**Autonomic dysfunction and cardiovascular disease: the ADDITION-PRO study**

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**Abbreviations**

CAN: Cardiovascular autonomic neuropathy

CVD: Cardiovascular disease

ECG: Electrocardiogram

HRV: Heart rate variability

rHR: Resting heart rate

SDNN: The standard deviation of normal-to-normal R-R intervals

**Abstract**

**Objective**

To examine the association between components in long-term heart rate variability and cardiovascular disease.

**Methods**

Week-long heart rate variability and mean heart rate (rHR) was measure in 2,088 participants from the ADDITION-PRO between 2009-2011. Cardiovascular events were followed-up in Danish patient registries until 2021.

**Results**

**-**

**Conclusion**

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Introduction

*CVD epidemiology in prediabetes – heart failure*

Cardiovascular disease ….

People with a high risk of diabetes have an increased risk of CVD and mortality. The increased risk consists of elevated levels of body weight, blood glucose, low-density lipid cholesterol, triglycerides, and blood pressure, as well as lifestyle factors of unhealthy diet, smoking, and physical inactivity. Among individuals with a high risk of diabetes, diabetes-related complications may accelerate the CVD risk. Autonomic cardiovascular dysfunction and cardiovascular autonomic neuropathy have been shown to be present throughout the diabetic continuum leading to an increased risk of CVD. Autonomic cardiovascular dysfunction leads to sympathetic overactivity that likely increases arterial shear stress and alteration in cardiac function. Heart rate variability (HRV) is recognized as a valid biomarker for assessing cardiovascular autonomic function. HRV expresses the beat-to-beat variation between normal RR intervals, which can be calculated into time- and frequency domain indices. Most studies have demonstrated autonomic dysfunction linked with CVD with changes in short-term heart rate variability which yield resting heart rate patterns in rest during inspiration and expiration. Few studies have investigated long-term 24-hour HRV and its association with CVD. However, the long-term measures of a single measurement day can reflect random activities on a particular day i.e. physical activity, sleep and more. Longer heart rate recordings over multiple days capture heart rate activity under more regular free-living conditions and thus may yield a more valid assessment of day-to-day autonomic function.

*Circadian variation in HRV and CVD*

Earlier studies have shown that the circadian variation in heart rate and HRV are present, presumably affected by a complex interplay between endogenous rhythmicity and response to external cardiovascular stressors. Hence, different timepoint could reflect autonomic responses in the body’s different physiological states. With the highest CVD incidence observed between early morning and noon, the variation timing of CVD events through the circadian rhythm is present [1]. No single mechanism can be pointed out to explain the variation, but one suggestion is to be linked to cardiovascular response to the increase in sympathetic activity in the morning. Hence, the diurnal variation in cardiovascular autonomic response may capture important information about future CVD risk.

*Usefulness of detecting autonomic dysfunction and CAN by HRV. Technologies facilitates opportunities of continuously monitoring in free-living conditions.*

In diabetes, we are observing more wearable technologies taken into use for treatment and prevention i.e., continuous glucose monitors. Additionally, the increase in the use of smartwatches and other wearable devices allows the monitoring of people's physiological data i.e. pulse, heart rate, blood oxygen, and lifestyle measurement of physical activity. Wearable devices have future potential for improved monitoring and target treatment based on physiological data. On the other hand, how to use the large data from wearables remains to be investigated.

*What to look for, at which time point and how well the predictor is*

Studies have investigated from 10 seconds to 24-hour recordings of HRV and its association with CVD. However, studies comparing short-term recordings with long-term recordings and comparing time points in the diurnal clock are scarce. Such comparisons could inform what specific types of data from free-living heart rate patterns have clinical implications for cardiovascular disease.

This study aims to zoom from week-long to hourly recordings of HRV and investigate the CVD risk information of long-term and diurnal variation in short-term hourly HRV. Our hypothesis is 1) weeklong HRV measures are more robust in capturing detailed HR patterns and giving information about CVD risk. 2) Risk of CVD varies between hourly HRV throughout the diurnal clock.

Methods

*Study population*

Data were obtained from 1,200 participants with a high risk of diabetes in the Danish ADDITION-PRO study 2009-2011.

