %	41	42	37	<0.001	43	34	0.001
Race/ethnicity, %				<0.001			<0.001
White	63	62	68		61	70	
Black	17	19	13		19	13	
Hispanic	7	7.6	6.9		7.7	6.5	
Other	12	12	11		12	9.9	
Treatment arm, %				0.647			0.654
Intensive glycaemic lowering	48	50	50		50	50	
Standard glycaemia lowering	50	50	50		50	50	
Body mass index, kg/m^2	32.3 (5.4)	32.2 (5.4)	32.6 (5.4)	0.021	32.2 (5.4)	32.7 (5.4)	0.008
Current smoking, %	15	14	17	0.004	14	17	0.009
Alcohol drinking, %	24	24	23	0.740	24	23	0.316
Systolic BP, mm Hg	135 (17)	136 (17)	135 (17)	0.140	136 (17)	135 (16)	0.066
Diastolic BP, mm Hg	75 (10)	75 (10)	75 (10)	0.817	75 (10)	76 (10)	0.003
Use of BP-lowering drug, %	82	823	81	0.288	83	81	0.273
Use of beta blocker, %	28	27	28	0.625	28	25	0.005
Use of insulin, %	30	28	36	<0.001	29	35	<0.001
Haemoglobin A_{1C}, mmol/mol	66 (11)	66 (11)	67 (12)	0.004	66 (11)	68 (12)	<0.001
Duration of diabetes, years	8 (5–13)	8 (4–13)	9 (5–15)	<0.001	8 (4–13)	9 (5–14)	<0.001
Prevalent cardiovascular disease, %	32	31	35	0.007	32	33	0.233
Total cholesterol, mmol/L	4.76 (1.08)	4.75 (1.07)	4.77 (1.12)	0.720	4.74 (1.06)	4.82 (1.15)	0.009
HDL-cholesterol, mmol/L	1.08 (0.29)	1.09 (0.29)	1.06 (0.29)	0.005	1.09 (0.29)	1.06 (0.29)	0.004
Total/HDL-cholesterol Ratio	4.7 (1.8)	4.6 (1.7)	4.8 (1.8)	0.019	4.6 (1.7)	4.8 (1.9)	<0.001
eGFR, $mL/min/1.73m^2$	92 (23)	93 (23)	91 (24)	0.008	92 (23)	92 (24)	0.370

Note: Data are mean (standard deviation), median (interquartile range), or proportion (%) unless otherwise indicated.

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; rMSSD, root mean square of successive differences between normal-to-normal R-R intervals; SDNN, standard deviation of all normal-to-normal R-R intervals.

Low SDNN was defined as SDNN <8.2 ms; low rMSSD as rMSSD <8.0 ms.

