Heart rate and heart rate variability changes are not related to future cardiovascular disease and death in people with and without dysglycemia: A downfall of risk markers? The Whitehall II cohort study

Short title: HR, HRV and CVD and mortality

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Word count: Main text: 3394 (including figure legends), Abstract: 250 words

Number of Figures and Tables: Tables: 3. Figures: 1 (2 supplementary tables)

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Abbreviations

CAN: cardiovascular autonomic neuropathy

CVD: cardiovascular disease

HF power: high-frequency power

HR: heart rate

HRV: heart rate variability

LF power: low-frequency power

LH/HF ratio: low frequency / high frequency power ratio

SDNN: the standard deviation of all normal-to-normal R-R intervals

rHR: resting heart rate variability

RMSSD: the root mean square of the sum of the squares of differences between consecutive normal-to-normal R-R intervals

Objective

Higher resting heart rate (rHR) and lower heart rate variability (HRV) are associated with increased risk of cardiovascular disease (CVD) and all-cause mortality in people with and without diabetes It is unknown whether temporal changes in rHR and HRV may contribute to this risk. We investigated associations between 5-year changes in rHR and HRV and risk of future CVD and death, taking into account participants' baseline glycemic state.

Research design and Methods

In this prospective population-based cohort study we investigated 4,611 CVD-free civil servants (mean age 60, SD=5.9 years, 70% men). rHR and/or 6 indices of HRV were measured. Associations of 5-year change in 5-minute rHR and HRV with fatal- and non-fatal CVD and all-cause mortality or the composite of the two were assessed with adjustments for relevant confounders. Effect modification by glycemic state was tested.

Results

At baseline, 63% of participants were normoglycemic, 29% had prediabetes and 8% had diabetes. During a median (IQR) follow-up of 11.9 (11.4;12.3) years, 298 participants (6.5%) experienced a CVD event and 279 (6.1%) died from non-CVD related causes. We found no association between 5-year changes in rHR and HRV and future events. Only baseline rHR was associated with all-cause mortality. A 10 beats per minute higher baseline level showed a 11.4% higher rate of all-cause mortality (95%CI:1.0;22.9%, P=0.032). Glycemic state did not modify associations**.**

Conclusion

Changes in rHR and HRV and possibly also baseline values of these measures are not associated with future CVD or mortality in people with or without dysglycemia.

Funding Source

The UK Medical Research Council (K013351, R024227), British Heart Foundation and the US National Institutes of Health (R01HL36310, R01AG013196) have supported collection of data in the Whitehall II study. DRW is supported by the Danish Diabetes Academy, which is funded by an unrestricted grant from the Novo Nordisk Foundation. MK had research grants from the UK Medical Research Council (K013351, R024227), the US National Institute on Aging (R01AG056477), NordForsk, the Academy of Finland (311492) and Helsinki Institute of Life Science during the conduct of the study. MM has a New Horizons grant from British Heart Foundation (NH/16/2/32499).

Cardiovascular disease (CDV) is the leading cause of death in patients with and without dysglycemia globally[1]. Thus, identifying persons at risk of CVD prior to overt disease by use of risk markers is essential to prevent later complications. In large longitudinal population-based cohort studies, single baseline assessments of high heart rate (rHR) and low heart rate variability (HRV), characterizing cardiac autonomic function, have been established as markers of increased risk of future CVD and mortality in both non-diabetic individuals[2-5] and patients with diabetes[6-9]. High rHR and low HRV are also associated with preclinical pathological disease states, such as subclinical inflammation[10], dysglycemia[11,12] and vascular damage[13], all of which contribute to increased risk of future CVD and mortality. Individuals with prediabetes[14] and diabetes[15,16] are particularly prone to adverse levels of rHR and HRV. This can be a sign of diabetic autonomic neuropathy, a prevalent complication to prediabetes and diabetes.

As measures of rHR and HRV are easily obtainable by short-term non-invasive measures derived from electrocardiograms (ECG), they are obvious candidates for risk stratification. Temporal changes in rHR and HRV could be associated with an additional risk of CVD and mortality, over and above the risk conveyed by baseline rHR and HRV levels. If this were the case, sequential measures could prove to be useful monitoring tools in patient care, as rHR and HRV assessments could be obtained regularly at many patient consultations with low cost and little effort. To date, however, associations between temporal changes in rHR and HRV and the risk of CVD and mortality have not been investigated in observational epidemiological settings of individuals free of CVD.

To address this limitation, we investigated the prospective associations of measures of 5-year changes in rHR and HRV with incident CVD and mortality in normoglycemic individuals and those with dysglycemia such as prediabetes and diabetes in the large population-based Whitehall II cohort study with repeated measurements of rHR and 6 indices of HRV.

Research Design and Methods

Access to data from the Whitehall study is possible by contacting the Whitehall team directly (whitehall2@ucl.ac.uk)

Study participants

The Whitehall II study is an occupational cohort of 10,308 British civil servants (6,896 men and 3,412 women aged 35–55 years) of mainly white ethnicity, followed with clinical examinations every 5 years since 1985[17].

Both rHR and HRV were measured at phase 5 (1997-1999), phase 7 (2002–2004) and phase 9 (2007–2009). While rHR was assessed from all participants, HRV measurement involved only a sub-cohort of Whitehall participants. We used data from phases 5, 7 and 9 to assess 5-year change in rHR and HRV with phase 7 being the baseline for this study. Changes were assessed for participants with data for phases 5 and 7. If participants also had additional data at phase 9, then changes between phase 7 and 9 were further included in the analyses.

From the 6,967 study participants at phase 7, we excluded 1,111 (15.9%) with events of study outcomes such as previous CVD and stroke (described in "Outcome Ascertainment" below). Another 1,245 (17.9%) with missing phase 5 data on rHR or HRV were excluded, leaving 4,611 participants for analyses. While 5-year changes in rHR were available for all 4,611 study participants, only 1,675 (36.3%) had information on 5-year changes in HRV.

The study was reviewed and approved by the UK NHS Health Research Authority London-Harrow Ethics Committee and written informed consent was obtained from each participant at each examination phase. The study was conducted according to the principles of the Helsinki Declaration.

