Resting heart rate trajectories and myocardial infarction, atrial fibrillation, ischemic stroke and death in the general population: the Tromsø Study

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Abstract

Background: Resting heart rate (RHR) is an established risk factor for cardiovascular disease (CVD), but long-term individual RHR trajectories and their effect on CVD morbidity and mortality have not yet been described.

Methods: This large population-based longitudinal study included 14,208 men and women aged 20 years or older, not pregnant, and not using blood pressure medications, who attended at least two of the three Tromsø Study surveys conducted between 1986 and 2001. RHR was measured using an automated Dinamap device. Participants were followed up from 2001 to 2012 with respect to myocardial infarction (MI), atrial fibrillation, ischemic stroke, CVD death, and total death. The Proc Traj statistical procedure was used to identify RHR trajectories.

Results: Five common long-term RHR trajectories were identified: low, moderate, decreasing, increasing, and elevated. In men, an elevated RHR trajectory was independently associated with an increased risk of MI when low RHR trajectory was used as a reference (hazard ratio 1.83, 1.11-3.02). Risk of total death in men was lowest in the low RHR trajectory group and highest in the increasing and elevated RHR trajectory groups. In women, the association between RHR trajectories and MI was similar to that in men, but it was not significant.

Conclusions: Among the five long-term RHR trajectories we identified, increasing and elevated trajectories were associated with an increased risk of MI and total death in men. Our results suggest that changes in long-term individual RHR in the general population may provide additional prognostic information.

Abstract word count: 244

Keywords: heart rate, pulse, longitudinal studies, cardiovascular disease, myocardial infarction, atrial fibrillation, stroke, death

Introduction

Resting heart rate (RHR) is an easily measured, modifiable cardiovascular parameter. To date, there is a lot of evidence that single measures of RHR predict cardiovascular disease (CVD) morbidity and mortality independently of traditional risk factors in both men and women (1-9). RHR has declined remarkably over the last decades in the general population in Europe, and CVD incidence has declined in turn (10-14). However, individual changes in RHR over time and their effect on CVD morbidity and mortality in the general population are poorly described. The Paris Prospective Study 1 showed that change in 5-year RHR was an independent predictor of total mortality in healthy middle-aged men, with a decrease in RHR being favorable and an increase unfavorable (15). A large population-based cohort study from Norway showed a U-shaped association between changes in 10-year RHR and ischemic heart disease (IHD) mortality and total mortality in both men and women, suggesting that an individual decrease in RHR was not beneficial with respect to mortality (16). The Cardiovascular Health Study concluded that variation in RHR over four years was a predictor of mortality in older adults whereas trend in RHR was not (17). Neither variation nor trend in RHR over four years was associated with incident myocardial infarction (MI). Another paper based on the Cardiovascular Health Study data concluded that elevations in RHR over 6 years were associated with an increased risk of mortality (18).

The patterns of change in RHR over time vary between individuals. These individual patterns of change in long-term RHR, as well as their effect on CVD, remain unknown. This study aimed to identify groups of men and women with common RHR trajectories in the Tromsø Study from 1986 to 2001, and to determine the associations between these trajectories and the risk of incident MI, incident atrial fibrillation (AF), incident ischemic stroke (IS), CVD death, and total death during 12 years of follow-up.

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Methods

Study design and participants

The Tromsø Study is a single-center population-based longitudinal study and has been described in detail elsewhere (19). Briefly, total birth cohorts as well as random samples from the general population of Tromsø, Northern Norway were invited to participate in six surveys. Invitations and the Tromsø Study questionnaire were sent to all prospective participants by mail. Participants completed the questionnaire at home and brought it to the survey. During the survey, trained personnel reviewed the questionnaire, performed a physical examination, and collected blood according to standardized protocols. In the present report we considered the 1986-87, 1994-95, and 2001 surveys, as RHR was measured in the same way and to allow for a longer follow-up period. The lowest participation rate of the three surveys considered was 75%.

We excluded information from surveys at which an individual was pregnant and/or had missing values for any of the considered variables at that survey. We also excluded information from all surveys of individuals who reported they had ever used blood pressure medication. Finally, we excluded information from all surveys of individuals who died or emigrated before 28 August 2001, and those who attended only one of the three surveys. Following all exclusions, 14,208 men and women were included in the study sample (Figure 1); 3486 (24.5%) of them attended all of the three surveys.

Data collection

Resting heart rate and other risk factors for cardiovascular disease

Information on current pregnancy (yes, no), use of blood pressure medication (yes, no), leisure time physical activity (sedentary, moderate, active/highly active), and daily cigarette smoking (yes, no) was taken from the Tromsø Study questionnaire. Questions on leisure time physical activity were different in the 1994-95 survey and for those 70 years of age or older in the 2001 survey; therefore we regrouped these answers to correspond to the categories used in the other surveys (20).

At each of the three surveys, RHR and blood pressure were measured using the Dinamap Vital Signs Monitor 1846 (Critikon Inc., Tampa, FL, USA) – an automated, non-invasive,

microprocessor-controlled device (21). The proper cuff size was selected out of four available according to the circumference of the upper right arm (10). After being seated for 2 minutes with the cuff on, three RHR and blood pressure measurements were taken at 1-minute intervals. We used the mean of the last two RHR (in beats per minute, bpm) and systolic blood pressure (SBP, in mmHg) measurements in the analyses. Body weight and height were measured with light clothing and without shoes, and were used to calculate body mass index (BMI, kg/m^2).

Non-fasting serum levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (mmol/L) were determined by the Department of Clinical Chemistry, Department of Medical Biology, University Hospital of North Norway, Tromsø (10).

