Temporal Changes in Resting Heart Rate and Deaths From Ischemic Heart Disease

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Context Resting heart rate (RHR) has long been recognized as an independent predictor of cardiovascular risk. However, whether temporal changes in RHR influence the risk of death from ischemic heart disease (IHD) in the general population is not known.

Objective To assess the association of long-term longitudinal changes in RHR with the risk of dying from IHD.

Design, Settings, and Participants A prospective cohort study of 13 499 men and 15 826 women without known cardiovascular disease in Norway. Resting heart rate was measured on 2 occasions around 10 years apart in the Nord-Trøndelag County Health Study. The second RHR measurement was obtained between August 1995 and June 1997, with subsequent mortality follow-up until December 31, 2008. A total of 60 participants were lost to follow-up, all due to emigration from Norway. Using Cox regression analyses, adjusted hazard ratios (AHRs) were estimated of death from IHD related to changes in RHR over time. In a corresponding analysis, death from all causes also was assessed.

Results During a mean (SD) of 12 (2) years of follow-up, 3038 people died, and 388 deaths were caused by IHD. An increase in RHR was associated with increased risk of death from IHD. Compared with participants with a RHR of less than 70 beats/min at both measurements (8.2 deaths/10 000 person-years), the AHR was 1.9 (95% CI, 1.0-3.6) for participants with a RHR of less than 70 beats/min at the first measurement but greater than 85 beats/min at the second measurement (17.2 deaths/10 000 person-years). For participants with RHRs between 70 and 85 beats/min at the first measurement and greater than 85 beats/min at the second measurement (17.4 deaths/10 000 person-years), the AHR was 1.8 (95% CI, 1.2-2.8). The association of change in RHR with IHD mortality was not linear (P=.003 for quadratic trend), suggesting that a decrease in RHR showed no general mortality benefit. Excluding the first 3 years of follow-up did not substantially alter the findings. The associations for total mortality were similar but generally weaker than those observed for IHD mortality.

Conclusion Among men and women without known cardiovascular disease, an increase in RHR over a 10-year period was associated with increased risk of death from IHD and also for all-cause mortality.

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EPIDEMIOLOGICAL EVIDENCE SUGgests that a high resting heart rate (RHR) is associated with increased cardiovascular morbidity and mortality in the general population, independent of conventional risk factors.[1-3] An elevated RHR also has been associated with poorer prognosis within subgroups of patients with cardiovascular disease.[4-6]

Resting heart rate is a modifiable factor that may change over time in response to the interaction of genes and environmental factors,[2,7] physical activity,[8] as well as clinical conditions, and medical treatment.[9-11] Few studies have assessed the associations of temporal changes in RHR with mortality.[12-15] The findings suggest that an increase in RHR over time may be associated with an increased risk of death from all causes.[13] In studies of patient groups with cardiovascular disease, an increase in RHR has been associated with increased case fatality.[12,14,15] However, the association of longitudinal changes in RHR with the risk of ischemic heart disease (IHD) has not been assessed in population studies.

Therefore, the aim of this study was to prospectively examine the association of longitudinal changes in RHR

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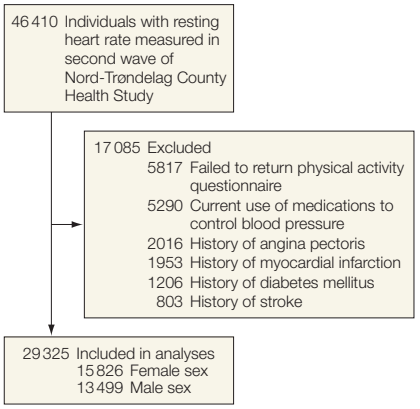
Figure 1. Flow of Patients in Study Cohort



with the risk of deaths from IHD in a large population-based cohort of apparently healthy men and women.

METHODS

Study Population

We followed up participants from the second wave of the Nord-Trøndelag County Health Study (HUNT-2) in which the entire adult population aged 20 years or older was invited to participate between August 1995 and June 1997. Of the 94 187 invited individuals, 65 442 participated in the study, filled out a questionnaire, and attended a clinical examination. All individuals provided written informed consent before volunteering to participate in the HUNT studies. Details about the HUNT study have been described elsewhere.[16] To be eligible for the present study, it was required that participants had also participated in the first wave of the HUNT Study (HUNT-1). The regional committee for ethics in medical research approved this study.

Resting Heart Rate

A total of 46 410 eligible individuals had RHR measured in HUNT-2, and also had RHR measured approximately 10 years earlier as part of HUNT-1, which was conducted from 1984 through 1986. As in HUNT-2, the total adult population aged 20 years or older was invited to participate in HUNT-1; among 85 100 eligible individuals, 75 043 participated. The participants of both HUNT-1 and HUNT-2 (n = 46 410) were compared with those who only participated in HUNT-1 (n = 28 507) (eTable 1 at http://www.jama.com). On average, the latter group had somewhat higher RHR compared with those who participated in both HUNT-1 and HUNT-2.

To assess longitudinal changes in RHR, we calculated the difference between mean RHR measured in HUNT-2 and that measured in HUNT-1. In HUNT-1, the RHR was measured by palpating the radial pulse over a period of 15 seconds with a stopwatch after at least 4 minutes of seated rest. If the pulse was irregular or difficult to count, the test was extended to 30 seconds, if necessary, with the aid of a stethoscope placed over the heart. In HUNT-2, the RHR was measured in parallel to the measurement of blood pressure (Critikon Dinamap 845XT, GE Medical Systems). The Dinamap was started after the participant had been seated for 2 minutes, with the arm resting on a table. Resting heart rate and blood pressure were measured automatically 3 times at 1-minute intervals. For the analysis, the mean of the second and third measurements was used. Trained nurses conducted the RHR measurements in both HUNT-1 and HUNT-2.