Measurements and definitions

The rHR and HRV indices were derived from 5-minute resting 12-lead ECG recordings obtained subsequent to 5-minute of rest in the supine position at phases 5, 7 and 9. Recordings were filtered through an automated algorithm, allowing the analyses of suitable normal-to-normal sinus rhythm R–R intervals without the presence of arrhythmias, ectopic beats and branch blocks (N-N intervals).

The following six indices of HRV were analyzed: (1) the standard deviation of all N-N intervals (SDNN); (2) the root mean square of the sum of the squares of differences between consecutive N-N intervals (RMSSD) as measures of the time domain; (3) low-frequency (LF) power (in the 0.04–0.15 Hz frequency band), (4) high-frequency (HF) power (in the 0.15–0.4 Hz frequency band) and (5) total power (in the ≤ 0.4 Hz frequency band) as measures of the frequency domain utilizing a Blackman-Tukey algorithm. The ratio between LF and HF power (LF/HF ratio) (6) was calculated. RMSSD and HF power outcomes are associated mainly with parasympathetic modulations, whereas the remaining measures characterize mixed sympathetic and parasympathetic influences.

rHR was obtained from either the 5-minutte resting heart rate measures mentioned above. If these measures were not assessable rHR was obtained from standard 10-second 12 lead ECG recordings by the Burdick Eclipse 850 ECG recorder.

Plasma glucose, serum insulin, HbA_{1c}, serum lipids and systolic and diastolic blood pressure at phases 5, 7 and 9 were measured as described previously[18].

Information on smoking habit (never/ex/current), physical activity (hours per week of mild, moderate and vigorous physical activity) and medication use were collected using self-administered questionnaires at phases 5, 7 and 9[19].

Glycemic status was determined by bA_{1c} using the ADA criteria:[20] normal glycemia (< 5.6% / 39 mmol/mol), prediabetes (5.6-6.4% / 39-47 mmol/mol) or diabetes (≥ 6.5% / 48 mmol/mol). Diabetes cases were also diagnosed outside the study by the treating physician.

Outcome Ascertainment

The primary outcomes were fatal and non-fatal CVD, total mortality and a composite end point of CVD or death. The participants' unique National Health Service (NHS) identification numbers were linked to the NHS Hospital Episode Statistics database[21]. Incidence of CVD was assessed over the follow-up period from 2002–2004 to the end of follow-up (30 June 2015) and included fatal and nonfatal coronary heart disease (defined by ICD-9 codes 410–414 or ICD-10 codes I20–25) and stroke. Nonfatal myocardial infarction was determined using data from questionnaires, study electrocardiograms, hospital acute electrocardiograms, cardiac enzymes, and physician records[22]. In the definition of stroke, cases identified by self-report only were excluded. Stroke included first subarachnoid hemorrhage, cerebral infarction, intracerebral hemorrhage, not specified stroke (ICD-10 codes I60–I64), and transient cerebral ischemic attacks (ICD-10 code G45). Cases of stroke were ascertained from participants' general practitioners, by information extracted from hospital medical records, or from the NHS Hospital Episode Statistics database. Cardiovascular event ascertainment in the Whitehall II study has recently been validated[23]. All-cause mortality was assessed from 2002–2004 to end of follow-up by flagging participants at the NHS Central Registry, which provided information on the cause and date of death.

Statistical analysis

Incidence rates for CVD, all-cause mortality or the composite of the two were estimated in separate models using Poisson regression analysis with the corresponding log-risk time as offset. For each participant, the follow-up period was split into 1-year age bands to account for the non-constant effect of age over time on CVD risk and mortality[24] Exposure was 5-year changes in heart rate or HRV measures between phase 5 and 7. Analyses were adjusted for age, sex, ethnicity and baseline rHR or HRV measures (Model 1) and additional adjustments were performed for glycemic state (normoglycemia, prediabetes, diabetes), BMI, physical activity, smoking, systolic blood pressure, total cholesterol, LDL cholesterol, triglycerides, tricyclic antidepressants, diuretics and β-blockers in a subsequent model (Model 2). In Model 2, we further tested for a modifying effect of baseline glycemic state on the outcome-exposure associations using an interaction term 'glycemic state x rHR or HRV'. If significant, associations were calculated for the glycemic states separately in both Model 1 and 2. For all HRV exposures, the models were additionally adjusted for the simultaneously measured heart rate at the current and previous phase.

For the subset of individuals with rHR or HRV measurements at phase 9 (86.6% for heart rate and 80.8% for HRV), we updated the covariates, accordingly, treating all covariates as time-varying. As an example, a participant with prediabetes at phase 7 who developed diabetes between phase 7 and 9, first contributed with risk time in the prediabetes group and subsequently to the diabetes group.

To allow direct comparisons of incidence rate ratios between the exposure variables, we further calculated standardized regression coefficients for the subset of the population for whom rHR and all six HRV indices were available at the same time points, i.e. the subset with autonomic function assessed.

In a subsidiary analysis, we repeated the analyses with baseline levels of rHR or HRV measurements as exposure, i.e. removing the covariate for the 5-year changes from the models.

To avoid exclusion of patients with missing values which may lead to biased results[25], multivariate Imputations by Chained Equations (MICE) method[26] with a missing-at-random assumptions (50 imputations), and including a number of auxiliary data on the participants not used in the analyses were used to impute missing data on the covariates at each phase. Exposure- and outcome variables were not imputed. Estimates of parameters of interest were averaged across the imputation copies according to Rubin rules[27].

Subset analyses on determinants and future events were performed for patients not in betablocker treatment.

Statistical analyses were performed in R version 3.6.1 (The R Foundation for Statistical Computing) and SAS, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Median (IQR) follow-up time was 11.9 years (11.4; 12.3) for death and 11.9 year (11.3; 12.2) for CVD and the composite outcome, respectively.

In the study population, rHR measures were available for analysis from 4,611, 4,611 and 4,029 individuals at phases 5, 7 and 9 respectively. A total of 4,611 participants had rHR measures at both phases 5 and 7 and 3,991 of these individuals had further rHR measures at phase 9. In total 8,602 pairs of measures of rHR at approximately five years apart were used for analyses of change.

