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Resting heart rate predicts incident myocardial infarction, atrial fibrillation, ischaemic stroke and death in the general population: the Tromsø Study

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ABSTRACT

Background Elevated resting heart rate (RHR) increases risk of death overall, but a comprehensive picture of the associations between RHR, cardiovascular morbidity and mortality events has not yet been presented. We aimed to investigate the effect of RHR on the risk of 5 cardiovascular events: incident myocardial infarction (MI), incident atrial fibrillation (AF), incident ischaemic stroke, total death and cardiovascular death in a general population from Norway.

Methods We followed 24 489 men and women from the Tromsø Study 1994–1995, a population-based cohort study, for 18 years, and analysed the association between RHR and the investigated cardiovascular events. Sex-specific Cox regression with time-dependent covariates was applied with the best-fitting fractional polynomials of RHR.

Results Among men, an independent positive relationship was observed for MI and AF (adjusted HR for AF per 20 bpm increase=1.14; 95% CI 1.02 to 1.27). In women, the corresponding HR for MI was 1.23 (1.09 to 1.40). A J-shaped association was observed for ischaemic stroke in women when compared with a RHR of 70 bpm (HR for 50 bpm=1.31; 0.90 to 1.90; HR for 100 bpm=1.32; 1.04 to 1.69). Total and cardiovascular death showed a strong positive association with RHR in men. In women, the pattern for total death was similar.

Conclusions RHR is an independent risk factor for several cardiovascular events. A novel finding is the positive association between RHR and AF in men and the sex difference in association with ischaemic stroke.

INTRODUCTION

Previous studies on the general population have reported an association between resting heart rate (RHR) and cardiovascular disease, but the results were inconsistent.[1–13] Some studies found elevated RHR to be a strong and independent risk factor for cardiovascular disease, in men as well as in women,[1–7] whereas others found no independent association.[8] Another study found an independent association in men, but not in women.[9] Previous studies reported that RHR independently predicted myocardial infarction (MI) and coronary death, but not stroke[7]; MI and all-cause death, but not ischaemic, haemorrhagic, or any stroke[10]; premature mortality and stroke, but not coronary heart disease[11]; and incident coronary heart disease, but not mortality from coronary heart disease.[12]

Small-scale studies may not reveal the association between RHR and cardiovascular disease, as this association may not be as strong as the relationship between established risk factors and cardiovascular disease. RHR is strongly associated with blood pressure[13] and physical activity.[14] Thus, studies that record high blood pressure as a yes-no variable,[7 10] or that do not adjust for physical activity,[1 6 11] may produce biased results. Moreover, when RHR is modelled as a continuous variable,[2–5 7 8 10 15] a non-linear relationship with cardiovascular disease could be missed. Dividing RHR into quartiles[3 11] or quintiles[2 4 7 10 12] will not provide estimates for extreme low or high RHR values.

Cardiovascular events may be ascertained and verified from hospital records or national registries.[3 4 15 16] They may also be ascertained through interviews with survivors or their relatives, but the use of self-reported data without clinical verification may raise questions regarding the validity of diagnoses.[5 11]

The aim of this study was to challenge the varying results of existing research by using data and applying methodologies that have the potential to overcome previous limitations. To this end, we investigated the effect of RHR on the risk of five cardiovascular morbidity and mortality events in a general population from Norway.

METHODS

Study design and participants

The Tromsø Study is a population-based cohort study with repeated surveys conducted on total birth cohorts and random samples of the general population of Tromsø, Northern Norway. The study procedures and response rate have been described previously in detail.[17] Briefly, participants were sent an invitation and questionnaire by mail. Participants completed the questionnaire at home and brought it to the survey, during which they underwent a physical examination and had a blood sample taken.

The Tromsø Study 1994–1995 included men and women aged 25 years or more (response rate 77%), and was considered the baseline in the present report. Of the 27 158 participants, we excluded 192 with no consent, 35 with missing RHR, 299 who were pregnant, 523 with missing cardiovascular covariates and 1620 blood pressure medication users, from the present analysis. Thus, our final study sample comprised 24 489 participants. Some of these participants (n=9086) also took part in additional surveys carried out in 2001–2002 and/or 2007–2008.