Follow-up and Ascertainment of Outcomes

The primary end point was death caused by IHD (*International Classification of Diseases, Ninth Revision*: 410-414; *International Statistical Classification of Diseases, Tenth Revision*: I20-I25); in addition, we assessed deaths from all causes. Our study had a virtually complete follow-up due to the unique 11-digit Norwegian person identification number that allows accurate matching to the National Cause of Death Register, and also because individual registration in population registers is mandatory in Norway. A total of 60 participants emigrated from Norway after participating in HUNT-2 until the end of follow-up on December 31, 2008; in the analyses, these participants were censored at the time of emigration.

Among participants who participated in both HUNT-1 and HUNT-2, we excluded those who reported a history of heart disease (myocardial infarction, angina pectoris, stroke, regular use of blood pressure medication, or prevalent diabetes mellitus). Thus, a total of 11 268 participants with these conditions were excluded from the analyses. In addition, 5817 participants were excluded because they failed to return the questionnaire about physical activity. Therefore, 29 325 individuals were included in the analyses of this study (FIGURE 1). We compared the 29 325 participants who were included with the 17 085 participants who were excluded. As expected, the excluded participants were older and had worse cardiovascular risk profiles than those who were included in the study (eTable 2).

The mortality follow-up of the HUNT cohort was approved by the regional committee for medical research ethics, the Norwegian Data Inspectorate, and by the National Directorate of Health. The study is in conformity with Norwegian laws and the Helsinki declaration.

Clinical Information

The clinical examination conducted by trained nurses included standardized measurements of body height and weight. Height and weight were recorded with participants wearing light clothes without shoes. Height was measured to the nearest 1 cm and weight to the nearest 0.5 kg. Body mass index was calculated as weight in kilograms divided by height in meters squared.

Information on recreational physical activity, smoking habits, alcohol consumption, family history of IHD, occupational status, and attained education was collected from a self-administered questionnaire. Participants also extensively assessed and reported their medical history

regarding common chronic somatic disorders.

Participants were divided into 4 categories of physical activity level (no activity, low, moderate, or high) based on their responses to the questions about hard and light physical activity during an ordinary week, with 4 response options for each intensity (none, <1 hour, 1-2 hours, or ≥3 hours). The questions about hard and light physical activity were not mutually exclusive, and the data allowed us to construct a physical activity index described elsewhere.[17] The physical activity questionnaire has been found to be valid,[18] and the physical activity index has been shown to be associated with mortality in a general population and among people with the metabolic syndrome.[17] We classified the participants into 3 categories of smoking habits (never, former, or current smokers) and 3 levels of education attainment (≤9 years, 10-12 years, or ≥13 years).

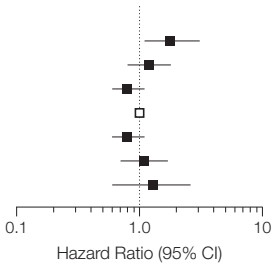
The participants were asked about their usual intake of wine, beer, and spirits, indicated by their usual number of drinks over a 2-week period. We categorized participants into 4 groups according to their alcohol consumption over a 2-week period (abstainers, 0 to ≤7 drinks, >7 to ≤14 drinks, or >14 drinks). Occupational status was divided in 5 categories: unskilled manual; skilled manual or clerical; professional, academic, or manager; self-employed, farmer, or fisherman; or retired, part-time, or not otherwise classified. Family history of IHD was defined as myocardial infarction in a first-degree relative (father, mother, siblings, or children) before the age of 60 years.

Laboratory Measurements

Nonfasting serum concentrations of total cholesterol and high-density lipoprotein cholesterol were analyzed by an enzymatic colorimetric cholesterol esterase method applying reagents from Boehringer Mannheim.

Figure 2. Death From Ischemic Heart Disease by Changes in Resting Heart Rate (RHR)

Change in RHR, beats/min	No. of Participants	IHD Deaths	Rate[a]	Hazard Ratio (95% CI)[b]
>25	759	20	22.6	1.80 (1.10-3.10)
16 to 25	1920	32	14.1	1.20 (0.80-1.80)
6 to 15	5907	68	9.6	0.80 (0.60-1.10)
−5 to 5	10694	137	10.7	1 [Reference]
−6 to −15	7251	89	10.3	0.80 (0.60-1.10)
−16 to −25	2230	33	12.4	1.10 (0.70-1.70)
<−25	564	9	13.4	1.30 (0.60-2.60)



The data markers indicate the hazard ratios and the error bars indicate the 95% confidence intervals. [a]Deaths/10 000 person-years. [b]Adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared; <18.5, 18.5-24.9, 25.0-29.9, or ≥30), physical activity level (high, medium, low, or inactive), smoking status (never, current, former, or unknown), systolic blood pressure (<120, 120-139, 140-159, or ≥160 mm Hg), family history of acute myocardial infarction, alcoholic drink consumption over a 2-week period (abstainers, 0-≤7, >7-≤14, or >14), occupational status (unskilled manual worker, skilled manual, or clerical worker; professional, academics, or managers; self-employed, farmer, or fisherman; or retired, part-time workers, or not otherwise classified), education (<10, 10-12, or ≥13 years), and levels of total serum cholesterol and high-density lipoprotein cholesterol.