In the study population, HRV measures were collected from 2,381, 3,069 and 3,495 individuals at phase 5, 7 and 9 respectively. A total of 1,675 participants had HRV measures at both phase 5 and 7 and 1,353 of these individuals had further HRV measures at phase 9. In total, 3,028 pairs of measures of HRV at approximately five years apart were used for analyses of 5-year HRV change.

All measures of HRV diminished during the study period as described previously[28]. Changes during study are presented in supplementary Figure 1. At baseline (phase 7) the study population consisted of mainly men 3,235 (70.2%) men vs 1,376 (29.8%) women, with a mean (SD) age of 60.5 (5.9) years and a resting heart rate of 68.0 (11.4) beats per minute. A majority of participants were normoglycemic and glycemic state was distributed as follows (% (IQR): 63.3 (61.9;64.7) were normoglycemia, 29.1 (27.8;30.5) had prediabetes, 1.8 (1.4;2.2) were screen detected with diabetes and 5.8 (5.1;6.5) had known diabetes. Detailed characteristics of the study population at phase 7 are shown in Table 1.

During follow-up, 298 (6.5%) of the study participants had a CVD event (47 fatal and 251 non-fatal). An additional 279 (6.1%) died from non-CVD related causes, giving a total of 577 (12.5%) events for the composite outcome (Table 2).

There was no modifying effect of glycemic state on any of the associations between 5-year change in rHR or HRV measures and the rate of an event ($P \geq 0.051$). Hence, the interaction term was removed from the model.

We found no statistically significant association of 5-year changes in rHR or HRV with risk of first CVD event, all-cause mortality or the composite (Table 3 and Figure 1. Supplementary table 1 for

estimates of a standard deviation in change in determinants). The range of rate ratios per 10-unit change in rHR or HRV measures was from 0.96 to 1.10 indicating small or neutral effect size. One association (between 5-year change in SDNN and rate of the composite event) reached statistical significance (p=0.046) suggesting a clinically not important negative association, which is expected given the number of tests performed. Subset analyses on patients not in betablocker treatment (Supplementary table 3) showed no difference in results.

In the subsidiary analyses of baseline levels of rHR and HRV, we found similar results. There was no modifying effect of glycemic state on any of the associations ($P \geq 0.298$), and there was no association between baseline levels of rHR or HRV and risk of first CVD event, all-cause mortality or the composite endpoint (Figure 1 and supplementary Table 2). The range of rate ratios per 10-unit higher baseline rHR or HRV measures was from 0.91 to 1.11 (most at approximately 1.00) indicating small or neutral effect size. Again, one association (between baseline rHR and rate all-cause mortality) with the expected direction reached statistical significance with a p-value of 0.040 with a rate ratio of 1.11 (95% CI1.00;1.22).

Discussion

In this large population-based longitudinal study of people free of CVD, 5-year changes in rHR indices or HRV were not associated with future events of CVD events in a median follow-up of 12 years. The null finding was observed irrespective of participants' glycemic state in the beginning of follow-up. In subsidiary analyses, high baseline resting heart rate was associated with increased mortality risk, but no other associations of baseline levels of HRV with subsequent events were found in this cohort.

To our knowledge, this is the first study to assess temporal changes in rHR and HRV in relation CVD and mortality in people free of CVD. In a post-hoc analysis of the double-blind randomized trials ONTARGET and TRANSCEND[6] with a 56-month follow-up, the associations of changes in rHR with cardiovascular events were studied in patients with coronary, peripheral, or cerebrovascular disease, or diabetes with end organ damage. Participants were assigned to have 10 mg of ramipril daily, 80 mg of telmisartan daily, or their combination or either 80 mg of telmisartan daily or placebo telmisartan daily, or their combination. Both higher baseline rHR and greater in-trial increases of rHR were associated with an increased CVD incidence with no threshold value for rHR[6]. These observations may suggest that temporal changes in rHR may be a valid risk marker only in patients at a high risk of CVD.

Except for greater mortality risk in participants with high baseline rHR, baseline levels of rHR and HRV were not associated with the endpoints of the present study. Previous investigations have reported partly inconsistent findings. In the US Framingham[3,29] and ARIC studies,[2] for example high rHR and low HRV were linked to increased risk of future CVD and all-cause mortality. Similar findings for rHR were seen in the FINRISK cohort with regards to CVD[4]. The baseline clinical markers of our study population were collected more recently (2002-2004) than the clinical markers from the Framingham (1948/1971), ARIC (1987-89), and FINRISK (1982-1997), reflecting a period of more aggressive preventive medication treatments which may explain weaker associations in the Whitehall II study. However, the level of HRV (measured in 1989-1990) was not associated with mortality in participants with and without diabetes in the MONICA-KORA study[30].

Among patients with diabetes in the DCCT/EDIC[31], ACCORD[8] and ADVANCE[9] trials, baseline measures of rHR and HRV were linked to future events. The baseline clinical markers were collected

in 1993-2006, 2001-2005 and 2001-2013, respectively, and thus recommendations for CVD prevention were similar as for the Whitehall population. These were interventional trials and assessments were done on either in-trial associations or post-trial follow-up. Hence, results cannot be regarded as observational and may be confounded by trial participation. On the other hand, a causal relationship cannot be ruled out either. It has been hypothesized that increased rHR and sympathetic overactivation as seen in prediabetes and diabetes can contribute to vascular disease through mechanisms such as the promotion of atherosclerosis, increasing oxygen demand of the heart and the promotion of cardiac arrythmias[32-34]. These mechanisms may play a role in the development of vascular disease in prediabetes and diabetes. However, a causal relationship has yet to be established. Notably, interventional trials targeted at a reduction of heart rate in patients with existing cardiovascular disease has only shown an improvement in heart failure outcomes[35] but not on vascular disease[36]. Three is not a tangible explanation as to why the present study does not exhibit any differences in association in different glycemic states. It could be speculated that autonomic dysfunction characterized as high rHR and low HRV could be signs of different pathogenic mechanisms in these states. Patients with normoglycemia are not exposed to high blood glucose and therefore autonomic dysfunction in this group may be a sign of other conditions than individuals with dysglycemia. However, the lack of differences between glycemic groups may just a sign of the possible lack of predictive value of rHR and HRV in general.