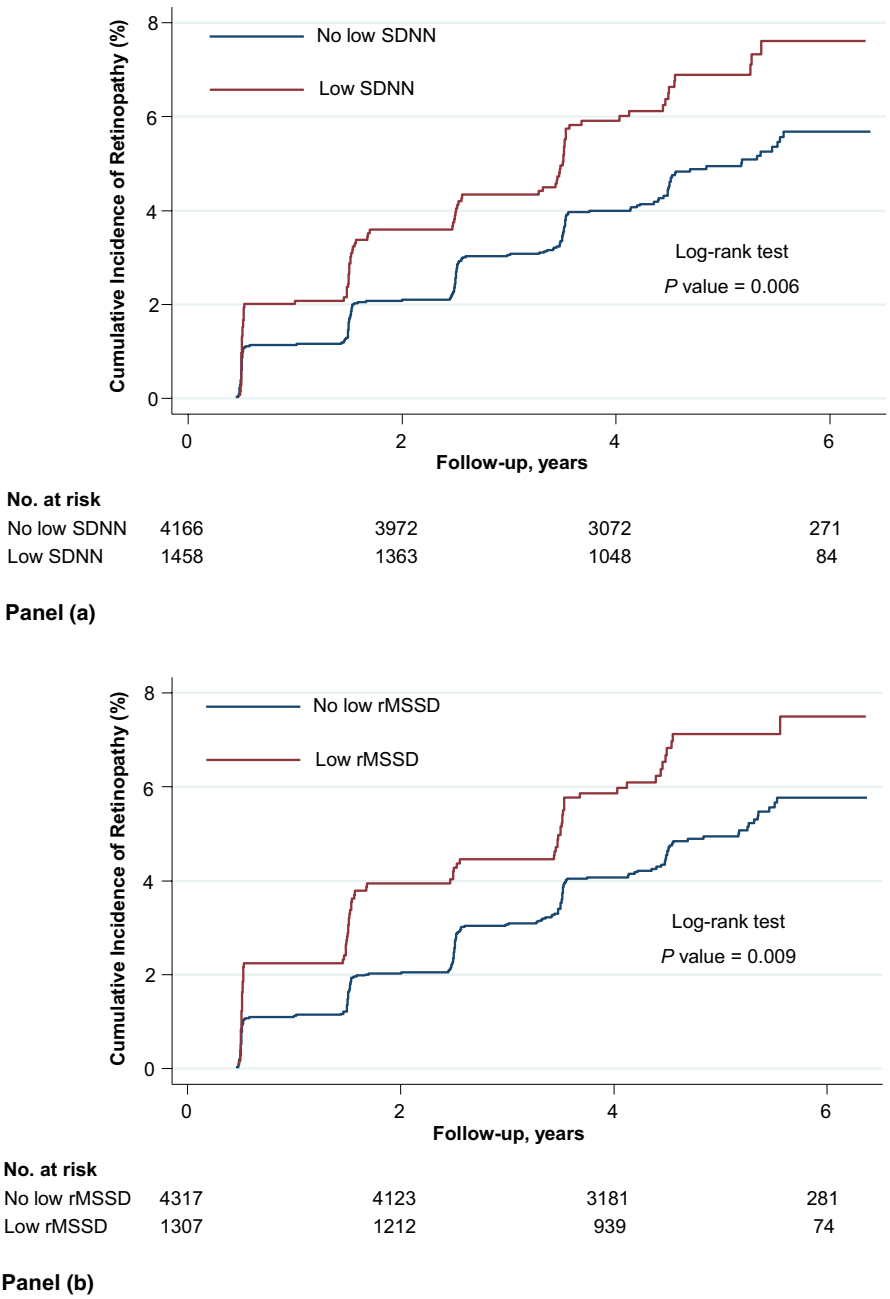

FIGURE 1 Cumulative incidence of incident vision-threatening retinopathy by heart rate variability status among individuals with type 2 diabetes. Low SDNN was defined as SDNN <8.2 ms; low rMSSD as rMSSD <8.0 ms. rMSSD, root mean square of successive differences between normal-to-normal R-R intervals; SDNN, standard deviation of all normal-to-normal R-R intervals. *P* value for log –rank test

with those with higher HRV, with RRs of 1.36 (95% CI 1.01–1.83), and 1.36 (95% CI 1.01–1.84) for low SDNN and rMSSD, respectively. The RRs per 1-SD decrease in HRV indices were 1.23 (95% CI 1.07–1.41) and 1.18 (95% CI 1.03–1.35) for SDNN and rMSSD, respectively (Table 3).

We did not observe any effect modification of the association HRV measures and retinal outcomes by glycaemic treatment arm (All *p* interaction >0.05).

4 | DISCUSSION

In a large cohort of adults with type 2 diabetes, we found that low HRV was associated with increased risks of incident vision-threatening proliferative diabetic retinopathy and overall retinopathy progression, independently of known risk factors including the degree of glycaemic control, diabetes duration, intensity of glycaemic management, kidney function and blood pressure. Our findings were consistent across measures of HRV.

Our study is unique in its evaluation of the relation of HRV with retinopathy using a large cohort of adults with type 2 diabetes. Our results are consistent with those of prior reports that found a positive association between markers of cardiovascular autonomic dysfunction and risks of diabetic retinopathy.[3-5] However, these prior investigations have primarily focused on patients with type 1 diabetes and are limited by smaller sample sizes as well

TABLE 2 Rates and hazard ratios for incident vision-threatening retinopathy by heart rate variability metrics ($N = 5810$)

	SDNN			rMSSD		
	Low SDNN		Per 1-SD lower log (SDNN)	Low rMSSD		Per 1-SD lower log (rMSSD)
	Absent	Present		Absent	Present	
No events/no at risk	188/4307	92/1503	280/5810	198/4459	82/1351	280/5810
Person-years	18,930.7	6502.9	25,433.6	19,655.1	5778.5	25,433.6
Rate/1000 person-years	9.9 (8.6–11.5)	14.1 (11.5–17.4)	11.0 (9.8–12.4)	10.1 (8.8–11.6)	14.2 (11.4–17.6)	11.0 (9.8–12.4)
Hazard ratio (95% CI)						
Model 1	1 (reference)	1.47 (1.14–1.88) †	1.16 (1.03–1.31) *	1 (reference)	1.49 (1.15–1.93) †	1.19 (1.05–1.34)†
Model 2	1 (reference)	1.33 (1.03–1.71) *	1.09 (0.97–1.23)	1 (reference)	1.33 (1.02–1.73) *	1.14 (1.01–1.28) *
Model 3	1 (reference)	1.32 (1.03–1.71) *	1.09 (0.97–1.23)	1 (reference)	1.33 (1.02–1.73) *	1.14 (1.01–1.28) *

Note: Data are hazard ratios (95% CI) unless otherwise specified. Model 1 adjusted for age, sex, race, treatment arm; model 2 includes model 1 plus duration of diabetes, glycated haemoglobin, cigarette smoking, alcohol intake, body mass index, systolic blood pressure, estimated glomerular filtration rate, total/high-density cholesterol ratio, use of insulin, use of antihypertensive medication; model 3 includes model 2 plus history of cardiovascular disease.