Statistical Analysis

Descriptive data are presented as mean (standard deviation), and baseline characteristics of participants were compared using linear regression analysis for continuous variables and χ^2 tests for categorical variables. The RHR measurements both in HUNT-2 and in HUNT-1 (10 years before) were divided into 3 categories (<70 beats/min, 70-85 beats/min, or >85 beats/min). The choice of these cut points was made a priori based on identical cut points in other studies of RHR and cardiovascular mortality.[4,9,19]

Cox regression analyses were used to assess whether changes in RHR from HUNT-1 to HUNT-2 were associated with subsequent risk of dying from IHD. Precision of the estimates was assessed by 95% confidence intervals. We tested the proportionality of hazards by evaluating interaction with time and log time and found evidence for nonproportional hazards by sex both in age-adjusted and in multivariable-adjusted models. Therefore, we used stratified Cox regression conditioning on sex in the analyses, but modeled no time-dependent effects. The basic models were age-adjusted and further adjustments were made for the following potentially confounding factors: body mass index (<18.5, 18.5-24.9, 25.0-29.9, or ≥30.0), systolic blood pressure (<120, 120-139, 140-159, or ≥160 mm Hg), smoking status, physical activity level, alcohol consumption, education, occupational status, family history of IHD, and levels of total serum cholesterol and high-density lipoprotein cholesterol.

We conducted several stratified analyses to assess whether the association of change in RHR with IHD could be modified by other factors. We investigated the potential effect modification by sex, age (dichotomized at the age of 70 years), body mass index (dichotomized at 25), systolic blood pressure (dichotomized at 140 mm Hg), smoking status (current vs not current smoking) and physical activity (sedentary vs any activity).

We also used RHR as a continuous variable and included the squared value of RHR to assess nonlinear trend. To allow visual assessment of the trend, we present hazard ratios in FIGURE 2 for the following categories of change in RHR: (1) a decrease of greater than 25 beats/min; (2) a decrease between 15 and 25 beats/min; (3) a decrease between 5 and 15 beats/min; (4) a change from −5 to 5 beats/min (reference); (5) an increase between 5 and 15 beats/min; (6) an increase between 15 and 25 beats/min; and (7) an increase of greater than 25 beats/min.

We also performed sensitivity analyses to assess the robustness of our findings. For example, the association between change in RHR and IHD mortality could be influenced by unknown preclinical disease. To take this possibility into account, we conducted a separate analysis where the first 3 years of follow-up were excluded. In another sensitivity analysis, we adjusted for the presence of common chronic disorders, such as asthma, goiter, hypothyroidism, hyperthyroidism, fibromyalgia, rheumatoid arthritis, ankylosing spondylitis, cancer, epilepsy, or osteoporosis in addition to the factors that were already included in the multivariable models. In a third sensitivity analysis, we adjusted for RHR measured in HUNT-1.

In addition to IHD mortality, we studied the prospective association of changes in RHR with all-cause mortality. All statistical tests were 2-sided and a *P* value of less than .05 was considered significant. The statistical analyses were conducted using Stata version 10.0 (StataCorp).

RESULTS

The mean value of RHR was 74.0 (interquartile range, 64-80) beats/min in HUNT-1 and 73.6 (interquartile range, 65-80.5) beats/min in HUNT-2 and showed a relatively strong correlation ($r=0.50$, $P<.001$). TABLE 1 shows that participants with a relatively low RHR in HUNT-1 or HUNT-2 tended to have a healthier lifestyle than those with a higher RHR. However, among participants for whom the RHR had increased from HUNT-1 to HUNT-2, the cardiovascular risk profile at baseline was slightly worse than for people who had a stable RHR over time (TABLE 2).

During a mean (SD) of 12 (2) years of follow-up (median, 12 years; range, 0.05-13 years), a total of 3038 people died. Among all deaths, 975 were caused by cardiovascular disease and 388 were due to IHD. Compared with participants with a RHR of less than 70 beats/min at both measurements (8.2 deaths/10 000 person-years), the adjusted hazard ratio for IHD mortality was 1.9 (95% CI, 1.0-3.6) for participants with a RHR of less than 70 beats/min at the first measurement but greater than 85 beats/min at the second measurement (17.2 deaths/10 000 person-years). For participants with RHRs between 70 and 85 beats/min at the first measurement and greater than 85 beats/min at the second measurement (17.4 deaths/10 000 person years), the adjusted hazard ratio was 1.8 (95% CI, 1.2-2.8).

In the analyses using RHR as a continuous variable, we found that the association of change in RHR with IHD mortality was not linear ($P=.003$ for quadratic trend), and displayed a U-shaped association, suggesting that a decrease in RHR showed no general mortality benefit (Figure 2). However, our results suggest that individuals with a RHR between 70 and 85 beats/min in HUNT-1 may have benefited from a decrease in RHR. In this subgroup, we compared those who had a decrease in RHR to below 70 beats/min in HUNT-2 with those whose RHR remained stable between 70 and 85 beats/min over the 10-year period, and found that the decrease in RHR was associated with a 40% lower risk of dying from IHD during follow-up (hazard ratio, 0.6; 95% CI, 0.4-0.9).

In separate stratified analyses, the results were not substantially different from the main analyses. Thus, analyses stratified by sex, age, body mass index, smoking status, physical activity, and systolic blood pressure are presented in eTable 3 at http://www.jama.com. We also conducted a series of sensitivity analyses. Thus, we excluded the first 3 years of follow-up to minimize the possibility that unknown preclinical disease could have influenced the association of changes in RHR, but the findings were not substantially altered (TABLE 3 and eFigure 1). We also adjusted for the presence of common chronic disorders in addition to the factors that were already included in the multivariable models, but the association of changes in RHR with IHD mortality remained nearly unchanged (eTable 4 and eFigure 2). In a separate analysis, we adjusted for RHR as measured in HUNT-1, and found that the results were similar to the results obtained without this adjustment (eTable 5).