The lack of associations in the present study could be attributed to recent changes the distribution of risk factors of CVD in younger birth cohorts. Such cohort effects have been described in the Whitehall II cohort study, showing that younger birth cohorts have a higher BMI compared to older cohorts but with lower levels of total cholesterol[37]. This may indicate a change in associations between CVD risk markers e.g. that higher BMI is not as strongly associated with cholesterol levels as previously, and

therefore may not be as strong a risk marker for CVD when preventive treatment with e.g. cholesterol lowering medication is implemented. It is possible that rHR and HRV may have lost their association with later events due to preventive medicine.

Strengths and weaknesses

Our study benefits from its large sample size, the comprehensive measurements of outcomes and exposures assessed simultaneously, and an extensive adjustment for confounders. Importantly, the prospective design with repeat data allowed us to assess associations changes in rHR and HRV with major future events. Endpoints were adjudicated by health care professionals ensuring valid diagnoses.

The study population was predominantly of European descent and based on people employed as civil servants at the study, so the results may not be generalizable to other ethnic groups, unemployed people, those employed in the private sector and people with manual labor. In addition, the cohort seems to have a high level of physical activity and a low prevalence of smokers compare to national surveys performed in the UK[38]. The study may therefore not be fully generalizable to the general population. In addition, the present cohort consists of a relatively small subset of participants with diabetes at baseline (n=343) and therefore interpretation of results for diabetes patients should be done with caution. HRV measures were short-term measures of 5 minutes. Such measures may be prone to some issues with reproducibility, which may affect out findings. Longer measuring periods may have shown association to endpoint, e.g. the circadian rhythm of HRV as shown associations to future event[39]. In addition, more robust measures for estimating autonomic dysfunction such as cardiovascular autonomic reflex tests may prove to the exhibit associations in contemporary cohorts to future CVD as show previously[40].

For cerebral vascular disease transient ischemic attack (TIA) was accepted as a valid diagnosis for cerebral CVD. TIA may be a less reliable diagnoses for cerebral ischemia, as it is a transient deficit that may not exhibit measurable paraclinical sign that can validate the diagnosis.

CONCLUSIONS

In summary, our study suggests that changes in resting heart rate and 5-minute heart rate variability may not be useful risk markers for the development of first event of cardiovascular disease or all-cause mortality in people both with and without dysglycemia. Also, baseline measures of theses markers may not be risk markers of future events in a contemporary general CVD-free population.

Acknowledgements

We thank all participating women and men in the Whitehall II Study, as well as all Whitehall II research scientists, study and data managers and clinical and administrative staff who make the study possible.

Guarantors statement

Christian Stevns Hansen 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.

Authors' contributions

CSH, MEJ, DRV, EJB, AGT, MK and DV contributed to the study concept and design. DRV, EJB, AGT, MK, MM contributed the data. CSH, DV planned the statistical analysis. DV conducted the statistical analysis. CSH, and DV drafted the paper. All authors contributed to, critically revised and approved the final version of the manuscript.

Sources of Funding

The UK Medical Research Council (K013351, R024227), British Heart Foundation and the US National Institutes of Health (R01HL36310, R01AG013196) have supported collection of data in the Whitehall II study. KF is supported by the Novo Nordisk Foundation. DRW is supported by the Danish Diabetes Academy, which is funded by an unrestricted grant from the Novo Nordisk Foundation. MK had research grants from the UK Medical Research Council (K013351, R024227), the US National Institute on Aging (R01AG056477), NordForsk, the Academy of Finland (311492) and Helsinki Institute of Life Science during the conduct of the study. MM has a New Horizons grant from British Heart Foundation (NH/16/2/32499).

Conflicts of interests

All the authors declare that there is no duality of interest associated with their contribution to this manuscript. The funders of the study had no role in study design, data collection, analysis, interpretation or writing of the report.

Ethics

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

Availability of data and materials

Whitehall II data, protocols, and other metadata are available to bona fide researchers for research purposes. Please refer to the Whitehall II data sharing policy at http://www.ucl.ac.uk/whitehallII/data-sharing

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Table 1 Baseline (phase 7) characteristics of the study participants by sex

	n (% available)	Total	Men	Women
N		4611	3235	1376
White ethnicity (%)	4611 (100)	93.0 (92.2;93.7)	95.0 (94.2;95.7)	88.2 (86.4;89.9)
Age (years)	4611 (100)	60.5 (5.9)	60.3 (5.8)	60.7 (5.9)
Height (cm)	4610 (100)	171.3 (9.1)	175.4 (6.6)	161.5 (6.5)
BMI (kg/m^2)	4599 (100)	26.4 (4.2)	26.3 (3.7)	26.7 (5.1)
Current smoker (%)	4580 (99)	7.4 (6.7;8.2)	6.9 (6.0;7.8)	8.8 (7.3;10.4)
Moderate to vigorous exercise (hours/week)	4538 (98)	11.5 (4.3;20.0)	12.8 (5.0;21.5)	8.5 (2.5;16.3)
Alcohol intake (units/week)	4541 (98)	8.0 (3.0;17.0)	10.0 (4.0;20.0)	4.0 (0.0;10.0)
Glycemic state				
Normoglycemia (%)	4525 (98)	63.3 (61.9;64.7)	63.8 (62.1;65.4)	62.3 (59.7;64.9)
Prediabetes (%)	4525 (98)	29.1 (27.8;30.5)	29.4 (27.8;31)	28.5 (26.1;31)
Screen detected diabetes (%)	4525 (98)	1.8 (1.4;2.2)	1.6 (1.2;2.1)	2.2 (1.5;3.2)
Known diabetes (%)	4525 (98)	5.8 (5.1;6.5)	5.3 (4.5;6.1)	6.9 (5.6;8.4)
Family history of diabetes (%)	4545 (99)	10.3 (9.4;11.2)	9.2 (8.2;10.3)	13.0 (11.2;14.9)
Medication				
Antihypertensive treatment (%)	4592 (100)	18.4 (17.3;19.5)	17.8 (16.5;19.1)	19.8 (17.7;22.0)
Lipid lowering treatment (%)	4592 (100)	6.9 (6.1;7.6)	6.5 (5.7;7.4)	7.7 (6.4;9.3)
Tricyclic antidepressants (%)	4611 (100)	2.6 (2.1;3.1)	2.1 (1.6;2.7)	3.7 (2.8;4.8)
Diuretics (%)	4592 (100)	6.9 (6.2;7.7)	5.9 (5.1;6.8)	9.2 (7.7;10.9)
Beta-blockers (%)	4592 (100)	6.8 (6.0;7.5)	6.6 (5.8;7.5)	7.1 (5.8;8.6)
Blood measurements				
Total cholesterol (mmol/l)	4574 (99)	5.8 (1.0)	5.7 (1.0)	6.0 (1.0)
HDL cholesterol (mmol(l)	4574 (99)	1.6 (0.5)	1.5 (0.4)	1.9 (0.5)
LDL cholesterol (mmol/l)	4526 (98)	3.6 (0.9)	3.6 (0.9)	3.6 (1.0)