*Exposure*

HRV index, and standard deviation of normal to-normal heartbeat intervals (SDNN), were stimated from 48 hours and up to seven days of continuous HR monitor (ActiHeart), based on mean inter-beat intervals for 30-second epochs. RHRV packages

Resting heart rate (rHR) was measured in 5-minute resting 12-lead ECG recordings obtained after 5 minutes of rest in the supine position. Then, the normal-to-normal (NN) sinus rhythm was determined from the recordings with an automated algorithm to identify R-R intervals without the presence of arrhythmias, ectopic beats and/or branch-blocks. These measurements were used to calculate HRV indices in the time and frequency domain [2]. We included the HRV exposures of time domain: standard deviation of the NN interval (SDNN) and root mean square of successive differences (RMSSD), and frequency domain by using a Blackman-Tukey algorithm: low frequency (in the 0.04–0.15 Hz frequency band) (LF) and high frequency (in the 0.15–0.4 Hz frequency band) (HF). To account for cardiac automatism from concurrent rHR, we also included inter-beat interval (IBI) corrected HRV indices (cHRV): cSDNN, cRMSSD, cHF, cLF, following the approach previously described in Van Roon et al (see formula in supplemental material) [3, 4]. rHR was included as a control exposure to supplement the analysis.

*Outcome*

We defined CVD by 5-point MACE including, stroke, myocardial infarction, heart failure, cardiovascular revascularization, and cardiovascular death. Information on CVD events and mortality, as well as all-cause mortality was followed up in the Danish registries until 2021.

*Covariates*

Blood measurement hbA1c, oral glucose tolerance test (OGTT), fasting plasma glucose (FPG), triglycerides, total, high density- (HDL) and low density (LDL) cholesterol were derived from blood samples. Body mass index (BMI), waist circumference, and systolic and diastolic blood pressure were measured at the participant visit. Lifestyle factors of smoking and alcohol consumption were self-reported.

Self-administered questionnaires included information on categorical covariates such as smoking (never, former, current), socioeconomic status (administrative, professional/executive, clerical support), medication use (antihypertensive, cardiovascular, and antidiabetic medication), incidence of hypertension and other CVD, and continuous variables such as physical activity (hours of moderate to vigorous exercise) and alcohol use (units last week). Information on body mass index (BMI), waist-hip ratio, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, triglycerides, haemoglobin A1c (HbA1c), oral glucose tolerance test (OGTT), and fasting plasma glucose (FPG) were collected as continuous covariates at clinical examination.

*Statistical analysis*

Baseline characteristics was described to characterize the distribution of continuous variables (median, 25th & 75th percentile) and frequencies (numbers, percentage) for categorical variables.

Zoom study:

* Weekly HRV
* Mean daily HRV
* Mean hour HRV
* CVD timepoint of the day???

Predictive value of most risk hour, day, and weekly.

Results

From the entire cohort, 6412 (62%) participants had at least one measurement of HRV, 5069 (49%) participants among them also had at least one measurement of PWV, where 4901 (48%) had full information on covariates (**Fig. 1**). Regarding HRV, 1071 (22%) had one measurement, 2312 (47%) had two, and 1518 (31%) had three. In total, 1494 (30%) had one PWV assessment and 3407 (70%) had two. In phase 5, the median (25th; 75th percentile) age was 54.0 years (50.2; 59.6), 26% were women, and the median SDNN was 35.4 ms (26.6; 46.2). In phase 9, considered the baseline for our analyses, median PWV was 8.04 m/s (7.02; 9.44). The median interval for collection of data was 10.4 years (10.2; 10.7) for the exposures (phase 5 to 9) and 4.1 years (4.0; 4.2) for the outcomes (phase 9 to 11). Further characteristics of the participants are summarised by phase in **Table 1**. The subpopulation included 4207 participants, as 694 participants were diagnosed with diabetes before phase 9.

Discussion

*Strengths and limitations*

*Conclusion*

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**Authors' contributions**

Study concept and design: JRS, DRW, LB, DV, CSH. Contributed the data: DRW, AGT. Planning the statistical analysis: JRS, DRW, AH, LB, MSC, DV. Conducted the statistical analysis: JRS. All authors contributed to, critically revised, and approved the final version of the manuscript. JRS 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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**Ethics**

The UK NHS Health Research Authority London-Harrow ethics committee approved the study, which was conducted in accordance with the Helsinki Declaration with written informed consent from all participants.

**Conflicts of interests**

All the authors declare that there is no duality of interest associated with their contribution to this manuscript.

**Availability of data and materials**

ADDITION-PRO data

References

**Tables and figures**

**Table 1:** Baseline characteristics

**Figure 1:** Study flowchart

**Figure 2*:***

**Figure 3:**

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