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RHR and other cardiovascular risk factors

At each survey, trained personnel reviewed the questionnaire, performed a physical examination and collected blood according to standardised protocols. Information on current pregnancy (yes/no), blood pressure medication use (yes/no), leisure time physical activity (4 levels) and daily cigarette smoking (yes/no) was taken from the Tromsø Study questionnaire. RHR and systolic blood pressure (SBP) values were determined using an automated, non-invasive, microprocessor-controlled Dinamap device.[18 19] The Dinamap Vital Signs Monitor 1846 (Critikon Inc, Tampa, Florida, USA) was used in the 1994–1995 and 2001–2002 surveys, and the Dinamap ProCare 300 (GE Medical Systems Information Technologies, Tampa, Florida, USA) was used in the 2007–2008 survey.[20 21] The devices were calibrated at regular intervals. The circumference of the upper right arm was measured and the proper cuff size was selected out of four available. After the participants had been seated for 2 min with the cuff on, three values were taken at 1 min intervals.[16] The mean value of the last two RHR measurements (in bpm) and of the last two SBP measurements (in mm Hg) was used in the present analysis. Body weight and height were measured with light clothing and no shoes, and were used to calculate body mass index (BMI, kg/m^2).[17]

Blood samples were used to determine non-fasting serum total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (mmol/L). The analyses were carried out at the Department of Clinical Chemistry, Department of Medical Biology, University Hospital of North Norway, Tromsø.[19] Information on all these variables was updated for participants who took part in the surveys in 2001–2002 and/or 2007–2008. We did not update this information for those who became pregnant and/or who started to use blood pressure medication.

Follow-up and identification of cardiovascular events

The study sample was followed for 18 years (from 1994 to 2012) for incident non-fatal or fatal MI, incident non-fatal or fatal atrial fibrillation (AF), incident non-fatal or fatal ischaemic stroke, total death and cardiovascular death. All cardiovascular outcome events were identified by linkage to the diagnosis registries 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, Ninth Revision (ICD-9) codes 410-414, 427, 428, 430-438, 798-799 and ICD-10 codes I20-I25, I46-I48, I50, I60-I69, R96, R98, R99. The University Hospital of North Norway is the only hospital serving this community, the other nearest hospital being located approximately 250 km away by road (148 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 the death took place in Norway or abroad.

All possible events were validated by an independent end point committee. The hospital medical records were retrieved for case validation. We performed manual searches in paper versions (used until 2001) and electronic text searches of digital versions of hospital records for notes on all outcome events in all participants with one or more of the diagnoses aforementioned. Information from the National Causes of Death Registry and from death certificates was used to collect relevant information of fatal events from additional sources such as autopsy reports and records from nursing homes, ambulance services and general practitioners. The definition and ascertainment of incident MI,[22] AF[16] and ischaemic stroke[23] used in the validation process have been described and are presented in detail in online supplementary material. Participants who had emigrated from Tromsø were identified through the Population Register of Norway. For morbidity cardiovascular events, the number of emigrants varied between 1923 and 1960 in men, and between 2050 and 2061 in women; for mortality events the numbers were 210 and 171, respectively.

Statistical analysis

Linear or logistic regression analyses were used to derive sex-specific age-adjusted means with SDs or proportions, respectively, for all considered covariates in 10 bpm RHR groups (<50, 50–59, 60–69, 70–79, 80–89, 90–99, ≥100).

All participants with MI, AF or ischaemic stroke before the date of inclusion were excluded from event-specific analyses. Baseline RHR, as well as information about the other cardiovascular risks factors, was updated if a participant attended the 2001–2002 and/or the 2007–2008 surveys and was not pregnant, and/or not on blood pressure medication at the time of these surveys. Follow-up started at the date of baseline examination in 1994–1995 and lasted until the date of the event of interest, date of death, date of emigration, or 31 December 2012, whichever came first.