Triglycerides (mmol/l)	4574 (99)	1.4 (0.9)	1.4 (1.0)	1.2 (0.7)
Systolic blood pressure (mmHg)	4608 (100)	127.2 (16.3)	127.9 (15.6)	125.6 (17.8)
Diastolic blood pressure (mmHg)	4608 (100)	74.2 (10.3)	74.7 (10.2)	72.8 (10.4)
Fasting plasma glucose (mmol/l)	4567 (99)	5.4 (1.1)	5.5 (1.1)	5.2 (1.0)
2-hour plasma glucose (mmol/l)	3852 (84)	6.5 (2.0)	6.5 (2.1)	6.5 (1.9)
HbA_{1c} (%)	4519 (98)	5.7 (0.6)	5.7 (0.6)	5.7 (0.7)
HbA_{1c} (mmol/mol)	4519 (98)	38.4 (6.7)	38.3 (6.4)	38.7 (7.3)
Hear rate indices				
Heart rate from ECG (bpm)	4611 (100)	68.0 (11.4)	67.7 (11.7)	68.9 (10.6)
SDNN (ms)	3069 (67)	33.9 (25.5;44.6)	33.8 (25.3;44.7)	34.1 (26.1;44.5)
RMSSD (ms)	3069 (67)	20.5 (13.6;30.1)	19.7 (13.2;28.7)	21.8 (14.6;32.7)
Low frequency power (ms^2)	3069 (67)	286.9 (158.8;528.7)	301.1 (165.0;554.2)	264.7 (151.6;474.4)
High frequency power (ms^2)	3069 (67)	115.0 (55.5;232.6)	105.9 (50.5;213.7)	146.4 (66.3;295.0)
LF/HF ratio	3069 (67)	2.59 (1.58;4.09)	2.91 (1.81;4.51)	1.92 (1.14;3.03)
Total power (ms^2)	3069 (67)	1011 (573;1742)	1010 (571;1778)	1012 (586;1678)

Data are means (SD), medians (25th; 75th percentiles) or proportions (95% CI); N: number of participants. n (%) = number of participants (percentage of total cohort) with data on the respective variable prior to multiple imputation. BMI, body mass index, SDNN, standard deviation of normal-to-normal R–R intervals; RMSSD, the root mean square of the sum of the squares of differences between consecutive normal-to-normal R–R intervals; LF, low-frequency; HF, high-frequency.

Table 2 Number of cardiovascular disease (CVD), all-cause mortality or the composite of the two by glycemic state in study population prior to imputation.

	CVD		All-cause mortality		Composite outcome	
	n	**%**	**n**	**%**	**n**	**%**
Normal glycemia	161	5.6	184	6.4	321	11.2
Prediabetes	90	6.8	102	9.7	181	13.7
Diabetes	38	11.1	33	8.1	61	17.8
Unclassifiable	9	10.5	7	8.1	14	16.3
Total population	**298**	**6.5**	**319**	**6.9**	**577**	**12.5**

Data are n = number of event and % = percent of group with an event.

Table 3 Rate ratios (RR) with 95% CI of 10-unit difference in 5-years changes in heart rate or HRV on the incidence of cardiovascular disease (CVD), all-cause mortality or the composite of the two

		CVD		All-cause mortality		Composite	
5-year change in	**Model**	**RR**	**P**	**RR**	**P**	**RR**	**P**
Resting heart rate (10 bpm)	1	1.08 (0.95;1.23)	0.258	1.01 (0.90;1.14)	0.855	1.03 (0.93;1.12)	0.602
	2	1.10 (0.96;1.25)	0.166	1.01 (0.90;1.14)	0.864	1.03 (0.94;1.13)	0.518
SDNN (10 ms)	1	0.96 (0.92;1.00)	0.058	0.97 (0.92;1.02)	0.250	**0.97 (0.93;1.00)**	**0.046**
	2	0.96 (0.93;1.00)	0.076	0.97 (0.92;1.02)	0.224	0.97 (0.94;1.00)	0.053
RMSSD (10 ms)	1	0.98 (0.95;1.00)	0.103	0.99 (0.95;1.03)	0.511	0.98 (0.96;1.00)	0.106
	2	0.98 (0.95;1.01)	0.150	0.99 (0.95;1.03)	0.538	0.98 (0.96;1.01)	0.155
Low frequency power (10 ms^2)	1	1.00 (1.00;1.00)	0.301	1.00 (1.00;1.00)	0.294	1.00 (1.00;1.00)	0.123
	2	1.00 (1.00;1.00)	0.371	1.00 (1.00;1.00)	0.342	1.00 (1.00;1.00)	0.172
High frequency power (10 ms^2)	1	1.00 (1.00;1.00)	0.559	1.00 (1.00;1.00)	0.316	1.00 (1.00;1.00)	0.259
	2	1.00 (1.00;1.00)	0.604	1.00 (1.00;1.00)	0.289	1.00 (1.00;1.00)	0.272
LF/HF ratio (10 units)	1	1.00 (0.37;2.66)	0.997	1.06 (0.40;2.80)	0.913	0.97 (0.48;1.97)	0.941
	2	0.95 (0.36;2.52)	0.924	1.02 (0.39;2.65)	0.968	0.95 (0.47;1.90)	0.882
Total power (10 ms^2)	1	1.00 (1.00;1.00)	0.424	1.00 (1.00;1.00)	0.420	1.00 (1.00;1.00)	0.240
	2	1.00 (1.00;1.00)	0.487	1.00 (1.00;1.00)	0.475	1.00 (1.00;1.00)	0.298

P: p-value for the test of the rate ratio being equal to unity (i.e. no effect).