Follow-up and identification of outcomes

Follow-up began at the date of attendance of the 2001 survey for all those who attended. For those who did not attend the 2001 survey, follow-up started on 28 August 2001 (the median date of the 2001 survey). All participants were followed through 31 December 2012 for incident non-fatal or fatal MI, incident non-fatal or fatal AF, incident non-fatal or fatal IS, CVD death, and total death. All CVD events were identified by linkage to the diagnosis registry at the University Hospital of North Norway (outpatient diagnoses included) and the National Causes of Death Registry, through a broad search for the International Classification of Diseases (ICD) Revision 9 codes 410-414, 427, 428, 430-438, and 798-799; and ICD Revision 10 codes I20-I25, I46-I48, I50, I60-I69, R96, R98, and R99. The University Hospital of North Norway is the only hospital serving the community under study; the next nearest hospital is located approximately 250 km away by road (148 km by air). The National Causes of Death Registry covers individuals registered as living in Norway at the time of their death, without regard to whether they died in Norway or abroad.

An independent endpoint committee validated all the CVD events found in the linkage. The committee first sought validation in hospital medical records, after which they turned to manual searches of paper records (used until 2001), and electronic text searches of digital records to find notes on all outcomes in participants with one or more of the diagnoses mentioned above. Finally, in addition to the fatal events information from the National Causes of Death Registry and death

certificates, the committee collected relevant information from autopsy reports and records from nursing homes, ambulance services, and general practitioners. The definition and ascertainment of incident MI, AF, and IS used in the validation process has been described in detail elsewhere (22). Participants who had emigrated from Tromsø were identified through the Population Register of Norway.

Statistical analysis

All analyses were sex-specific and performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Long-term RHR trajectory groups were determined using latent class models (SAS Proc Traj) (23, 24) and the year of the survey was used as the time scale. Bayesian Information Criterion was used to assess the model fit. After testing models with different numbers of trajectory groups, we chose to use five groups. Indeed, this fit better than four groups, and increasing the number of trajectory groups led to small group sizes. Thus in our final model we had five trajectories up to quadratic order terms. The posterior predicted probability of belonging to each of the five RHR trajectory groups was then calculated for each individual, and individuals were assigned to a trajectory group based on the highest posterior probability.

Descriptive characteristics of the RHR trajectory groups are presented as means (standard deviations) and numbers (percentages). Means and percentages were adjusted for age between the surveys and the RHR trajectory groups using linear mixed models or generalized estimating equations, respectively.

Cox proportional hazard regression analysis was used to estimate associations between belonging to a certain RHR trajectory group and the risk of each investigated outcome. In the analysis of morbidity end-points, we excluded those who had had the event of interest or had moved from Tromsø before the start of follow-up; those who moved or died of other causes after the start of follow-up were censored. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated for each trajectory group, using the low RHR trajectory group as a reference. HRs were adjusted first for age alone, and then for age and other CVD risk factors: SBP, total cholesterol, HDL

cholesterol, triglycerides, BMI, leisure time physical activity, and smoking status. Smoking status was measured at the last survey attended. For the other covariates we used mean across the surveys values.

Ethical considerations

The Tromsø Study was approved by the Data Inspectorate and by the Regional Committee for Medical Research Ethics, North Norway, and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants provided written informed consent.

Results

We found five common long-term RHR trajectory groups in our study sample and named them according to their visual shape: low, moderate, decreasing, increasing, and elevated (Figure 2). Out of 6898 men in the study sample, 22.4% were in the low RHR trajectory group, 53.9% were in the moderate trajectory group, 11.0% in the decreasing trajectory group, 10.1% in the figure increasing trajectory group, and 2.7% in the elevated trajectory group. Corresponding numbers in women (n=7310) were 24.6%, 58.6%, 8.6%, 6.9%, and 1.3%, respectively. A supplementary figure demonstrates both means and individual values of RHR by the surveys and by the trajectory groups. In general, women had slightly higher RHRs than men. Over the years, mean RHR decreased to a different extent in all the RHR trajectory groups except the increasing group in both sexes and the elevated group in women.

Mean age was similar across the RHR trajectory groups in both men (Table 1) and women (Table 2). Age-adjusted mean SBP in 1986-87 was higher in the elevated RHR trajectory group in both sexes, and over the years it increased in all the groups except the decreasing RHR trajectory group in women. The largest increase in SBP was in the increasing and the elevated RHR trajectory groups. The levels of total and HDL cholesterol were more favorable in the low RHR trajectory group in both sexes, and these levels decreased during the survey period in all the groups. Triglyceride levels in 1986-87 were higher in the decreasing and elevated RHR trajectory groups, and the highest increase in triglycerides over the survey period was seen in the increasing RHR trajectory group. BMI increased over the survey period in all the RHR trajectory groups.

Men (Table 1) and women (Table 2) in the low RHR trajectory group were more physically active, and the level of leisure time physical activity decreased gradually from the low RHR to the elevated RHR trajectory group. Over the years, the level of leisure time physical activity increased in most of the trajectory groups, especially in women, although there was no clear association between RHR trajectory groups and changes in physical activity. In 1986-87 the highest proportion of smokers was observed in the decreasing RHR trajectory group and the lowest proportion in the low RHR trajectory group in both sexes. The proportion of smokers decreased over time in all the groups except

the low and the increasing RHR trajectory groups in women. It decreased the most in the decreasing RHR trajectory group.

In men, being in the moderate, decreasing, increasing, or elevated RHR trajectory groups compared to the low RHR group was a marker of a gradually increasing risk of MI (Table 3). Elevated RHR trajectory independently increased the risk of MI by 83% when compared to low RHR trajectory. The RHR trajectories had no effect on the risk of AF and IS in men. The independent risk of CVD death in men was 86% higher in the increasing RHR trajectory group compared to the low trajectory group. Adjusted HRs of total death were 1.26 (95% CI: 1.02-1.56) for the moderate, 1.37 (95% CI: 1.03-1.82) for the decreasing, 1.82 (95% CI: 1.40-2.38) for the increasing, and 2.44 (95% CI: 1.69-3.53) for the elevated trajectory groups.

