

Wearable-Derived Long-Term Heart Rate Variability Predicts Major Adverse Cardiovascular Events in Middle Aged Individuals Without Previous Cardiovascular Disease

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Abstract

Wearable devices enable continuous heart rate (HR) monitoring at scale. However, it is unclear how long-term HR recorded with wearable devices can be harnessed to predict cardiovascular (CV) disease, especially in view of a lower accuracy and temporal resolution compared to clinical ECGs. We hypothesized that robust HRV estimator can identify individuals at higher risk of major adverse CV events (MACE) in the general population. In the National Survey of Health and Development (NSHD), the Actiheart monitor was used to measure 30-second averaged HR in 1,462 participants aged 60-64 (53.2% female) without previous CV disease for up to 5 days. The median absolute deviation of 5-min averaged HR (MAD_{AHR}) and median absolute deviation of 30-sec averaged successive HR differences (MAD_{SDHR}) were used as robust estimates of the established metrics $SDANN$ and $SDSD$, respectively. After a median follow-up of 11.3 years, $n=136$ (9.3%) MACE occurred. Reduced MAD_{AHR} and MAD_{SDHR} were associated with MACE with hazard ratio (95% confidence interval) equal to 1.33 (1.10-1.62, $p<0.01$), and 2.15 (1.39-3.32, $p<0.01$) after adjusting for average heart rate, sex, body-mass index, hypertension, diabetes, and beta-blockers. These data demonstrate for the first time that wearable derived long-term HRV can predict CV events in the general population.

1. Introduction

Heart rate (HR) variability (HRV) refers to the measure of the fluctuations in the duration of the cardiac cycle between consecutive heart beats and it is considered a non-invasive cardiac autonomic marker [1]–[3]. Low HRV is considered to reflect impaired autonomic function and it has an established predictive value in post-myocardium infarction patients [3]. An association between low HRV and increased risk of developing cardiovascular disease has also been identified in the general population, as shown in selected population-based cohorts such as UK Biobank [4], Framingham [5], [6], ARIC [7], [8], Rotterdam [9] and Ohasama [10] studies.

Recent advancement in wearable and mobile-based devices [11] provide new opportunities for continuous HR and HRV monitoring at scale [12], [13]. Novel wearable cardiac monitors can be categorised in two groups: those that record and store the raw ECG and those that only provide averaged heart rate every few seconds or minutes. The first group represents the new generation of Holter monitors and can be used to estimate standard and advanced beat-to-beat HRV metrics [1], [2], but are expensive and their use is limited to specialized clinical applications. The second group includes consumer-grade devices, which are becoming ever more affordable and easier to wear for many consecutive days but cannot be used to measure standard beat-to-beat HRV due to insufficient accuracy and temporal resolution. It is currently unclear if HR time-series obtained through these cardiac monitors can be harnessed to assess cardiovascular risk. The aim of this study was to address this knowledge gap by using data collected in a population-based cohort study, the MRC National Survey of Health and Development (NSHD) [14], between 2006 and 2011 using a cardiac monitor which provided averaged HR data every 30 seconds for up to 5 consecutive days.

2. Methods

2.1 Cohort description and outcomes

The MRC NSHD study recruited a representative sample of 5,362 men and women born in England, Scotland and Wales in a single week in March 1946 [14], and it is the longest running birth cohort in the UK. Between 2006 and 2011, 1,880 participants were given a cardiac monitor (Actiheart, Camntech) and were instructed to wear it for 5 consecutive days. The cardiac monitor used a chest patch to acquire a single-lead ECG and provided measurements of heart rate in beats per minute every 30 seconds. The raw ECG was not recorded. After data collection, $n=418$ participants were excluded from the study for meeting any of the following criteria: >25% of missing HR samples ($n=82$); HR monitored for less than 36 hours ($n=116$); prevalent cardiovascular disease,