We estimated sex-specific crude and age-standardised (direct standardisation) incidence rates as events per 1000 person-years at risk by 10 bpm RHR group. We used sex-specific Cox proportional hazards regression analysis with time-dependent covariates to estimate HRs with 95% CIs for each of the five investigated cardiovascular events as a function of RHR and other cardiovascular risk factors. RHR was used as a continuous variable. To reveal possible non-linear associations between RHR and each of the cardiovascular events, we used fractional polynomials of RHR adjusted for age. For each of the cardiovascular events, we chose the best-fitting fractional polynomials out of a maximum of 2° using the Akaike information criterion.[24] HRs were estimated for RHRs of 50, 60, 80, 90 and 100 bmp, using 70 bpm as the reference value, for men and women separately. HRs were adjusted for age only, and then for age, SBP, total cholesterol, HDL cholesterol, triglycerides, BMI, physical activity and smoking, simultaneously. Likelihood ratio test between a model with and a model without fractional polynomial terms of RHR was used to test the associations. The proportional hazard assumption was verified by comparing log minus log of survival curves between RHR groups. All analyses were performed using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA) and STATA/MP V.13.0 (StataCorp LP, College Station, Texas, USA).

Ethical considerations

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

RESULTS

Table 1 shows the baseline characteristics of the study sample by sex and RHR group. Men and women were both slightly older in the lowest and especially the highest RHR groups. With increasing RHR, means of SBP, total cholesterol, HDL cholesterol, triglycerides and the proportion of smokers gradually increased, whereas physical activity level decreased.

Table 1 Baseline characteristics of 11 773 men and 12 716 women according to RHR group; the Tromsø Study 1994–1995

Characteristics	RHR, bpm							p Value
	<50	50–59	60–69	70–79	80–89	90–99	≥100	
Men								
n	233	1698	3855	3451	1671	616	249	
Age, years	46.4 (14.6)	45.2 (13.9)	45.3 (13.8)	44.7 (14.0)	46.9 (14.2)	48.0 (14.8)	49.4 (15.2)	<0.001
Systolic blood pressure, mm Hg	131.4 (15.1)	133.5 (14.7)	134.5 (15.3)	137.0 (16.0)	139.5 (17.6)	142.5 (19.6)	148.0 (20.8)	<0.001
Total cholesterol, mmol/L	5.64 (1.16)	5.80 (1.16)	5.95 (1.18)	6.08 (1.23)	6.18 (1.26)	6.20 (1.27)	6.29 (1.29)	<0.001
HDL cholesterol, mmol/L	1.37 (0.36)	1.40 (0.35)	1.35 (0.35)	1.33 (0.33)	1.33 (0.37)	1.31 (0.37)	1.35 (0.43)	<0.001
Triglycerides, mmol/L	1.32 (0.72)	1.47 (0.87)	1.66 (1.02)	1.80 (1.11)	2.04 (1.34)	2.10 (1.41)	2.11 (1.38)	<0.001
BMI, kg/m^2	25.0 (2.7)	25.2 (2.8)	25.3 (3.1)	25.6 (3.3)	25.8 (3.6)	26.1 (4.0)	25.8 (3.9)	<0.001
Physical activity, %								<0.001
Sedentary	17 (6.9)	72 (4.1)	245 (6.2)	334 (9.5)	190 (10.7)	74 (11.0)	38 (13.7)	
Moderate	51 (21.9)	548 (32.2)	1478 (38.3)	1450 (41.9)	728 (43.7)	264 (43.1)	103 (41.7)	
Active	121 (51.9)	837 (49.4)	1745 (45.3)	1402 (40.7)	649 (38.8)	239 (38.6)	94 (37.5)	
Very active	44 (18.5)	241 (13.5)	387 (9.5)	265 (7.2)	104 (6.1)	39 (6.3)	14 (5.8)	
Smoking, %	31 (13.3)	430 (25.1)	1308 (33.8)	1472 (42.4)	818 (49.1)	300 (49.1)	120 (48.9)	<0.001
Women								
n	58	902	3539	4394	2530	886	407	
Age, years	47.6 (16.4)	45.4 (14.5)	45.5 (14.4)	45.8 (14.9)	46.7 (15.2)	48.0 (15.8)	50.6 (15.4)	<0.001
Systolic blood pressure, mm Hg	122.6 (19.1)	126.2 (20.1)	127.6 (19.6)	129.8 (19.8)	133.0 (21.1)	137.5 (22.9)	144.4 (25.2)	<0.001
Total cholesterol, mmol/L	5.64 (1.41)	5.76 (1.32)	5.88 (1.33)	5.97 (1.35)	6.13 (1.39)	6.18 (1.32)	6.14 (1.47)	<0.001
HDL cholesterol, mmol/L	1.66 (0.49)	1.71 (0.40)	1.65 (0.39)	1.64 (0.40)	1.61 (0.41)	1.61 (0.41)	1.63 (0.43)	<0.001
Triglycerides, mmol/L	1.16 (0.64)	1.07 (0.62)	1.20 (0.70)	1.30 (0.82)	1.41 (0.86)	1.47 (0.91)	1.52 (1.01)	<0.001
BMI, kg/m^2	24.0 (3.6)	24.2 (3.6)	24.4 (3.7)	24.6 (4.0)	24.7 (4.4)	25.1 (5.2)	25.0 (4.8)	<0.001
Physical activity, %								<0.001
Sedentary	6 (7.6)	71 (6.6)	299 (7.1)	397 (7.4)	251 (7.8)	112 (9.5)	58 (9.8)	
Moderate	21 (36.3)	317 (35.1)	1426 (40.3)	1932 (44.0)	1177 (46.5)	399 (45.1)	164 (40.4)	
Active	25 (43.6)	446 (49.2)	1641 (46.2)	1903 (43.2)	1017 (40.3)	350 (40.0)	176 (44.7)	
Very active	6 (10.0)	68 (7.0)	173 (4.5)	162 (3.4)	85 (3.2)	25 (2.7)	9 (2.3)	
Smoking, %	13 (22.5)	237 (25.6)	1179 (32.8)	1672 (37.7)	1150 (45.7)	399 (45.9)	169 (43.6)	<0.001