In women, the age-adjusted risk of MI was 1.68 (95% CI: 1.11-2.55), 2.52 (95% CI: 1.46-4.36), and 3.33 (95% CI: 1.29-8.62) times higher in the moderate, increasing, and elevated RHR trajectory groups, respectively, compared to the low trajectory group, but these associations became insignificant after additional adjustment for other CVD risk factors (Table 3). Among women, decreasing RHR seemed to be protective for AF compared to low RHR: adjusted HR=0.31 (95% CI: 0.14-0.68). We did not observe any significant association between the RHR trajectory groups and IS, CVD death, or total death in the fully-adjusted model in women.

Discussion

Using trajectory analysis, we identified five common long-term RHR trajectories, which reflected individual RHR change over the 15-year survey period. These long-term individual RHR trajectories provided additional information to assess the risk of CVD events. We found that a steadily elevated RHR over the survey period independently increased the risk of MI in men compared to a steadily low RHR. A similar, but insignificant association was also seen in women. Low RHR trajectory was associated with a lower risk of death in men compared to other trajectories, and this was most pronounced when low RHR trajectory was compared to increasing and elevated RHR trajectories. The decreasing RHR trajectory was associated with a lower risk of AF in women.

We found three population-based studies that estimated the health effect of individual change in RHR over time. The Paris Prospective Study 1 from 2009 included 5139 healthy men aged 42 to 53 years (15). RHR change was calculated as the difference between RHR at inclusion and after 5 years, and then divided into decreased, unchanged, and increased groups. Participants were followed up for death for more than 20 years. The authors concluded that men with a decreased RHR had a 14% decreased mortality risk, whereas men with an increased RHR had a 19% increased mortality risk compared to the unchanged group. The Nord-Trøndelag County Health Study (HUNT) from Norway included both men and women aged 20 years or older without CVD (n=29,325) (16). RHR was measured twice at an interval of approximately 10 years, and the difference was calculated. Participants were followed up with respect to mortality during a mean of 12 years. The conclusion was that an increase in RHR over a 10-year period was associated with an increased risk of IHD and all-cause death, but a decrease in RHR showed no benefit.

These two studies used the difference in RHR at two time points to determine temporal changes (15, 16). However, this measure cannot provide a comprehensive picture of RHR changes over a long time period. The Paris paper clearly demonstrated the interaction effect between baseline RHR and RHR change over time: in men with a low baseline RHR the effect of RHR change during 5 years was not as strong as in men with high baseline RHR (15). In the Norwegian study the associations were adjusted for baseline RHR, but the authors did not check whether baseline RHR was an effect modifier (16). However, they showed that in a subgroup with a baseline RHR between

70 and 85 bpm, a decrease in RHR over a 10-year period was associated with a 40% lower risk of dying from IHD compared to those whose RHR remained stable. Our trajectory analysis approach allowed us to use three RHR measurements and to identify more realistic and prudent long-time patterns in RHR, taking into account both baseline level and temporal change in RHR. Furthermore, the Paris study measured RHR by the wrist palpation method (15). In the Norwegian study, RHR at baseline was measured by wrist palpation during 15 seconds, but after 10 years they switched to a Dinamap automated device (16). Indeed, palpation values may be subject to measurement error.

The Cardiovascular Health Study from USA included 1991 men and women aged 68 to 96 years, and their RHR was recorded using electrocardiography annually over a 4 years period (17). For each participant, linear regression analysis was used to estimate RHR mean value, trend in RHR (the slope of the regression line, in 2 bpm per year) and RHR variation (the standard deviation of the five residuals around the regression line, in 2 bpm). Long-term variation in RHR, but not RHR trend was independently associated with the risk of death: fully-adjusted HR=1.06 (95% CI: 1.02-1.12). The authors did not reveal independent association between any of the RHR variables and the risk of incident MI, however fully-adjusted HR for the RHR trend was 1.08 (95% CI: 0.95-1.23). Although the slope of the regression line based on the five RHR recordings is a better approximation of an individual long-term trend in RHR compared to the difference between two RHR measurements it does not provide a comprehensive picture of RHR changes over time. Effects of the RHR mean, RHR trend and RHR variation were adjusted for each other in the models, but interaction between RHR trend and the other RHR variables was not taken into account. The inconsistency with our results can also be due to differences in the study populations, shorter study period, and lack of power in the USA study.

Another paper from the above mentioned Cardiovascular Health Study used seven annual recordings of RHR, and ran Cox regression analysis with RHR as a time-varying covariate to estimate its effect on all-cause mortality (18). The authors concluded that elevations of RHR over the course of 6 years were associated with an increased risk of mortality. Although it is an accurate way to assess the association between RHR and the outcome as the most resent RHR value is consistently used for

the prognostic estimation, this method does not provide any information on RHR change over time or its effect on mortality.

RHR is a low-cost, clinical parameter that is easily and quickly measured and can be used as an important prognostic marker not only for secondary prevention in specific groups of patients, but for primary prevention in the general population as well. Elevated RHR causes chronic hemodynamic stress on the arterial wall, increases mean blood pressure, increases cardiac work and oxygen consumption, and desynchronizes ventricular muscle cells, thereby worsening coronary perfusion (25,). Elevated RHR is associated with a prothrombotic state (26). Through these possible underlying mechanisms, elevated RHR can independently increase the risk of hypertension and facilitate the progression of atherosclerosis, arrhythmias, acute cardiovascular events, and death. However, RHR can be changed, either intentionally or unintentionally (25). RHR in normal subjects is regulated by the pacemaker activity of the sinoatrial node cells, which are in turn influenced by many nonmodifiable factors, such as genetics, sex, and age, and modifiable factors like smoking, physical activity, blood pressure, and drugs (27).

Long-term RHR trajectories provide additional diagnostic, prognostic, and therapeutic information for cardiovascular and overall health. Although the trajectories are correlated with the last measured RHR, the changes in RHR address additional information, such as control of sympathetic and parasympathetic activity. Single recordings do not depict longitudinal patterns in RHR and therefore may not be a proper measure of the total exposure (28). For example, increasing and decreasing RHR trajectories in our study crossed each other over the time period. Single recordings of RHR at the cross point would place these individuals together though they have different longitudinal patterns of RHR and are at different risk of CVD morbidity and mortality. However, this study was observational, and therefore we could not draw conclusions on causality. Further studies are needed to investigate an effect of induced RHR reduction on CVD risk.