As expected from the general baseline good health of the study participants, the absolute risks of IHD mortality associated with changes in RHR were small in this study (Table 3 and Figure 2).

In a separate analysis, we assessed the association of changes in RHR with all-cause mortality. The associations with total mortality were similar to those observed for IHD mortality, but the estimates of effect were generally weaker (TABLE 4). In contrast to the U-shaped association observed for IHD mortality, there was both a linear ($P=.006$) and a quadratic component ($P=.045$) in the analysis using RHR as a continuous variable, suggesting a J-shaped curve for total mortality.

COMMENT

In this prospective study of apparently healthy men and women, we found that participants whose RHR had increased during a 10-year period were at increased risk of death from IHD compared with participants whose RHR remained relatively stable. We found a similar but weaker risk increase for all causes of death. The association between changes in RHR and IHD mortality was not linear; among participants whose RHR decreased over time, there was no general benefit in relation to IHD mortality.

Resting heart rate has long been recognized as an independent predictor of cardiovascular risk.[1-6] However, comparatively less is known about the possible implications of temporal changes in RHR. The Paris Prospective Study[13] of healthy middle-aged men showed that an increase of 4 beats/min or more in RHR during a 5-year period was associated with a 19% increase in all-cause mortality. An increase in RHR also was associated with a poorer outcome in patients with hypertension or coronary artery disease.[12,14,15] In line with this, we found that compared with

participants with a RHR of less than 70 beats/min at both measurements about 10 years apart, participants with a RHR of less than 70 beats/min at the first measurement but greater than 85 beats/min at the second measurement had a risk of death from IHD that was 90% higher, and a risk of death from all causes that was 50% higher.

Table 1. Baseline Characteristics of Study Participants by Resting Heart Rate (RHR) in HUNT-1 and HUNT-2 (N = 29 325)

	HUNT-1 RHR, beats/min				HUNT-2 RHR, beats/min			
	<70 (n = 11 336)	70-85 (n = 13 793)	>85 (n = 4196)	*P* Value[a]	<70 (n = 12 491)	70-85 (n = 12 343)	>85 (n = 4491)	*P* Value[a]
Female sex, No. (%)	5310 (46.8)	7961 (57.7)	2555 (60.9)	<.001	5750 (46.0)	7278 (59.0)	2798 (62.3)	<.001
Age, mean (range), y	51.8 (30-95)	51.9 (31-98)	52.1 (31-96)	.14	51.6 (31-95)	51.6 (30-98)	53.2 (31-96)	<.001
Cholesterol, mean (SD), mmol/L								
Total	6.0 (1.2)	6.1 (1.2)	6.2 (1.2)	<.001	5.9 (1.1)	6.0 (1.2)	6.2 (1.2)	<.001
High-density lipoprotein	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	.30	1.4 (0.3)	1.4 (0.4)	1.4 (0.4)	<.001
Body mass index, mean (SD)[b]								
<18.5	17.8 (0.5)	17.6 (0.8)	17.5 (0.9)	<.001	17.9 (0.6)	17.7 (0.7)	17.3 (0.9)	<.001
18.5-24.9	23.1 (1.4)	22.9 (1.5)	22.8 (1.5)		23.0 (1.4)	22.8 (1.5)	22.7 (1.6)	
25.0-29.9	27.1 (1.4)	27.2 (1.4)	27.2 (1.4)		27.0 (1.3)	27.2 (1.4)	27.3 (1.4)	
≥30.0	32.6 (2.6)	32.9 (2.9)	33.0 (2.8)		32.5 (2.5)	32.9 (2.8)	33.3 (3.0)	
Blood pressure, mean (SD), mm Hg								
Systolic								
<120	112.1 (5.6)	112.1 (5.6)	112.0 (5.6)	<.001	111.9 (5.6)	112.2 (5.5)	112.4 (5.6)	<.001
120-139	129.5 (5.6)	129.6 (5.6)	130.1 (5.7)		129.4 (5.5)	129.7 (5.6)	130.2 (5.7)	
140-159	147.7 (5.5)	147.9 (5.6)	148.4 (5.7)		147.7 (5.5)	147.9 (5.6)	148.4 (5.7)	
≥160	173.5 (12.5)	174.6 (13.7)	176.4 (14.1)		173.5 (12.6)	173.8 (12.7)	177.2 (15.0)	
Diastolic								
≤79	71.5 (5.7)	72.0 (5.5)	72.5 (5.3)	<.001	71.2 (5.8)	72.3 (5.4)	73.1 (4.9)	<.001
>79	88.3 (7.4)	89.5 (8.4)	90.7 (9.1)		87.8 (7.2)	89.3 (8.1)	91.6 (9.4)	
Smoking status, No. (%)[c]								
Never	4824 (42.6)	5055 (36.6)	1379 (32.9)	<.001	5263 (42.1)	4489 (36.4)	1506 (33.5)	<.001
Current	2943 (26.0)	4707 (34.1)	1624 (38.7)		3157 (25.3)	4314 (35.0)	1803 (40.1)	
Former	3151 (27.8)	3562 (25.8)	1062 (25.3)		3624 (29.0)	3114 (25.2)	1037 (23.1)	
Education, No. (%)[c]								
<10 y	3911 (34.5)	5446 (39.5)	1767 (42.1)	<.001	4192 (33.6)	4847 (39.3)	2085 (46.4)	<.001
10-12 y	4845 (42.7)	5720 (41.5)	1746 (41.6)		5385 (43.1)	5214 (42.2)	1712 (38.1)	
≥13 y	2371 (21.0)	2285 (16.6)	568 (13.5)		2667 (21.3)	2001 (16.2)	556 (12.4)	
Physical activity level, No. (%)								
Inactive	806 (7.1)	1106 (8.0)	396 (9.4)	<.001	770 (6.2)	1074 (8.7)	464 (10.3)	<.001
Low	3813 (33.6)	5159 (37.4)	1581 (37.7)		4045 (32.4)	4728 (38.3)	1780 (39.6)	
Medium	3183 (28.1)	4049 (29.4)	1266 (30.2)		3574 (28.6)	3572 (28.9)	1352 (30.2)	
High	3534 (31.2)	3479 (25.2)	953 (22.7)		4102 (32.8)	2969 (24.1)	895 (19.9)	
Occupational status, No. (%)								
Unskilled manual worker	1213 (10.7)	1693 (12.3)	533 (12.7)	<.001	1311 (10.5)	1537 (12.4)	591 (13.2)	<.001
Skilled manual or clerical worker	2980 (26.3)	3681 (26.7)	1113 (26.5)		3339 (26.7)	3347 (27.1)	1088 (24.2)	
Professionals, academics, or managers	2415 (21.3)	2394 (17.4)	622 (14.8)		2670 (21.4)	2137 (17.3)	624 (13.9)	
Self-employed, farmers, or fishermen	1446 (12.8)	1542 (11.2)	434 (10.3)		1627 (13.0)	1363 (11.0)	432 (9.6)	
Retired, part-time workers, or not otherwise classified	3282 (29.0)	4483 (32.5)	1494 (35.6)		3544 (28.4)	3959 (32.1)	1756 (39.1)	
Alcoholic drinks, No. (%)[c,d]								
Abstainers	3896 (34.4)	5291 (38.4)	1708 (40.7)	<.001	4202 (33.6)	4745 (38.4)	1948 (43.4)	<.001
0-≤7	5424 (47.8)	6254 (45.3)	1829 (43.6)		6083 (48.7)	5600 (45.4)	1824 (41.0)	
>7-≤14	1256 (11.1)	1268 (9.2)	353 (8.4)		1371 (11.0)	1141 (9.2)	365 (8.1)	
>14	289 (2.5)	293 (2.1)	85 (2.0)		311 (2.5)	255 (2.1)	101 (2.2)	
Family history of AMI, No. (%)								
No	9654 (85.2)	11 693 (84.8)	3603 (85.9)	<.001	10 651 (85.3)	10 488 (85.0)	3811 (84.8)	<.001
Yes	1682 (14.8)	2100 (15.2)	593 (14.1)		1840 (14.7)	1855 (15.0)	680 (15.2)	