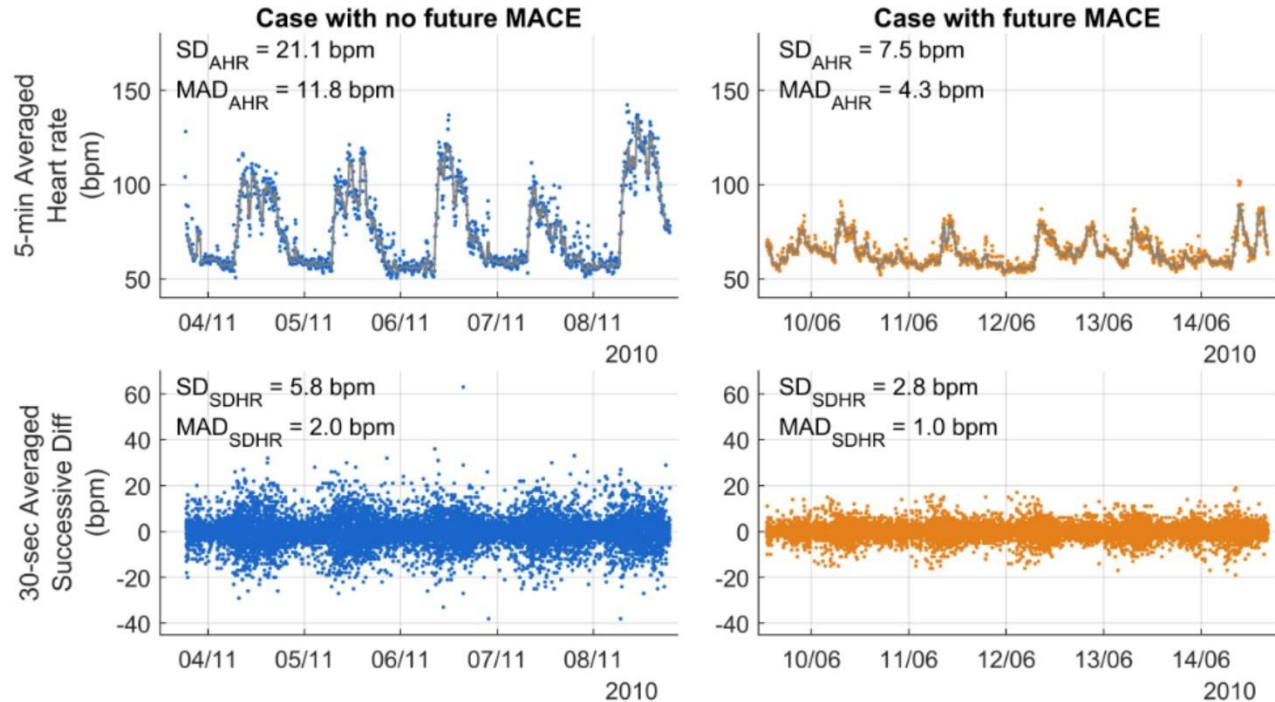


Figure 1. Examples of 5-min averaged heart rate and successive differences of 30-sec averaged heart rate in two cases, one with (right) and one without (left) future major adverse cardiovascular events during follow-up. HRV metrics are reported in the panels.

identified using hospital records or self-reported ($n=313$). Statistical analyses were conducted in the remaining 1,462 participants. Follow-up data was available until the 1st of December 2021, for a median (interquartile range) of 11.3 (10.7-12.0) years. Major adverse cardiovascular events were identified using Hospital Episode Statistics and included ischaemic heart disease, myocardial infarction, angina, heart failure, and stroke.

2.2 Heart rate variability analysis

Standard and robust estimators of HRV in the temporal domain were derived from the time-series of 30-second averaged HR provided by the device. That is, the wearable device recorded one averaged HR value every 30 second for 5 consecutive days. Since data were measured by the device with 1 beat per minute (bpm) resolution, HRV metrics were not converted in ms. The following metrics were included:

- SD_{AHR} : Standard deviation of 5-min averaged HR.
- MAD_{AHR} : Median absolute deviation of 5-min averaged HR.
- SD_{SDHR} : Standard deviation of 30-second averaged successive HR differences.
- MAD_{SDHR} : Median absolute deviation of 30-second successive averaged HR differences.