This is the first and only large population-based longitudinal study conducted on both sexes with a wide range of ages, with up to three measurements of RHR per participant over a 15-year period and 12 years of follow-up with respect to incident MI, incident AF, incident IS, CVD death

and total death. Another major strength of our study is our thorough methods of detection of MI, AF and IS cases.

We applied statistical analysis that allowed us to identify detailed RHR trajectories during the 15-year survey period. The most common way to construct categories of developmental trajectories for more than two repeated measurements so far is using assignment rules based on subjective categorization criteria. Although this method is reasonable, there are some important limitations, such as an a priori assumption of the existence of distinct developmental trajectories, and that the uncertainty about an individual's group membership cannot be quantified in the form of probabilities (24). The trajectory analysis has the capacity to identify qualitatively distinct developmental progressions and to distinguish variations due to chance from real differences across individuals. As recommended, in order to choose the number of trajectories in the final models, we used both a careful weighting of formal statistical criteria against explanatory power and usability in the analyses (24).

However, several limitations need to be mentioned. Many participants attended only two of the three surveys that could result in low robustness of latent class analysis and might have introduced some between groups bias. However, the supplementary figure demonstrates that the trajectory analysis managed well to assign participants to the trajectory groups. Moreover, a further adjustment of the risk analyses for the number of attended surveys per subject had virtually no effect on the results. In order to avoid potential bias the 2001 survey was defined as the final survey for trajectory modeling and the survey from which the follow-up period started. Thereby we lost some cases occurred between the 1994-95 and 2001 surveys among those who did not attend the 2001 survey. However, a sensitivity analysis with the follow-up started at the last survey attended showed almost identical results. Excluding participants who reported taking blood pressure medications notably reduced our sample size, which could have resulted in the loss of some cases, as hypertension is an important risk factor for MI, AF, and IS. Unfortunately, we had no detailed information on treatment, such as type of drugs interacting with RHR or doses, to properly adjust for it. We did not include diastolic blood pressure in the analysis due to strong correlation with systolic blood pressure. Due to an inconsistency, we had to modify the variable of physical activity in the 1994-95 survey, and partly

in the 2001 survey, which led to figures that were quite different from those of other surveys. In addition, it is possible that there were persons with undiagnosed MI, AF, or IS. Finally, the associations were not adjusted for heart rate variability, cardiorespiratory fitness, markers of inflammation, and diet.

Conclusion

RHR is an established independent predictor of CVD and death, but it is modifiable and can change over time. Our findings showed that men with consistently low levels of RHR had the lowest risk of MI and total death, whereas men with constantly elevated RHR had the highest risk of these events. Substantially increased RHR over the survey period increased the risk of MI and total death, but it was still lower than that in individuals with constantly elevated RHR. Men with a substantial decrease in RHR over time had a lower risk of MI and total death compared to men with increasing or elevated RHR trajectories. The direction of the association and the point estimates of relative risk for MI in women were similar to men's. The substantial decrease in RHR over time in women had protective effect on AF risk.

Author contribution

All authors contributed to the conception and/or design of the work. MLL, EBM and IN contributed to the acquisition of data for the work. ES ran the analysis for the work. All authors contributed to the interpretation of data for the work. ES drafted the manuscript. All authors critically revised the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Figure 1. Flowchart of participants, the Tromsø Study1986-2001.

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┌──────────────────────────────────────────────────────────────────────┐
│  Completed questionnaire and attended at least one of the three        │
│              Tromsø Study surveys from 1986-87 to 2001                  │
│                     n=32,708; 55,529 visits:                           │
│                The 1986-87 survey: n=20,517 visits                     │
│                The 1994-95 survey: n=26,966 visits                     │
│                  The 2001 survey: n=8046 visits                        │
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Excluded due to:

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│  Pregnancy and/or missing values                                       │
│  n=595; 2560 visits:                                                   │
│  - from the 1986-87 survey, n=414 visits                               │
│  - from the 1994-95 survey, n=857 visits                               │
│  - from the 2001 survey, n=1289 visits                                 │
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│  Reported taking blood pressure medication                             │
│  n=2807; 5595 visits:                                                  │
│  - from the 1986-87 survey, n=1631 visits                              │
│  - from the 1994-95 survey, n=2624 visits                              │
│  - from the 2001 survey, n=1340 visits                                 │
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│  Death or emigration from Norway before 28 August 2001                 │
│  n=1698; 2342 visits:                                                  │
│  - from the 1986-87 survey, n=1087 visits                              │
│  - from the 1994-95 survey, n=1255 visits                              │
│  - from the 2001 survey, n=0 visits                                    │
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│  Attending only one of the three surveys                               │
│  n=13,130                                                              │
│  - from the 1986-87 survey, n=4248                                     │
│  - from the 1994-95 survey, n=8158                                     │
│  - from the 2001 survey, n=724                                         │
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┌──────────────────────────────────────────────────────────────────────┐
│                       Data used in analysis                            │
│                     n=14,208; 31,902 visits:                           │
│                The 1986-87 survey: n=13,137 visits                     │
│                The 1994-95 survey: n=14,072 visits                     │
│                  The 2001 survey: n=4693 visits                        │
└──────────────────────────────────────────────────────────────────────┘
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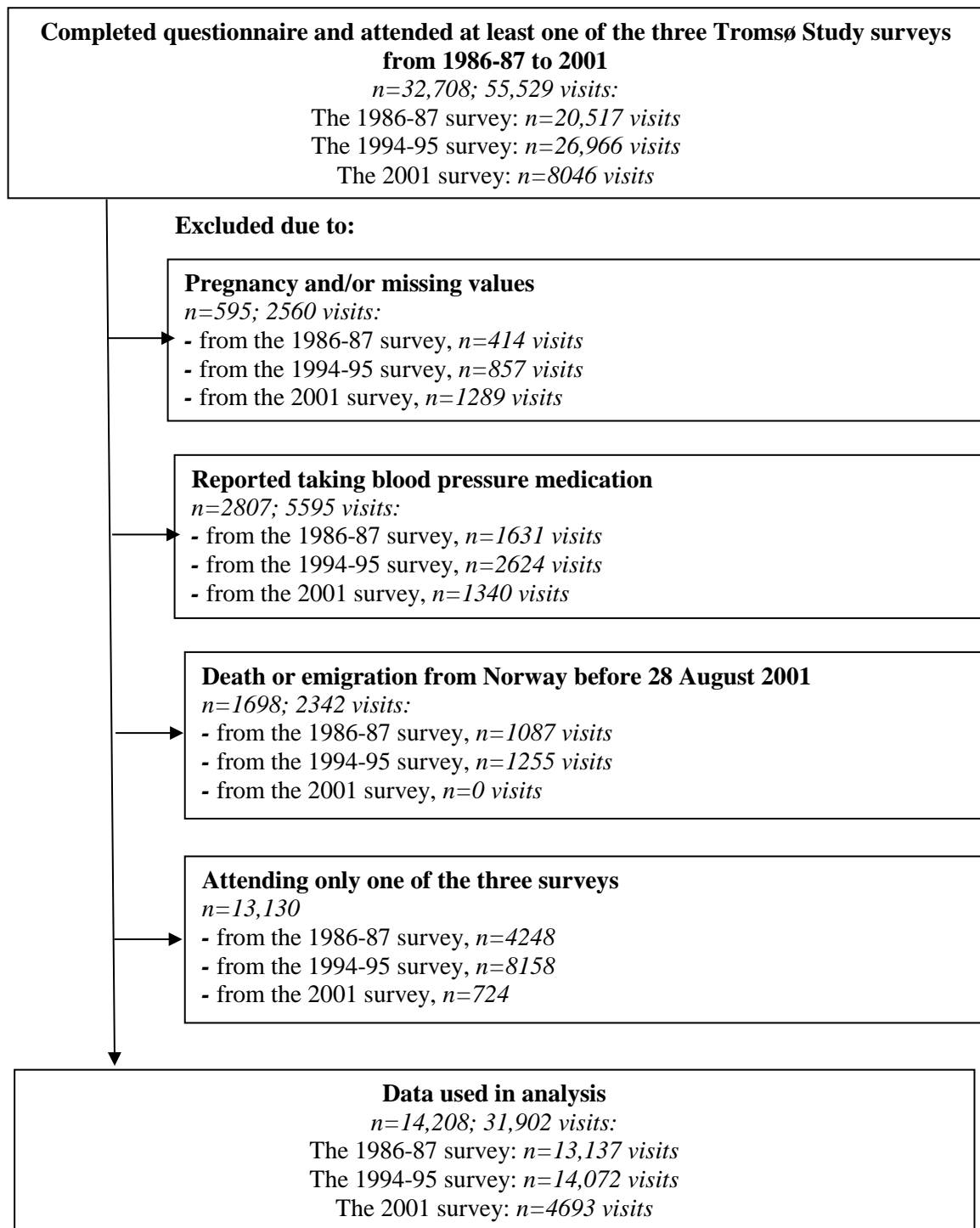
Figure 2. Resting heart rate trajectories in men and women, the Tromsø Study, 1986-2001.

Sex-specific means and 95% confidence intervals of resting heart rate (beats per minute, bpm) presented according the three Tromsø Study surveys and the five resting heart rate trajectory groups. Resting heart rate trajectory groups were determined using latent class models (SAS Proc Traj).
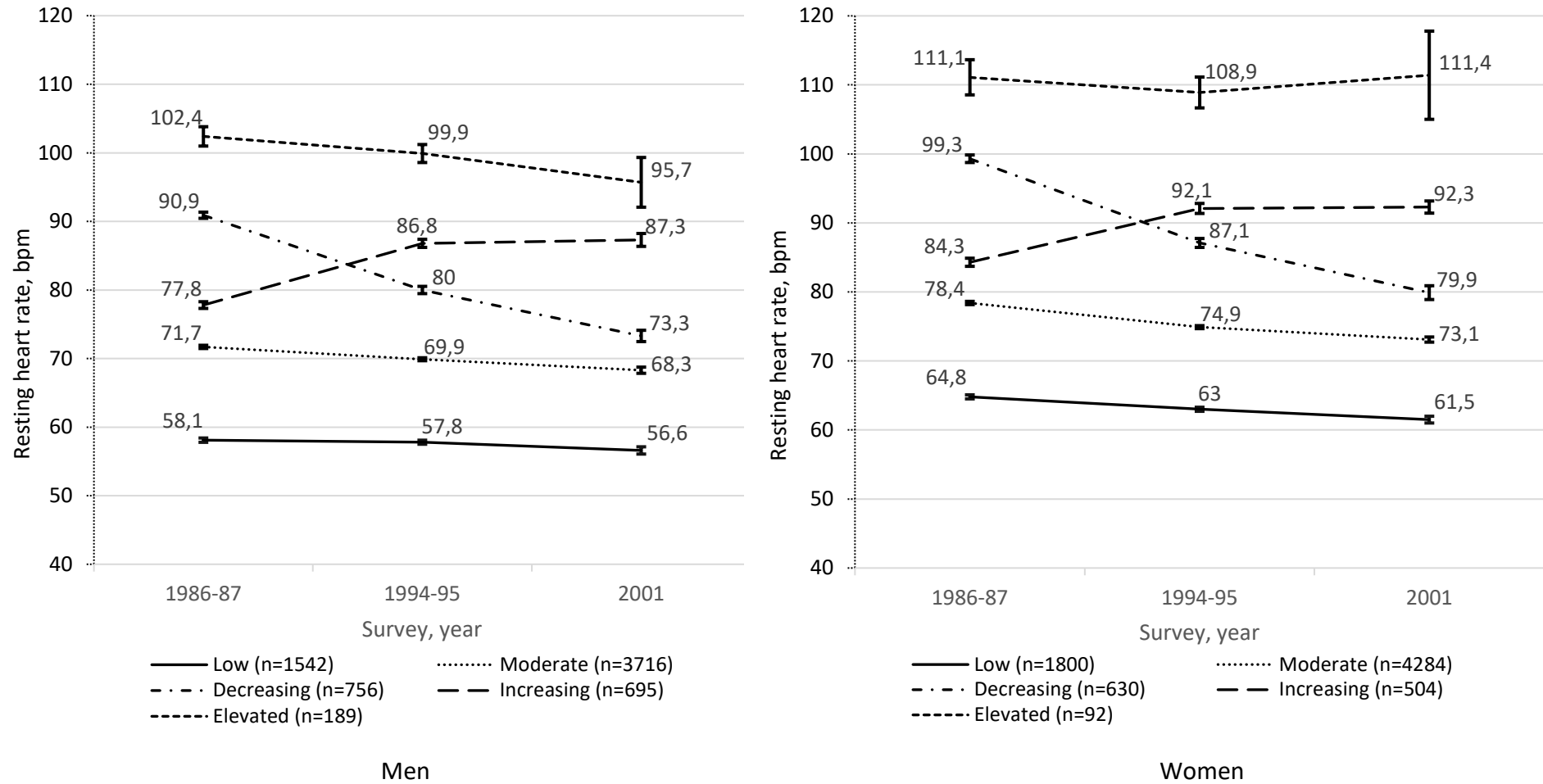
Table 1. Descriptive characteristics of RHR trajectory groups in men, the Tromsø Study, 1986-2001.[a]