Abbreviations: AMI, acute myocardial infarction; HUNT, Nord-Trøndelag County Health Study.
SI conversion factors: To convert high-density lipoprotein and total cholesterol to mg/dL, divide by 0.0259.
[a] For linear trend, regression analyses were used for continuous variables; χ^2 tests were used for proportions of categorical variables.
[b] Calculated as weight in kilograms divided by height in meters squared.
[c] Data are missing for this category.
[d] Based on consumption over a 2-week period.

Table 2. Characteristics of Study Participants According to Temporal Changes in Resting Heart Rate (RHR) in HUNT-1 and HUNT-2 (N = 29 325)[a]

	HUNT-2 RHR, beats/min								
	HUNT-1 RHR <70 beats/min			HUNT-1 RHR of 70-85 beats/min			HUNT-1 RHR >85 beats/min		
	<70 (n = 7149)	70-85 (n = 3497)	>85 (n = 690)	<70 (n = 4784)	70-85 (n = 6899)	>85 (n = 2110)	<70 (n = 558)	70-85 (n = 1947)	>85 (n = 1691)
Female sex, No. (%)	2981 (41.7)	1932 (55.2)	397 (57.5)	2477 (51.8)	4163 (60.3)	1321 (62.6)	292 (52.3)	1183 (60.8)	1080 (63.9)
Age, mean (range),y[b]	51.7 (31-93)	51.6 (30-95)	52.4 (32-94)	51.5 (31-95)	51.7 (31-98)	53.3 (31-94)	50.9 (32-93)	51.2 (31-91)	53.5 (31-96)
Cholesterol, mean (SD), mmol/L									
Total	5.9 (1.1)	6.1 (1.2)	6.2 (1.2)	5.9 (1.2)	6.1 (1.2)	6.2 (1.2)	5.9 (1.2)	6.1 (1.2)	6.3 (1.3)
HDL[c]	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)
BMI, mean (SD)[d]									
<18.5	17.8 (0.6)	17.7 (0.5)	17.7 (0.5)	18.0 (0.4)	17.7 (0.8)	17.3 (0.9)	17.8 (0.9)	17.6 (0.7)	17.2 (1.1)
18.5-24.9	23.1 (1.4)	22.9 (1.5)	22.8 (1.5)	22.9 (1.5)	22.8 (1.5)	22.7 (1.6)	22.8 (1.4)	22.8 (1.5)	22.7 (1.6)
25.0-29.9	27.0 (1.3)	27.3 (1.4)	27.4 (1.4)	27.1 (1.4)	27.2 (1.4)	27.3 (1.4)	27.0 (1.3)	27.2 (1.4)	27.2 (1.4)
≥30.0	32.4 (2.3)	32.8 (2.9)	33.4 (2.7)	32.6 (2.7)	32.9 (2.9)	33.1 (3.1)	32.5 (2.0)	32.8 (2.6)	33.3 (3.0)
Blood pressure, mean (SD), mm Hg									
Systolic									
<120	112.0 (5.6)	112.2 (5.6)	112.2 (5.7)	111.8 (5.7)	112.2 (5.6)	112.6 (5.4)	111.4 (5.7)	112.1 (5.4)	112.2 (5.8)
120-139	129.4 (5.6)	129.7 (5.6)	129.9 (5.7)	129.5 (5.5)	129.6 (5.6)	130.0 (5.7)	129.8 (5.5)	129.9 (5.7)	130.4 (5.7)
140-159	147.6 (5.4)	147.7 (5.5)	148.0 (5.6)	147.7 (5.5)	147.9 (5.5)	148.4 (5.7)	148.3 (5.9)	148.2 (5.7)	148.6 (5.7)
≥160	173.1 (11.9)	173.2 (12.5)	177.1 (14.9)	174.0 (13.6)	174.0 (12.8)	176.3 (15.1)	174.5 (11.7)	174.0 (12.6)	178.0 (15.0)
Diastolic									
≤79	71.2 (5.8)	72.2 (5.4)	72.5 (5.2)	71.5 (5.7)	72.2 (5.4)	73.0 (4.9)	71.6 (5.6)	72.4 (5.4)	73.3 (4.7)
>79	87.6 (7.0)	88.8 (7.4)	90.8 (8.5)	88.0 (7.4)	89.4 (8.2)	91.7 (9.4)	88.4 (7.5)	89.8 (8.4)	92.1 (9.8)