Abbreviations: CI, confidence interval; rMSSD, root mean square of successive differences between normal-to-normal R-R intervals; SD, standard deviation; SDNN, standard deviation of all normal-to-normal R-R intervals.

*$p < 0.05$, †$p < 0.01$. Low SDNN was defined as SDNN < 8.2 ms; low rMSSD as rMSSD < 8.0 ms.

TABLE 3 Incidence and risk ratios for retinopathy progression by heart rate variability metrics ($N = 2184$)

	SDNN			rMSSD		
	Low SDNN		Per 1-SD lower log (SDNN)	Low rMSSD		Per 1-SD lower log (rMSSD)
	Absent	Present		Absent	Present	
No events/no at risk	131/1654	60/530	191/2184	132/1684	59/500	191/2184
Risk ratio (95% CI)						
Model 1	1 (reference)	1.48 (1.11–1.97) †	1.29 (1.13–1.49) ‡	1 (reference)	1.54 (1.15–2.06) †	1.24 (1.08–1.42)†
Model 2	1 (reference)	1.35 (1.01–1.82) *	1.23 (1.07–1.41) †	1 (reference)	1.35 (1.01–1.82) *	1.17 (1.02–1.34) *
Model 3	1 (reference)	1.36 (1.01–1.83) *	1.23 (1.07–1.41) †	1 (reference)	1.36 (1.01–1.84) *	1.18 (1.03–1.35) *

Note: Data are risk ratios (95% CI) unless otherwise specified. Model 1 adjusted for age, sex, race, treatment arm; model 2 includes model 1 plus duration of diabetes, glycated haemoglobin, cigarette smoking, alcohol intake, body mass index, systolic blood pressure, estimated glomerular filtration rate, total/high-density cholesterol ratio, use of insulin, use of antihypertensive medication; model 3 includes model 2 plus history of cardiovascular disease.

Abbreviations: CI, confidence interval; rMSSD, root mean square of successive differences between normal-to-normal R-R intervals; SD, standard deviation; SDNN, standard deviation of all normal-to-normal R-R intervals.

*$p < 0.05$, †$p < 0.01$, ‡ $p < 0.001$. Low SDNN was defined as SDNN < 8.2 ms; low rMSSD as rMSSD < 8.0 ms.

as their retrospective or cross-sectional study design,[3-5] making these prone to biases.

The pathophysiological pathways linking low HRV to a higher risk of retinopathy are incompletely understood but may involve the interplay between the autonomous nervous system and retinal neurodegeneration that occurs early in the course of diabetic retinopathy. In some animal models, loss of retinal ganglion cells was noted to precede microvascular changes that have been the hallmark of diabetic retinopathy.[17] Additionally, significant thinning of the inner retinal layers has been described in individuals with diabetes but without clinical retinopathy, supporting an early neurodegenerative component to the pathogenesis of diabetic retinopathy.[18] It is also possible that the observed association noted in our study simply represents a systemic phenomenon affecting the microvasculature in diabetes mellitus.

The implications of our findings are numerous. Our study suggests that the identification of autonomic dysfunction can be predictive of the occurrence and progression of retinopathy in the context of type 2 diabetes. Thus, the incorporation of HRV indices in diabetic retinopathy risk prediction tools deserves further exploration. Another practical implication of our results is that the presence of

autonomic dysfunction can be considered as a criterion for more frequent screening for diabetic retinopathy. Our results also suggest that interventions targeting the autonomic nervous system may be relevant for the prevention of retinopathy progression in type 2 diabetes. Further experimental research is warranted to evaluate the effect of medications known to influence HRV such as beta blockers or calcium channel blockers on the progression of retinopathy among individuals with type 2 diabetes.

Our study has some limitations, which include the assessment of HRV using only two time-domain indices derived from short ECG recordings, and the observational study design with the possibility of residual confounding. These limitations notwithstanding, the strengths of this study include a large sample of type 2 diabetes adults with HRV measures, the standardized adjudication of retinopathy outcomes based on retinal photographs and the robust adjustment for relevant confounders.

In conclusion, in a large cohort of adults with type 2 diabetes, autonomic dysfunction was associated with higher risks of incident vision-threatening proliferative diabetic retinopathy and overall progression of diabetic retinopathy, independently of other risk factors. This highlights the utmost importance of blood glucose lowering in addressing diabetes-related microvascular complications. Further research is needed to clarify the pathways underpinning this association and evaluate the predictive value of HRV for risk of diabetic retinopathy.

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CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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