	RHR trajectory groups					
	Low	Moderate	Decreasing	Increasing	Elevated	P value
	n=1542	n=3716	n=756	n=695	n=189	
N, 1986-87	1443	3526	723	641	180	
N, 1994-95	1532	3681	750	683	188	
N, 2001	481	1073	204	257	53	
Age, years						
1986-87	38.2 (10.1)	37.6 (10.1)	37.9 (10.3)	38.9 (9.9)	39.4 (10.8)	0.004
1994-95	46.7 (11.0)	45.8 (10.6)	45.9 (10.6)	47.6 (10.7)	47.7 (11.1)	<0.001
2001	60.8 (12.1)	59.2 (12.0)	58.7 (11.6)	59.7 (11.4)	62.0 (10.4)	0.051
RHR, bpm						
1986-87	58.1 (6.0)	71.6 (7.0)	90.9 (6.2)	77.8 (6.2)	102.3 (9.7)	<0.001
1994-95	57.8 (5.9)	69.9 (6.7)	80.0 (7.5)	86.8 (7.8)	100.0 (9.2)	<0.001
2001	56.8 (5.8)	68.4 (7.7)	73.5 (6.0)	87.3 (7.7)	95.9 (13.5)	<0.001
Systolic blood pressure, mmHg						
1986-87	130.2 (11.5)	131.2 (11.6)	136.0 (12.7)	133.5 (12.8)	142.0 (16.3)	<0.001

1994-95	131.9 (13.6)	133.5 (13.7)	138.2 (15.5)	139.0 (16.2)	146.0 (18.6)	<0.001
2001	131.5 (17.3)	132.9 (17.7)	138.6 (18.0)	140.5 (21.4)	146.4 (20.2)	<0.001
Total cholesterol, mmol/L					
1986-87	5.79 (1.18)	6.00 (1.23)	6.22 (1.23)	6.15 (1.12)	6.23 (1.12)	<0.001
1994-95	5.83 (1.15)	6.05 (1.18)	6.23 (1.22)	6.26 (1.18)	6.24 (1.12)	<0.001
2001	5.37 (1.01)	5.58 (1.10)	5.74 (1.16)	5.86 (1.05)	5.45 (1.13)	<0.001
HDL cholesterol, mmol/L					
1986-87	1.43 (0.34)	1.39 (0.32)	1.36 (0.34)	1.35 (0.32)	1.36 (0.38)	<0.001
1994-95	1.39 (0.35)	1.36 (0.35)	1.33 (0.35)	1.32 (0.38)	1.34 (0.35)	<0.001
2001	1.35 (0.37)	1.29 (0.36)	1.27 (0.35)	1.26 (0.38)	1.28 (0.34)	<0.001
Triglycerides, mmol/L					
1986-87	1.41 (0.76)	1.58 (0.92)	1.82 (1.14)	1.66 (0.98)	1.79 (1.05)	<0.001
1994-95	1.56 (0.96)	1.75 (1.10)	1.93 (1.27)	2.09 (1.35)	1.97 (1.31)	<0.001
2001	1.44 (0.81)	1.65 (1.01)	1.79 (1.09)	1.93 (1.20)	1.70 (1.43)	<0.001
BMI, kg/m^2					
1986-87	24.6 (2.4)	24.7 (2.9)	25.0 (3.3)	25.3 (3.1)	24.9 (3.5)	<0.001
1994-95	25.2 (2.7)	25.4 (3.1)	25.7 (3.5)	26.2 (3.6)	25.7 (3.8)	<0.001

2001	25.5 (3.0)	25.9 (3.4)	26.1 (3.5)	26.8 (3.9)	25.1 (3.8)	<0.001
Physical activity, %						
1986-87:						<0.001
- sedentary	202 (13.5)	764 (21.0)	192 (25.7)	172 (26.3)	54 (29.7)	
- moderate	583 (41.2)	1807 (52.1)	394 (55.4)	331 (52.3)	102 (57.2)	
- active or highly active	658 (45.3)	955 (26.7)	137 (18.8)	138 (21.3)	24 (13.2)	
1994-95:						<0.001
- sedentary	64 (4.3)	276 (7.6)	72 (9.7)	69 (10.3)	21 (11.4)	
- moderate	540 (34.9)	1550 (41.8)	317 (42.0)	312 (45.1)	92 (48.4)	
- active or highly active	928 (60.8)	1855 (50.6)	361 (48.3)	302 (44.5)	75 (40.1)	
2001:						<0.001
- sedentary	53 (11.9)	207 (21.2)	40 (22.5)	61 (26.2)	10 (20.6)	
- moderate	248 (48.7)	561 (49.8)	121 (56.5)	141 (52.1)	36 (65.3)	
- active or highly active	180 (38.6)	305 (28.8)	43 (21.6)	55 (22.1)	7 (13.9)	
Smoking status, %						
1986-87	374 (25.1)	1662 (45.8)	452 (61.3)	337 (50.5)	110 (60.0)	<0.001
1994-95	328 (21.6)	1463 (40.1)	391 (52.5)	317 (46.7)	95 (51.3)	<0.001