Values are mean (SD) or number (%); the means (except age) and percentages are adjusted for age, using linear or logistic regression, respectively.
BMI, body mass index; HDL, high-density lipoprotein; RHR, resting heart rate.

Table 2 shows the number of events and incidence rates of the investigated cardiovascular events by RHR group. Incidence rates increased gradually with RHR in men, except for AF and ischaemic stroke. For AF, the association was U-shaped. In women, the associations for all the cardiovascular events were J-shaped or U-shaped, with elevated incidences in the RHR group of <50 bpm.

Table 3 shows HRs and 95% CIs of the cardiovascular events for the selected RHR values with 70 bpm as a reference. The multivariable-adjusted risk of MI increased gradually with increasing RHR in both sexes, HR for RHR of 100 bpm was 1.16 (95% CI 1.04 to 1.30) in men and 1.37 (95% CI 1.13 to 1.66) in women. In men, the association with AF was similar to that with MI, but the association between AF and RHR was not significant in women. RHR was associated with ischaemic stroke in women, but not in men. Women with a RHR of 50 bpm had similar or even slightly higher risk of ischaemic stroke compared with those with a RHR of 70 bpm (HR=1.31; 95% CI 0.90 to 1.90), women with RHR of 100 bpm had 32% increased risk (HR=1.32; 95% CI 1.04 to 1.69). There was a strong positive association with RHR in men for both mortality events, with HRs for RHR of 100 bpm 1.72 (95% CI 1.52 to 1.94) for total death and 1.77 (95% CI 1.49 to 2.10) for cardiovascular death. In women, the pattern for total death was similar, but for cardiovascular death the risk increased gradually starting from 70 bpm of RHR. The proportional hazard assumption was met in all of the models.

DISCUSSION

Principal findings

The study showed that RHR is independently associated with various cardiovascular events and total mortality. The risk of incident MI and total mortality in both sexes and the risk of incident AF and cardiovascular death in men increased gradually with increasing RHR. Elevated RHR increased risk of incident ischaemic stroke and cardiovascular death in women. Low RHR in women was neither protective for incident ischaemic stroke nor for cardiovascular death.

Myocardial infarction

The relationship between RHR and incident MI in the general population is not well documented. The Women's Health Initiative study presented a HR of 1.26 (95% CI 1.11 to 1.42) for RHRs over 76 bpm relative to 62 bpm for MI or coronary death in postmenopausal women.[7] We found strong and consistent positive relationship: increase in RHR from 50 to 100 bpm gradually increased the risk of incident MI. The National FINRISK Study found an independent association with fatal and non-fatal coronary heart disease in women only, with a HR per 15 bpm increase in RHR of 1.20 (95% CI 1.03 to 1.40).[2] The Kailuan Study also revealed an independent positive linear