SD_{AHR} is equivalent to the established HRV metrics SD_{ANN} [2], with the caveats that using the cardiac monitor data it is not possible to establish if the underlying

rhythm is normal (NN) and that units were kept in bpm instead of milliseconds. MAD_{AHR} is a robust estimate of SD_{AHR} which uses the median absolute deviation instead of the standard deviation. Similarly to the established HRV metric SD_{SD} [2], SD_{SDHR} was designed to capture faster HR oscillations. However, the two are not equivalent since SD_{SDHR} uses successive differences derived from 30-sec averaged HR, whereas SD_{SD} uses successive differences of beat-to-beat RR-intervals.

2.3 Statistical analysis

Data distributions are reported as median (interquartile range) and differences across distributions were assessed using the rank-sum Wilcoxon test. Differences in frequency across groups were assessed with the Fisher's exact test.

Survival analysis was conducted using Cox regression models. Models were adjusted for mean heart rate, sex, body mass index (BMI), and self-reported hypertension, diabetes, and use of beta-blockers. All HRV parameters, except MAD_{SDHR} , were log-transformed to account for right skewness and then normalized as in previous studies [8]. MAD_{SDHR} was composed of integer numbers ranging between 1 and 8, and it was therefore dichotomised as $MAD_{SDHR} \leq 1$ bpm.

3. Results

Table 1. Association between HRV metrics and MACE. HR: Hazard Ratio; CI: Confidence Interval. The adjusted models included average heart rate, sex, BMI, hypertension, diabetes, and beta-blockers.

	No MACE	MACE	P
N	1326 (90.7%)	136 (9.3%)	
Age (years)	63.0 (62.0, 64.0)	63.0 (62.0, 64.0)	8.7E-01
Sex (Male)	608 (45.9%)	86 (63.2%)	1.4E-04
BMI (kg/m ²)	27.0 (24.0, 30.0)	27.0 (25.0, 31.0)	2.9E-01
Hypertension (yes)	399 (30.1%)	58 (42.6%)	1.2E-03
β-blockers (yes)	60 (4.5%)	13 (9.6%)	2.0E-02
Diabetes (yes)	114 (8.6%)	11 (8.1%)	2.4E-01
Mean HR (bpm)	74.0 (68.8, 79.4)	74.6 (67.3, 80.2)	9.5E-01
SD _{AHR} (bpm)	14.7 (12.2, 19.6)	14.1 (11.5, 19.6)	1.8E-01
SD _{SDHR} (bpm)	5.4 (4.7, 6.7)	5.4 (4.4, 6.6)	3.6E-01
MAD _{AHR} (bpm)	8.2 (6.7, 10.1)	7.5 (6.1, 9.3)	2.8E-03
MAD _{SDHR} ≤1 (yes)	157 (11.8%)	31 (22.8%)	6.8E-04

After exclusions, 1,462 participants were monitored for 4.7 (4.1, 5.0) consecutive days. During the follow-up, n=136 (9.3%) participants registered a MACE. Participants' baseline characteristics are reported in Table 1. At baseline, participants with future MACE were more prevalently male and beta-blockers users and had more frequently hypertension. Age, BMI, diabetes, mean heart rate, SD_{AHR} and SD_{SDHR} did not differ between the two groups, whereas robust HRV estimates MAD_{AHR} and MAD_{SDHR} were lower in participants who developed MACE compared to participants who did not. This is reflected in Figure 1, which shows 5-min averaged HR (above) and successive difference in 30-sec averaged HR (below) over 5 days in a participant who did (right) and did not (left) develop MACE during the follow-up. In the figure, the participant who developed MACE showed a smaller range of variation in HR as well as in HR successive differences.