2001	80 (18.4)	345 (34.8)	84 (47.7)	101 (43.9)	26 (51.9)	<0.001

RHR: resting heart rate, bpm: beats per minute, HDL: high-density lipoprotein, BMI: body mass index.

[a]Values are mean (standard deviation) or number (%); the means (except age) and percentages are adjusted for age between the surveys and trajectory groups

using linear mixed models or generalized estimating equations, respectively.

Table 2. Descriptive characteristics of RHR trajectory groups in women, the Tromsø Study, 1986-2001.[a]

	RHR trajectory group					
	Low	Moderate	Decreasing	Increasing	Elevated	P value
	n=*1800*	n=*4284*	n=*630*	n=*504*	n=*92*	
N, 1986-87	1646	3867	598	432	81	
N, 1994-95	1779	4245	624	498	92	
N, 2001	654	1511	199	235	26	
Age at baseline, years						
1986-87	37.1 (9.1)	36.6 (9.2)	36.2 (9.3)	37.7 (9.6)	38.4 (9.7)	0.013
1994-95	45.7 (10.2)	45.6 (10.6)	44.7 (10.0)	47.6 (11.4)	47.4 (11.1)	<0.001
2001	58.8 (11.0)	58.9 (11.7)	57.1 (11.0)	60.1 (12.0)	59.7 (13.3)	0.125
RHR, bpm						
1986-87	64.8 (6.1)	78.3 (7.5)	99.2 (6.8)	84.3 (6.3)	111.1 (11.7)	<0.001
1994-95	63.0 (6.0)	74.9 (7.0)	87.1 (8.1)	92.1 (8.3)	108.9 (10.9)	<0.001
2001	61.6 (6.5)	73.3 (7.3)	80.0 (7.2)	92.5 (6.8)	111.6 (16.6)	<0.001
Systolic blood pressure, mmHg						
1986-87	120.8 (10.8)	124.2 (11.7)	132.7 (14.6)	127.5 (14.7)	143.3 (18.1)	<0.001

1994-95	122.5 (14.9)	126.2 (15.8)	133.0 (18.0)	133.3 (18.2)	150.7 (23.6)	<0.001
2001	123.4 (21.8)	126.9 (21.7)	132.1 (20.1)	133.0 (22.9)	151.9 (23.3)	<0.001
Total cholesterol, mmol/L						
1986-87	5.83 (1.15)	5.99 (1.20)	6.20 (1.23)	6.10 (1.20)	6.46 (1.37)	<0.001
1994-95	5.75 (1.25)	5.93 (1.29)	6.22 (1.36)	6.06 (1.31)	6.28 (1.29)	<0.001
2001	5.31 (1.14)	5.49 (1.21)	5.63 (1.15)	5.55 (1.20)	5.55 (1.26)	<0.001
HDL cholesterol, mmol/L						
1986-87	1.72 (0.37)	1.68 (0.37)	1.67 (0.36)	1.67 (0.38)	1.70 (0.34)	<0.001
1994-95	1.69 (0.40)	1.63 (0.39)	1.65 (0.42)	1.61 (0.43)	1.68 (0.38)	<0.001
2001	1.54 (0.40)	1.50 (0.40)	1.51 (0.42)	1.44 (0.42)	1.54 (0.38)	<0.001
Triglycerides, mmol/L						
1986-87	1.05 (0.48)	1.17 (0.60)	1.27 (0.66)	1.21 (0.55)	1.25 (0.55)	<0.001
1994-95	1.12 (0.65)	1.27 (0.79)	1.35 (0.81)	1.43 (0.88)	1.31 (0.71)	<0.001
2001	1.14 (0.65)	1.27 (0.75)	1.30 (0.66)	1.44 (0.80)	1.41 (1.09)	<0.001
BMI, kg/m^2						
1986-87	23.4 (2.9)	23.4 (3.2)	23.4 (3.8)	23.9 (3.8)	23.4 (4.2)	0.032
1994-95	24.2 (3.5)	24.4 (3.8)	24.3 (4.4)	25.0 (5.0)	24.5 (4.5)	<0.001

2001	24.7 (4.0)	25.0 (4.2)	25.2 (4.7)	25.6 (5.3)	25.4 (4.9)	0.005
Physical activity, %						
1986-87:						<0.001
- sedentary	296 (18.3)	937 (24.6)	146 (24.7)	126 (29.5)	23 (28.7)	
- moderate	1095 (65.9)	2,579 (66.1)	416 (69.0)	285 (65.2)	56 (69.0)	
- active or highly active	255 (15.7)	351 (9.3)	36 (6.3)	21 (5.1)	2 (2.4)	
1994-95:						<0.001
- sedentary	105 (5.9)	301 (7.1)	44 (7.0)	49 (9.8)	8 (8.6)	
- moderate	708 (39.9)	1992 (47.0)	298 (47.8)	231 (46.6)	36 (39.3)	
- active or highly active	966 (54.2)	1952 (46.0)	282 (45.2)	218 (43.8)	48 (52.1)	
2001:						<0.001
- sedentary	85 (12.5)	276 (18.2)	38 (19.1)	63 (26.0)	4 (13.4)	
- moderate	438 (68.0)	974 (64.8)	140 (70.4)	141 (61.1)	20 (77.8)	
- active or highly active	131 (20.0)	261 (17.0)	21 (10.1)	31 (13.0)	2 (8.8)	
Smoking status, %						
1986-87	564 (30.5)	1903 (44.4)	337 (50.9)	225 (48.1)	42 (44.4)	<0.001
1994-95	527 (30.3)	1793 (43.0)	313 (50.6)	243 (50.8)	37 (41.8)	<0.001

| 2001 | 157 (30.9) | 468 (40.9) | 72 (45.8) | 93 (50.9) | 6 (42.5) | <0.001 |

RHR: resting heart rate, bpm: beats per minute, HDL: high-density lipoprotein, BMI: body mass index.