Smoking status, No. (%)[e]									
Never	3215 (45.0)	1364 (39.0)	245 (35.5)	1858 (38.8)	2506 (36.3)	691 (32.7)	190 (34.1)	619 (31.8)	570 (33.7)
Current	1614 (22.6)	1085 (31.0)	244 (35.4)	1365 (28.5)	2471 (35.8)	871 (41.3)	178 (31.9)	758 (38.9)	688 (41.0)
Former	2059 (28.8)	911 (26.1)	181 (26.2)	1394 (29.1)	1684 (24.4)	484 (22.9)	171 (30.6)	519 (26.7)	372 (22.0)
Education, No. (%)[e]									
<10 y	2251 (31.5)	1341 (38.3)	319 (46.2)	1729 (36.1)	2728 (39.5)	989 (46.9)	212 (38.0)	778 (40.0)	777 (45.9)
10-12 y	3140 (43.9)	1443 (41.3)	262 (38.0)	1998 (41.8)	2936 (42.6)	786 (37.3)	247 (44.3)	835 (42.9)	664 (39.3)
≥13 y	1623 (22.7)	656 (18.8)	92 (13.3)	960 (20.1)	1058 (15.3)	267 (12.7)	84 (15.1)	287 (14.7)	197 (11.6)
Physical activity level, No. (%)									
Inactive	416 (5.8)	319 (9.1)	71 (10.3)	311 (6.5)	581 (8.4)	214 (10.1)	43 (7.7)	174 (8.9)	179 (10.6)
Low	2224 (31.1)	1319 (37.7)	270 (39.1)	1640 (34.3)	2675 (38.8)	844 (40.0)	181 (32.4)	734 (37.7)	666 (39.4)
Medium	1997 (27.9)	985 (28.2)	201 (29.1)	1412 (29.5)	2021 (29.3)	616 (29.2)	165 (29.6)	566 (29.1)	535 (31.6)
High	2512 (35.1)	874 (25.0)	148 (21.4)	1421 (29.7)	1622 (23.5)	436 (20.7)	169 (30.3)	473 (24.3)	311 (18.4)
Occupational status, No. (%)									
Unskilled manual worker	702 (9.8)	426 (12.2)	85 (12.3)	543 (11.3)	876 (12.7)	274 (13.0)	66 (11.8)	235 (12.1)	232 (13.7)
Skilled manual or clerical worker	1913 (26.8)	904 (25.9)	163 (23.6)	1284 (26.8)	1885 (27.3)	512 (24.3)	142 (25.4)	558 (28.7)	413 (24.4)
Professionals, academics, or managers	1642 (23.0)	668 (19.1)	105 (15.2)	939 (19.6)	1148 (16.6)	307 (14.5)	89 (15.9)	321 (16.5)	212 (12.5)
Self-employed, farmers, or fishermen	967 (13.5)	385 (11.0)	94 (13.6)	576 (12.0)	772 (11.2)	194 (9.2)	84 (15.1)	206 (10.6)	144 (8.5)
Retired, part-time workers, or not otherwise classified	1925 (26.9)	1114 (31.9)	243 (35.2)	1442 (30.1)	2218 (32.1)	823 (39.0)	177 (31.7)	627 (32.2)	690 (40.8)
Alcoholic drinks, No. (%)[e,f]									
Abstainers	2299 (32.2)	1297 (37.1)	300 (43.5)	1714 (35.8)	2680 (38.8)	897 (42.5)	189 (33.9)	768 (39.4)	751 (44.4)
0-≤7	3540 (49.5)	1609 (46.0)	275 (39.9)	2277 (47.6)	3119 (45.2)	858 (40.7)	266 (47.7)	872 (44.8)	691 (40.9)
>7-≤14	845 (11.8)	347 (9.9)	64 (9.3)	468 (9.8)	625 (9.1)	175 (8.3)	58 (10.4)	169 (8.7)	126 (7.4)
>14	191 (2.7)	80 (2.3)	18 (2.6)	104 (2.2)	140 (2.0)	49 (2.3)	16 (2.9)	35 (1.8)	34 (2.0)
Family history of AMI, No. (%)									
No	6102 (85.4)	2975 (85.1)	577 (83.6)	4060 (84.9)	5843 (84.7)	1790 (84.8)	489 (87.6)	1670 (85.8)	1444 (85.4)
Yes	1047 (14.6)	522 (14.9)	113 (16.4)	724 (15.1)	1056 (15.3)	320 (15.2)	69 (12.4)	277 (14.2)	247 (14.6)