Table 2 IRs* of cardiovascular morbidity and mortality events according to RHR group; the Tromsø Study 1994–2012

	RHR, bpm						
	<50	50–59	60–69	70–79	80–89	90–99	≥100
Men							
MI							
Events/person years	10/3952	127/26 233	289/55 078	306/46 799	161/21 387	75/7645	28/3067
Crude IR	2.5	4.8	5.2	6.5	7.5	9.8	9.1
Age-standardised IR (95% CI)	2.2 (0.7 to 3.3)	4.4 (3.7 to 5.1)	5.1 (4.7 to 5.8)	6.9 (6.2 to 8.0)	7.7 (6.6 to 8.8)	9.5 (7.3 to 11.7)	8.4 (5.5 to 11.7)
AF							
Events/person years	30/4031	159/26 704	263/56 437	216/47 913	123/21 723	56/7720	16/3048
Crude IR	7.4	6.0	4.7	4.5	5.7	7.3	5.2
Age-standardised IR (95% CI)	5.5 (3.7 to 7.7)	5.5 (4.4 to 6.2)	4.7 (4.0 to 5.1)	5.1 (4.4 to 5.5)	5.8 (4.7 to 6.9)	7.3 (5.5 to 9.1)	4.7 (2.6 to 6.9)
Ischaemic stroke							
Events/person years	15/4157	77/27 249	175/56 950	168/48 150	73/22 130	28/7887	13/3150
Crude IR	3.6	2.8	3.1	3.5	3.3	3.5	4.1
Age-standardised IR (95% CI)	2.9 (1.5 to 4.4)	2.6 (1.8 to 2.9)	2.9 (2.6 to 3.7)	4.0 (3.3 to 4.4)	3.3 (2.6 to 4.0)	3.7 (2.2 to 4.7)	3.7 (1.8 to 5.8)
Total mortality							
Events/person years	36/4710	238/31 071	544/64 061	522/54 996	340/25 297	162/8863	76/3562
Crude IR	7.6	7.7	8.5	9.5	13.4	18.3	21.3
Age-standardised IR (95% CI)	5.5 (3.7 to 7.3)	6.6 (5.8 to 7.7)	8.4 (7.7 to 9.1)	11.0 (9.9 to 11.7)	13.9 (12.4 to 15.3)	17.5 (15.0 to 20.5)	18.6 (14.6 to 23.0)
Cardiovascular mortality							
Events/person years	14/4710	70/31 071	170/64 061	176/54 996	120/25 297	62/8863	22/3562
Crude IR	3.0	2.3	2.7	3.2	4.7	7.0	6.2
Age-standardised IR (95% CI)	2.2 (1.1 to 3.3)	1.8 (1.5 to 2.6)	2.6 (2.2 to 2.9)	3.7 (3.3 to 4.4)	5.1 (4.0 to 5.8)	6.9 (5.1 to 8.4)	5.5 (2.9 to 7.7)
Women							
MI							
Events/person years	4/1245	31/16 143	135/54 388	185/62 732	133/35 480	52/11 871	40/5488
Crude IR	3.2	1.9	2.5	2.9	3.7	4.4	7.3
Age standardised IR (95% CI)	4.4 (0.0 to 8.4)	1.8 (1.1 to 2.6)	2.6 (2.2 to 2.9)	2.9 (2.6 to 3.7)	3.7 (3.3 to 4.4)	4.0 (2.9 to 5.1)	6.2 (4.4 to 8.0)
AF							
Events/person years	7/1250	49/16 095	174/54 303	210/62 764	136/35 498	46/11 849	27/5411
Crude IR	5.6	3.0	3.2	3.3	3.8	3.9	5.0
Age-standardised IR (95% CI)	4.7 (1.1 to 8.4)	2.9 (2.2 to 4.0)	3.3 (2.9 to 3.7)	3.3 (2.9 to 4.0)	4.0 (3.3 to 4.4)	3.7 (2.6 to 4.7)	4.4 (2.6 to 5.8)
Ischaemic stroke							
Events/person years	6/1288	28/16 238	108/54 681	119/63 251	91/35 763	44/11 961	21/5480
Crude IR	4.7	1.7	2.0	1.9	2.5	3.7	3.8
Age-standardised IR (95% CI)	4.4 (0.7 to 7.7)	1.8 (1.1 to 2.2)	2.2 (1.5 to 2.6)	1.8 (1.5 to 2.2)	2.6 (2.2 to 3.3)	3.3 (2.6 to 4.4)	3.3 (1.8 to 4.7)
Total mortality							
Events/person years	12/1402	121/18 217	437/62 350	571/70 922	380/39 775	175/13 513	100/6099
Crude IR	8.6	6.6	7.0	8.1	9.6	13.0	16.4
Age-standardised IR (95% CI)	7.3 (3.3 to 11.7)	6.9 (5.5 to 8.0)	7.3 (6.6 to 7.7)	8.4 (7.7 to 9.1)	9.5 (8.4 to 10.6)	12.1 (10.2 to 13.9)	13.9 (11.0 to 16.4)