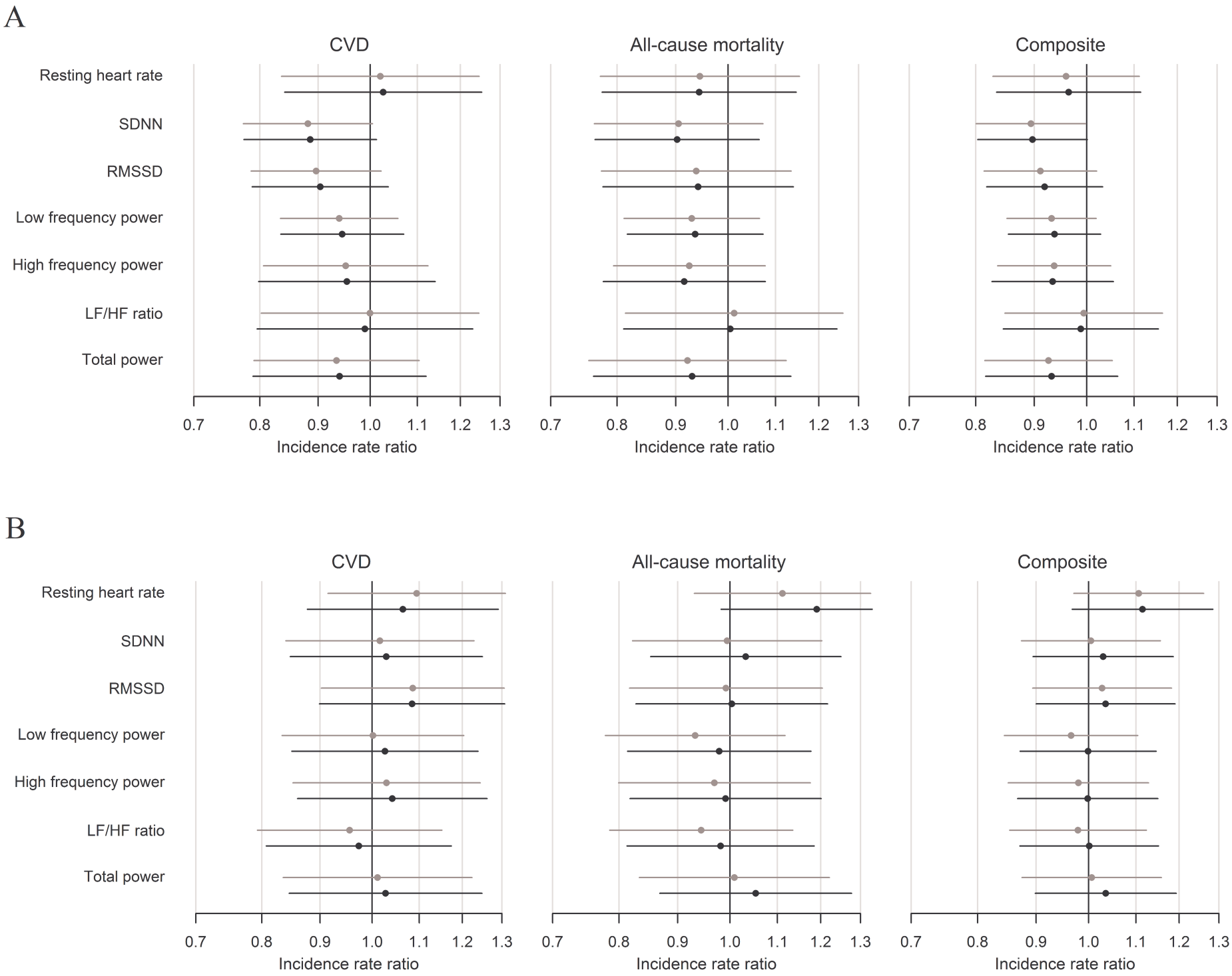
SDNN, standard deviation of normal-to-normal R–R intervals; RMSSD, the root mean square of the sum of the squares of differences between consecutive normal-to-normal R–R intervals; LF, low-frequency; HF, high-frequency.

Figure legends

Figure 1 Association 5-year change in heart rate and heart rate variability(A) or higher baseline values of the measures (B) with incidence of events.