Survival analysis demonstrated that MAD_{AHR} and MAD_{SDHR}≤1 bpm were associated with future MACE, even after adjusting for mean heart rate and several traditional risk factors (Table 2), while SD_{AHR} and SD_{SDHR} were not.

3. Discussion

The aim of this study was to test if wearable-derived heart rate could be harnessed to predict MACE in individuals without underlying cardiovascular disease. We demonstrated that robust HRV estimates derived from 5-min averaged heart rate and successive differences in 30-sec averaged heart rate were associated with increased long-term risk of developing MACE. The association between HRV metrics and MACE remained significant after adjusting for mean heart rate and traditional risk factors including sex, body mass index, hypertension, diabetes, and use of beta-blockers. We did not adjust for

Table 2. Hazard ratio (HR) and 95% confidence interval (CI) for HRV parameters. Models were adjusted for mean heart, sex, body mass index, hypertension, diabetes, and use of beta-blockers. Significant associations (P<0.05) are reported in bold. SD: Standard deviation; Dec: Decrease. Ln: Logarithmic transformation

	Unadjusted		Adjusted	
	HR (95% CI)	P	HR (95% CI)	P
LnSD _{AHR} (1 SD dec.)	1.14 (0.96, 1.37)	1.4E-01	1.16 (0.97, 1.39)	1.0E-01
LnMAD _{AHR} (1 SD dec.)	1.33 (1.12, 1.59)	1.1E-03	1.33 (1.10, 1.62)	4.1E-03
LnSD _{SDHR} (1 SD dec.)	1.13 (0.95, 1.35)	1.6E-01	1.14 (0.96, 1.37)	1.4E-01
MAD _{SDHR} (≤1 bpm)	2.17 (1.46, 3.25)	1.5E-04	2.15 (1.39, 3.32)	5.9E-04

age because all participants had the same age ± 1 year at the time of recording. To the extent of our knowledge, this is the first study to demonstrate that cardiac monitors that measure heart rate every few seconds for several days can be used to identify individuals with long-term risk of developing MACE. A limited number of previous studies had established an association between low beat-to-beat HRV derived from ambulatory ECG recordings and cardiac events [6], [10], but it was not clear if heart rate series sampled at a lower temporal resolution (i.e. every 30 seconds instead of every beat) and with coarser quantization (1 bpm instead of 1 ms) could be harnessed to predict cardiac events. Our data show that traditional estimators based for example on the standard deviation fail to discriminate individuals with elevated cardiovascular risk, most probably because of the effect of outliers, noise and artefacts which are inevitably present in automated measures from cardiac monitors worn during free-living activity. However, the simple use of robust estimators such as the median absolute deviation was enough to increase the predictive value of wearable derived HRV.

This study has important clinical ramifications because it suggests that popular consumer-grade wearable devices such as smartwatches could be used to assess cardiovascular risk at unprecedented scale and low cost and, importantly, during free-living conditions. There is an urgent need to find innovative solutions to tackle cardiovascular disease, whose incidence is expected to dramatically increase in the next few years, and this study suggests that it may be possible to transform data seamlessly recorded during free-living activity into accurate prognostic information.

Future work is required to clarify what MAD_{AHR} and MAD_{SDHR} represent. Despite the reduced temporal resolution of wearable derived heart rate, they may reflect cardiac autonomic function, but they may also reflect physical activity or cardiac reserve. Comparing them with standard short-term HRV metrics and with markers of physical activity and cardiorespiratory fitness may help better understanding their association with MACE. Longitudinal studies using PPG-based cardiac monitors are required to assess the potential of consumer-grade wearable devices for predictions of cardiovascular events.

4. Conclusions

Robust estimates of heart rate variability from long-term wearable-based cardiac monitoring are associated with increased risk of major adverse cardiovascular events in middle-aged individuals without previous cardiovascular disease.

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