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index; HDL, high-density lipoprotein; HUNT, Nord-Trøndelag County Health Study.
SI conversion factors: To convert HDL and total cholesterol to mg/dL, divide by 0.0259.
[a] For all of the trend comparisons, the *P* values were less .001 unless otherwise indicated. For linear trend, regression analyses were used for continuous variables; χ^2 tests were used for proportions of categorical variables.
[b] For those with HUNT-1 RHR of less than 70 beats/min, the *P* value was .50; for those with a HUNT-1 RHR between 70 and 85 beats/min, the *P* value was less than .001; and for those with a HUNT-1 RHR greater than 85 beats/min, the *P* value was less than .001.
[c] For those with HUNT-1 RHR of less than 70 beats/min, the *P* value was .02; for those with a HUNT-1 RHR between 70 and 85 beats/min, the *P* value was less than .001; and for those with a HUNT-1 RHR greater than 85 beats/min, the *P* value was .67.
[d] Calculated as weight in kilograms divided by height in meters squared.
[e] Data are missing for this category.
[f] Based on consumption over a 2-week period.

To our knowledge, no previous population-based study has assessed longitudinal changes in RHR in relation to the risk of death from IHD. Although we found that an increase in RHR was associated with an increased risk of death from IHD, the association was nonlinear, and suggested that a decrease in RHR over time is not likely to be beneficial in relation to IHD mortality. Other studies also have found nonlinear associations related to RHR measured at baseline and subsequent IHD mortality, suggesting that both high and low RHR could have adverse consequences.[6,12,20] However, in a subgroup of participants with RHR between 70 and 85 beats/min at the first measurement, and below 70 beats/min about 10 years later, IHD mortality was 40% lower compared with those whose RHR remained between 70 and 85 beats/min at the second measurement. In patients with heart failure and coronary heart disease, clinical trials have shown that drugs to lower RHR may be beneficial in relation to cardiovascular disease.[9,11] The nonlinear association of RHR with IHD mortality, and our subgroup finding, suggest that

Table 3. Hazard Ratios of Death From Ischemic Heart Disease (IHD) by Resting Heart Rate (RHR) in HUNT-1 and HUNT-2

	HUNT-2 RHR, beats/min								
	HUNT-1 RHR <70 beats/min			HUNT-1 RHR of 70-85 beats/min			HUNT-1 RHR >85 beats/min		
	<70 (n = 7149)	70-85 (n = 3497)	>85 (n = 690)	<70 (n = 4784)	70-85 (n = 6899)	>85 (n = 2110)	<70 (n = 558)	70-85 (n = 1947)	>85 (n = 1691)
IHD deaths	71	35	14	52	104	43	9	33	27
Rate/10 000 person-years	8.2	8.3	17.2	9.1	12.6	17.4	13.5	14.2	13.6
AHR (95% CI)[a]	1 [Reference]	0.9 (0.6-1.3)	1.8 (1.1-3.2)	1.1 (0.7-1.5)	1.4 (1.1-1.9)	1.7 (1.2-2.5)	1.6 (0.8-3.3)	1.7 (1.2-2.6)	1.2 (0.7-1.8)
AHR (95% CI)[b]	1 [Reference]	0.9 (0.6-1.5)	1.9 (1.0-3.6)	1.0 (0.6-1.5)	1.5 (1.1-2.1)	1.8 (1.2-2.8)	1.7 (0.8-3.6)	1.7 (1.1-2.7)	1.1 (0.6-1.7)
Excluding first 3 y of mortality follow-up									
IHD deaths	56	25	13	44	87	29	8	29	24
Rate/10 000 person-years	8.7	7.9	21.4	10.2	14.1	15.8	16.0	16.7	16.2
AHR (95% CI)[b]	1 [Reference]	0.9 (0.6-1.6)	2.3 (1.2-4.6)	1.1 (0.6-1.6)	1.7 (1.2-2.5)	1.7 (1.0-2.8)	1.9 (0.9-4.3)	2.1 (1.2-3.4)	1.2 (0.7-2.1)

Abbreviations: AHR, adjusted hazard ratio; HUNT, Nord-Trøndelag County Health Study.
[a] Adjusted for age.
[b] Adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared; <18.5, 18.5-24.9, 25.0-29.9, or ≥30), physical activity level (high, medium, low, or inactive), smoking status (never, current, former, or unknown), systolic blood pressure (<120, 120-139, 140-159, or ≥160 mm Hg), family history of acute myocardial infarction, alcoholic drink consumption over a 2-week period (abstainers, 0-≤7, >7-≤14, or >14), occupational status (unskilled manual worker, skilled manual, or clerical worker; professional, academics, or managers; self-employed, farmer, or fisherman; or retired, part-time workers, or not otherwise classified), education (<10, 10-12, or ≥13 years), total serum cholesterol level, and high-density lipoprotein cholesterol level.

Table 4. Hazard Ratios of Death From All Causes by Resting Heart Rate (RHR) in HUNT-1 and HUNT-2