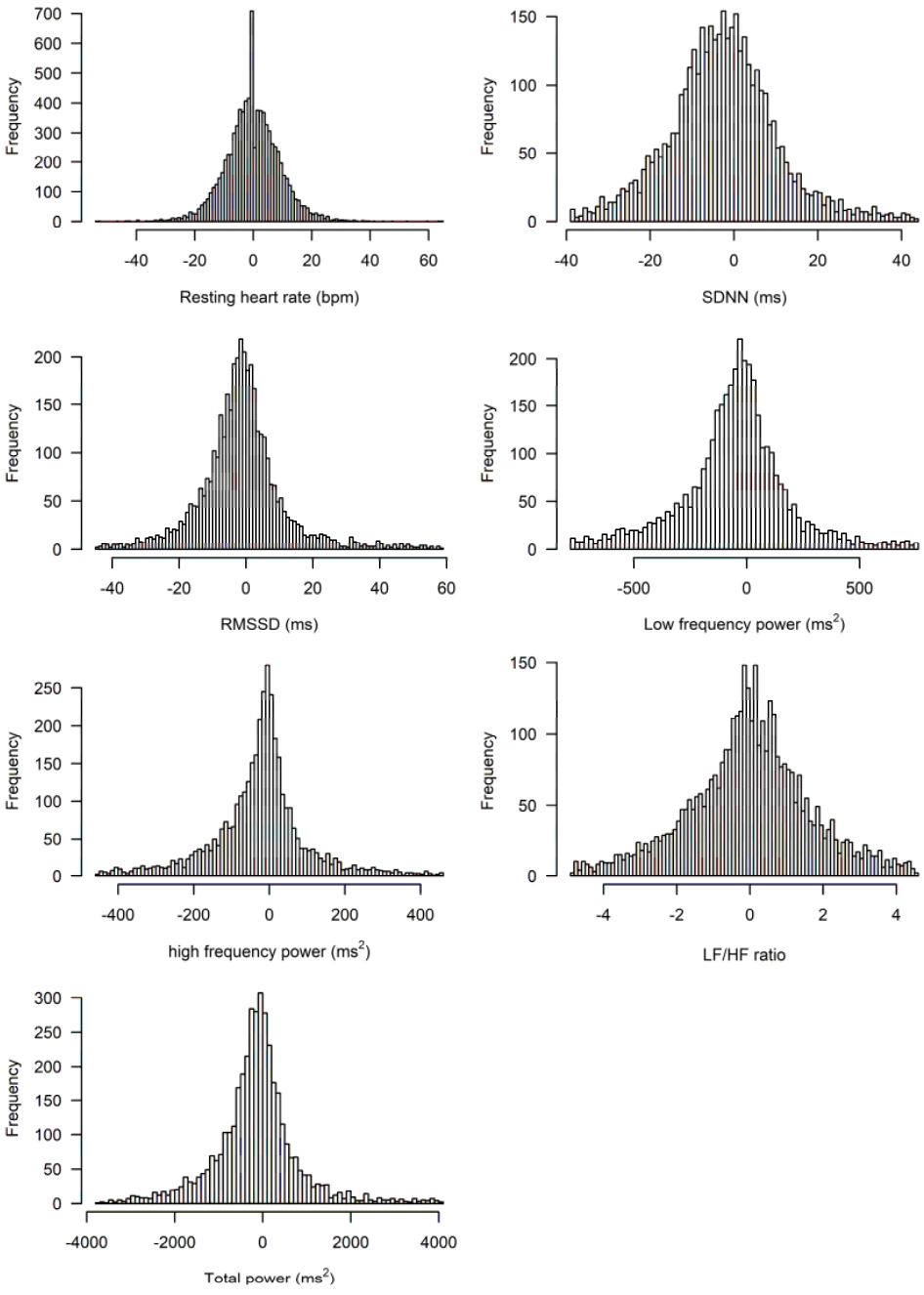
Figure 1 Association of (A) one standard deviation difference in 5-year change in resting heart rate and heart rate variability of (B) of one population standard deviation higher baseline value in heart rate or in the Log of HRV indices at baseline with incidence of a fatal- or non-fatal cardiovascular disease (CVD), all-cause mortality or the composite of the two.

Data shown for resting heart rate are only for participant with simultaneous HRV measures. Analyses adjusted for age, sex, ethnicity (and for (A) also baseline HR/HRV) (model 1: grey lines). HRV indices were further adjusted for the simultaneously measured heart rate. Additional adjustments for glycemic state, BMI, physical activity, smoking, systolic blood pressure, total cholesterol, LDL cholesterol, triglycerides, tricyclic antidepressants, diuretics and β-blockers (model 2: black lines). The x-axis is logarithmic.


A
CVD
All-cause mortality
Composite
Resting heart rate
SDNN
RMSSD
Low frequency power
High frequency power
LF/HF ratio
Total power
0.7
0.8
0.9
1.0
1.1
1.2
1.3
Incidence rate ratio
B
CVD
All-cause mortality
Composite
Resting heart rate
SDNN
RMSSD
Low frequency power
High frequency power
LF/HF ratio
Total power
0.7
0.8
0.9
1.0
1.1
1.2
1.3
Incidence rate ratio

Supplementary material

Supplementary Figure 1



Supplementary Figure 1: 5-year change in heart rate and heart rate variability

Supplementary Table 1 Rate ratios (RR) with 95% CI of a standard deviation difference in 5-years change in heart rate or HRV on the incidence of cardiovascular disease (CVD), all-cause mortality or the composite of the two

		CVD		All-cause mortality		Composite	
Baseline difference	**Model**	**RR**	**P**	**RR**	**P**	**RR**	**P**
Resting heart rate (9.4bpm)*	1	1.02 (0.84;1.25)	0.841	0.94 (0.77;1.15)	0.578	0.96 (0.83;1.11)	0.581
	2	1.03 (0.84;1.25)	0.797	0.94 (0.78;1.15)	0.559	0.96 (0.83;1.11)	0.623
SDNN (32.9 ms)	1	0.88 (0.77;1.00)	0.058	0.91 (0.76;1.07)	0.250	**0.89 (0.80;1.00)**	**0.046**
	2	0.89 (0.77;1.01)	0.076	0.90 (0.77;1.06)	0.224	0.90 (0.80;1.00)	0.053
RMSSD (47.6 ms)	1	0.90 (0.79;1.02)	0.103	0.94 (0.78;1.14)	0.511	0.91 (0.81;1.02)	0.106
	2	0.90 (0.79;1.04)	0.150	0.94 (0.78;1.14)	0.538	0.92 (0.82;1.03)	0.155
Low frequency power (5151 ms^2)	1	0.94 (0.83;1.06)	0.301	0.93 (0.81;1.07)	0.294	0.93 (0.85;1.02)	0.123
	2	0.94 (0.83;1.07)	0.371	0.94 (0.82;1.07)	0.342	0.94 (0.85;1.03)	0.172
High frequency power (3889 ms^2)	1	0.95 (0.81;1.12)	0.559	0.93 (0.79;1.08)	0.316	0.94 (0.84;1.05)	0.259
	2	0.95 (0.80;1.14)	0.604	0.92 (0.78;1.08)	0.289	0.93 (0.83;1.06)	0.272
LF/HF ratio (2.2 units)	1	1.00 (0.80;1.25)	0.997	1.01 (0.81;1.26)	0.913	0.99 (0.85;1.16)	0.941
	2	0.99 (0.80;1.23)	0.924	1.00 (0.81;1.24)	0.968	0.99 (0.85;1.15)	0.882
Total power (18707 ms^2)	1	0.93 (0.79;1.10)	0.424	0.92 (0.76;1.12)	0.420	0.93 (0.81;1.05)	0.240
	2	0.94 (0.79;1.12)	0.487	0.93 (0.76;1.13)	0.475	0.93 (0.82;1.06)	0.298