[a]Values are mean (standard deviation) or number (%); the means (except age) and percentages are adjusted for age between the surveys and trajectory groups

using linear mixed models or generalized estimating equations, respectively.

Table 3. Associations of RHR trajectory group with myocardial infarction, atrial fibrillation, ischemic stroke, cardiovascular death, and total death, the Tromsø Study, 1986-2001.

	Men			Women		
	Cases (%)	HR (95% CI)[a]	HR (95% CI)[b]	Cases (%)	HR (95% CI)[a]	HR (95% CI)[b]
Myocardial infarction		406/6351			185/6903	
Low	68 (4.8)	1.00	1.00	28 (1.7)	1.00	1.00
Moderate	206 (6.0)	1.37 (1.04-1.81)	1.15 (0.87-1.52)	114 (2.8)	1.68 (1.11-2.55)	1.27 (0.84-1.93)
Decreasing	52 (7.5)	1.74 (1.21-2.50)	1.12 (0.77-1.63)	14 (2.3)	1.57 (0.83-2.98)	0.95 (0.49-1.83)
Increasing	58 (9.2)	2.00 (1.41-2.84)	1.36 (0.95-1.95)	24 (5.0)	2.52 (1.46-4.36)	1.50 (0.86-2.61)
Elevated	22 (12.5)	2.90 (1.80-4.70)	1.83 (1.11-3.02)	5 (5.7)	3.33 (1.29-8.62)	1.79 (0.67-4.77)
Atrial fibrillation		439/6462			225/6904	
Low	118 (8.2)	1.00	1.00	54 (3.2)	1.00	1.00
Moderate	222 (6.3)	0.89 (0.71-1.11)	0.86 (0.69-1.08)	135 (3.3)	0.99 (0.72-1.36)	0.89 (0.65-1.22)
Decreasing	45 (6.4)	0.92 (0.66-1.30)	0.87 (0.61-1.23)	7 (1.2)	0.40 (0.18-0.87)	0.31 (0.14-0.68)
Increasing	46 (7.3)	0.94 (0.67-1.33)	0.87 (0.61-1.23)	25 (5.3)	1.30 (0.81-2.10)	1.04 (0.64-1.68)
Elevated	8 (4.7)	0.67 (0.33-1.36)	0.61 (0.30-1.27)	4 (4.6)	1.55 (0.56-4.29)	0.84 (0.29-2.41)
Ischemic stroke		231/6513			137/6936	

Trajectory	N (%)	HR (95% CI)	HR (95% CI)	N (%)	HR (95% CI)	HR (95% CI)
Low	54 (3.7)	1.00	1.00	26 (1.5)	1.00	1.00
Moderate	112 (3.2)	0.99 (0.72-1.37)	0.82 (0.59-1.15)	80 (2.0)	1.27 (0.82-1.98)	1.09 (0.70-1.71)
Decreasing	34 (4.8)	1.54 (1.00-2.37)	1.03 (0.66-1.61)	8 (1.3)	0.96 (0.43-2.12)	0.68 (0.30-1.53)
Increasing	23 (3.6)	1.03 (0.63-1.68)	0.70 (0.42-1.15)	20 (4.1)	2.24 (1.25-4.03)	1.69 (0.93-3.06)
Elevated	8 (4.5)	1.44 (0.69-3.03)	0.82 (0.38-1.76)	3 (3.4)	2.15 (0.65-7.10)	1.13 (0.33-3.92)
CVD death		179/6898			98/7310	
Low	28 (1.8)	1.00	1.00	14 (0.8)	1.00	1.00
Moderate	84 (2.3)	1.43 (0.93-2.20)	1.20 (0.78-1.85)	63 (1.5)	1.76 (0.98-3.14)	1.46 (0.81-2.62)
Decreasing	21 (2.8)	1.81 (1.03-3.19)	1.17 (0.65-2.09)	9 (1.4)	2.35 (1.01-5.43)	1.55 (0.66-3.64)
Increasing	34 (4.9)	2.67 (1.62-4.41)	1.86 (1.11-3.11)	10 (2.0)	1.67 (0.74-3.77)	1.16 (0.51-2.65)
Elevated	12 (6.4)	3.67 (1.87-7.23)	1.94 (0.95-3.96)	2 (2.2)	2.07 (0.47-9.10)	0.96 (0.21-4.40)
Total death		707/6898			472/7310	
Low	118 (7.7)	1.00	1.00	98 (5.4)	1.00	1.00
Moderate	349 (9.4)	1.47 (1.19-1.81)	1.26 (1.02-1.56)	273 (6.4)	1.14 (0.91-1.44)	1.01 (0.80-1.27)
Decreasing	86 (11.4)	1.81 (1.37-2.39)	1.37 (1.03-1.82)	34 (5.4)	1.14 (0.77-1.68)	0.87 (0.58-1.29)
Increasing	112 (16.1)	2.33 (1.80-3.02)	1.82 (1.40-2.38)	58 (11.5)	1.66 (1.20-2.30)	1.31 (0.94-1.82)
Elevated	42 (22.2)	3.54 (2.49-5.03)	2.44 (1.69-3.53)	9 (9.8)	1.72 (0.87-3.41)	1.17 (0.58-2.35)

RHR: resting heart rate, HR: hazard ratio, CI: confidence interval, CVD: cardiovascular disease.

[a]Adjusted for age. [b]Adjusted for age, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index and

physical activity, and smoking at last attended survey.