	HUNT-2 RHR, beats/min								
	HUNT-1 RHR <70 beats/min			HUNT-1 RHR of 70-85 beats/min			HUNT-1 RHR >85 beats/min		
	<70 (n = 7149)	70-85 (n = 3497)	>85 (n = 690)	<70 (n = 4784)	70-85 (n = 6899)	>85 (n = 2110)	<70 (n = 558)	70-85 (n = 1947)	>85 (n = 1691)
Deaths	590	349	95	437	755	304	57	212	239
Rate/per 10 000 person-years	68.6	83.1	116.7	76.2	91.7	123.1	85.4	91.5	120.3
AHR (95% CI)[a]	1 [Reference]	1.1 (1.0-1.3)	1.5 (1.2-1.9)	1.1 (1.0-1.2)	1.3 (1.1-1.4)	1.5 (1.3-1.7)	1.2 (0.9-1.6)	1.3 (1.1-1.6)	1.3 (1.1-1.5)
AHR (95% CI)[b]	1 [Reference]	1.2 (1.0-1.3)	1.5 (1.2-1.9)	1.1 (1.0-1.2)	1.3 (1.1-1.4)	1.4 (1.2-1.7)	1.2 (0.9-1.6)	1.4 (1.1-1.6)	1.3 (1.1-1.5)
Excluding first 3 y of mortality follow-up									
Deaths	502	296	80	380	651	259	51	175	204
Rate/per 10 000 person-years	77.7	94.0	131.7	88.4	105.6	141.1	102.0	101.0	137.9
AHR (95% CI)[a]	1 [Reference]	1.1 (1.0-1.3)	1.6 (1.2-2.0)	1.1 (1.0-1.3)	1.3 (1.2-1.5)	1.5 (1.3-1.7)	1.3 (1.0-1.8)	1.3 (1.1-1.6)	1.3 (1.1-1.5)
AHR (95% CI)[b]	1 [Reference]	1.2 (1.0-1.3)	1.5 (1.2-2.0)	1.1 (1.0-1.3)	1.3 (1.2-1.5)	1.5 (1.2-1.7)	1.3 (0.9-1.8)	1.3 (1.1-1.6)	1.3 (1.1-1.6)

Abbreviations: AHR, adjusted hazard ratio; HUNT, Nord-Trøndelag County Health Study.
[a] Adjusted for age.
[b] Adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared; <18.5, 18.5-24.9, 25.0-29.9, or ≥30), physical activity level (high, medium, low, or inactive), smoking status (never, current, former, or unknown), systolic blood pressure (<120, 120-139, 140-159, or ≥160 mm Hg), family history of acute myocardial infarction, alcoholic drink consumption over a 2-week period (abstainers, 0-≤7, >7-≤14, or >14), occupational status (unskilled manual worker, skilled manual, or clerical worker; professional, academics, or managers; self-employed, farmer, or fisherman; or retired, part-time workers, or not otherwise classified), education (<10, 10-12, or ≥13 years), total serum cholesterol level, and high-density lipoprotein cholesterol level.

certain groups of individuals may benefit from a decrease in RHR, whereas for others, the opposite may be true. This finding warrants further investigation.

The strengths of this study include the population-based cohort of healthy men and women, the relatively large sample size, the long-term and virtually complete follow-up, and the detailed information on several potentially confounding factors.

A limitation of this study is that the assessment of RHR is likely to be prone to measurement error. This was especially true for RHR in HUNT-1, which was assessed by palpating the radial pulse over a period of 15 seconds with a stopwatch. However, efforts were made to minimize this measurement error. In ambiguous cases, if the pulse was difficult to count, the test was extended to 30 seconds or a stethoscope placed over the heart. Previous studies have indicated that pulse measurements by palpation or by auscultation are both strongly correlated with electrocardiographic findings, and may be adequate surrogate measures for RHR in the absence of electrocardiography.[21,22] Although measurement error is a common weakness, it is not likely to be systematically related to the risk of subsequent IHD, and therefore, a potential measurement error is expected to lead to an underestimation of the true association and not to create a spurious overestimate.

We had no information on medications to lower RHR or medical interventions that might have taken place during the follow-up. However, this is not likely to be a major limitation of the study because people who took blood pressure medication were excluded from the analysis, and as far as we could ascertain, the study population was without known cardiovascular disease at baseline.

It is likely that a temporal reduction in RHR will reflect good underlying health, and could therefore be a marker of a healthy lifestyle,[23-25] including engagement in physical activity[8,26] and low prevalence of smoking,[27,28] as observed in the present study. We controlled for these and other potentially confounding factors in the multivariable-adjusted analyses, but the possibility of residual confounding cannot be completely eliminated. Any remaining potentially confounding factor would need to be associated with both temporal changes in RHR and IHD mortality, and simultaneously be unrelated to the factors included in our multivariable models.

As expected from the good general health of the study participants, the observed moderate-to-strong increases in relative risk corresponded to small risk increases in absolute terms. However, it is not clear to what extent we can extrapolate our findings to less healthy individuals in whom the underlying risk is likely to be higher.

Despite the large number of study participants, the number of events in certain subgroups was low. Consequently, the precision of the corresponding effect estimates was low, and therefore, one should be careful in drawing firm conclusions related to these subgroups.

In summary, we found that a temporal increase in RHR over a 10-year period was associated with an increased risk of dying from IHD and from all causes of death. Our findings provide further support for the hypothesis that RHR may be an important prognostic marker for IHD and total mortality. Information on RHR and its time-related changes are easy to obtain and follow-up and may be useful in identifying asymptomatic people who could benefit from measures of primary prevention, but further study in this area is warranted.

Author Contributions: Dr Nauman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Nauman, Vatten, Wisløff.
Acquisition of data: Nauman, Vatten.
Analysis and interpretation of data: Nauman, Janszky, Vatten, Wisløff.
Drafting of the manuscript: Nauman, Janszky, Vatten, Wisløff.
Critical revision of the manuscript for important intellectual content: Nauman, Janszky, Vatten, Wisløff.
Statistical analysis: Nauman, Janszky.
Obtained funding: Wisløff.
Study supervision: Vatten, Wisløff.

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Online-Only Material: eTables 1 through 5 and eFigures 1 and 2 are available at http://www.jama.com.

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Often when I write I am trying to make words do the work of line and color. I have the painter's sensitivity to light. Much . . . of my writing is verbal painting.

—Elizabeth Bowen (1899-1973)