P: p-value for the test of the rate ratio being equal to unity (i.e. no effect)

*For the subset with HRV data

Supplementary Table 2 Rate ratios (RR) with 95% CI of 10-unit difference in heart rate or a doubling in HRV indices at baseline on the incidence of cardiovascular disease (CVD), all-cause mortality or the composite of the two.

		CVD		All-cause mortality		Composite	
Baseline difference	**Model**	**RR**	**P**	**RR**	**P**	**RR**	**P**
Resting heart rate (10 bpm)*	1	0.94 (0.85;1.04)	0.230	1.09 (1.00;1.2)	0.058	1.01 (0.95;1.09)	0.690
	2	0.91 (0.82;1.01)	0.077	**1.11 (1.00;1.22)**	**0.040**	1.00 (0.93;1.08)	0.925
SDNN (doubling)	1	1.02 (0.78;1.34)	0.871	0.99 (0.76;1.30)	0.953	1.01 (0.82;1.23)	0.947
	2	1.04 (0.79;1.38)	0.772	1.05 (0.80;1.38)	0.745	1.04 (0.85;1.28)	0.682
RMSSD (doubling)	1	1.09 (0.90;1.31)	0.384	0.99 (0.82;1.21)	0.934	1.03 (0.89;1.18)	0.701
	2	1.08 (0.90;1.31)	0.398	1.00 (0.83;1.22)	0.970	1.04 (0.90;1.19)	0.629
Low frequency power (doubling)	1	1.00 (0.89;1.13)	0.986	0.96 (0.85;1.07)	0.448	0.98 (0.90;1.07)	0.608
	2	1.02 (0.90;1.15)	0.787	0.99 (0.88;1.11)	0.819	1.00 (0.91;1.09)	0.990
High frequency power (doubling)	1	1.02 (0.91;1.13)	0.763	0.98 (0.88;1.10)	0.751	0.99 (0.91;1.07)	0.776
	2	1.02 (0.92;1.14)	0.677	1.00 (0.89;1.11)	0.929	1.00 (0.92;1.08)	0.982
LF/HF ratio (doubling)	1	0.96 (0.80;1.14)	0.632	0.95 (0.79;1.13)	0.539	0.98 (0.86;1.12)	0.762
	2	0.97 (0.81;1.17)	0.777	0.98 (0.82;1.18)	0.844	1.00 (0.88;1.14)	0.985
Total power (doubling)	1	1.01 (0.88;1.16)	0.910	1.01 (0.88;1.15)	0.928	1.00 (0.91;1.11)	0.929
	2	1.02 (0.89;1.17)	0.785	1.04 (0.90;1.19)	0.599	1.03 (0.93;1.14)	0.633

P: p-value for the test of the rate ratio being equal to unity (i.e. no effect). *For the subset with HRV data

Supplementary Table 3 Rate ratios (RR) with 95% CI of 10-unit difference in 5-years changes in heart rate or HRV on the incidence of cardiovascular disease (CVD), all-cause mortality or the composite of the two – **for the subset not on beta blockers!**

		CVD		All-cause mortality		Composite	
5-year change in	**Model**	**RR**	**P**	**RR**	**P**	**RR**	**P**
Resting heart rate (10 bpm)	1	1.10 (0.96;1.26)	0.188	1.02 (0.89;1.16)	0.815	1.03 (0.93;1.13)	0.610
	2	1.11 (0.97;1.28)	0.133	1.01 (0.89;1.15)	0.821	1.03 (0.93;1.14)	0.558
SDNN (10 ms)	1	0.98 (0.91;1.05)	0.518	0.97 (0.91;1.04)	0.383	0.97 (0.92;1.02)	0.266
	2	0.99 (0.92;1.06)	0.694	0.97 (0.91;1.04)	0.411	0.98 (0.93;1.03)	0.399
RMSSD (10 ms)	1	0.99 (0.94;1.05)	0.745	0.98 (0.94;1.03)	0.497	0.98 (0.95;1.02)	0.404
	2	1.00 (0.94;1.06)	0.965	0.99 (0.94;1.04)	0.580	0.99 (0.95;1.03)	0.637
Low frequency power (10 ms^2)	1	1.00 (1.00;1.00)	0.620	1.00 (1.00;1.00)	0.067	1.00 (1.00;1.00)	0.252
	2	1.00 (1.00;1.00)	0.598	1.00 (1.00;1.00)	0.129	1.00 (1.00;1.00)	0.534
High frequency power (10 ms^2)	1	1.00 (1.00;1.00)	0.836	1.00 (1.00;1.00)	0.213	1.00 (1.00;1.00)	0.396
	2	1.00 (1.00;1.00)	0.696	1.00 (1.00;1.00)	0.212	1.00 (1.00;1.00)	0.559
LF/HF ratio (10 units)	1	1.02 (0.36;2.85)	0.971	1.10 (0.39;3.10)	0.854	1.07 (0.51;2.27)	0.853
	2	1.01 (0.36;2.81)	0.986	1.16 (0.42;3.19)	0.768	1.09 (0.52;2.28)	0.814
Total power (10 ms^2)	1	1.00 (1.00;1.00)	0.739	1.00 (1.00;1.00)	0.104	1.00 (1.00;1.00)	0.278
	2	1.00 (1.00;1.00)	0.630	1.00 (1.00;1.00)	0.169	1.00 (1.00;1.00)	0.548

P: p-value for the test of the rate ratio being equal to unity (i.e. no effect).