Continued

Table 2 Continued

	RHR, bpm						
	<50	50–59	60–69	70–79	80–89	90–99	≥100
Cardiovascular mortality							
Events/person years	8/1402	35/18 217	134/62 350	191/70 922	115/39 775	69/13 513	33/6099
Crude IR	5.7	1.9	2.1	2.7	2.9	5.1	5.4
Age-standardised IR (95% CI)	4.7 (1.5 to 8.0)	2.2 (1.5 to 2.6)	2.2 (1.8 to 2.6)	2.9 (2.6 to 3.3)	2.9 (2.2 to 3.3)	4.7 (3.7 to 5.8)	4.4 (2.9 to 5.8)

*IR per 1000 person-years.
AF, atrial fibrillation; IR, incidence rate; MI, myocardial infarction; RHR, resting heart rate.

association between RHR and incident MI with a HR of 1.10 (95% CI 1.01 to 1.20) per 10 bpm increase in RHR in both sexes combined,[10] which coincides with our results in both men and women.

Atrial fibrillation

Our results conflict with those of a population-based cohort study of 309 540 men and women aged 40–45 years from Norway, which showed that low RHR increases the risk of AF in both sexes.[15] The outcome was paroxysmal or persistent lone AF, defined as having at least one prescription of flecainid or sotalol. Adjusted HRs per 10 bpm decrease in RHR for flecainid-defined AF were 1.26 (95% CI 1.17 to 1.35) and 1.15 (95% CI 1.05 to 1.27) in men and women, respectively. For sotalol-defined AF the effect was seen in men only.

A balance between parasympathetic and sympathetic activity is considered to be involved in the initiation of AF. Among those with lone AF, it is likely that physical activity is related to increased vagal tone, lower RHR and a shortening of the atrial refractory period, which triggers AF. In the Tromsø Study, only 6% of participants had lone AF[16]; most had a more adrenergic or mixed type of AF, which was associated with higher RHR and was caused by risk factors other than exercise. This may explain why the previously published results differ from ours. Moreover, they had up to 20 years between baseline examination and ascertainment of outcome.

No point estimates were reported in another paper based on data from the Tromsø Study, but RHR was found to have no association with AF in either sex.[16] However, we had five more years of follow-up, more identified cases and used a different statistical method.

Ischaemic stroke

A Chinese study on a variety of end points demonstrated no association between RHR and ischaemic stroke in either men or women,[5] whereas we found a J-shaped association in women with the lowest risk for RHR of 70 bpm and the highest for high RHR. However, our study methods were quite different from the Chinese study, and the number of cases relative to the sample size in that study was small.

In a study from the Asia-Pacific region, RHR was an independent predictor of ischaemic stroke in both sexes combined (adjusted HR for the highest RHR quartile vs the lowest 1.38; 95% CI 1.03 to 1.85).[11] This is not fully in agreement with our study, in which the association differed between men and women. This difference in results may be due to the fact that the Asia-Pacific study lacked a standardised protocol to measure RHR between the pooled cohorts and also lacked local verification procedures of stroke classification. Finally, the Asia-Pacific study did not adjust for physical activity, and half of the participants were Asian.

The Kailuan Study analysed men and women together, with men constituting 80% of the participants, and showed that elevated RHR was an indicator, but not an independent predictor of increased risk of ischaemic stroke.[10] This is consistent with our findings in men.

The Women's Health Initiative study showed that an RHR higher than 76 bpm independently predicted risk of any stroke (HR=1.24; 95% CI 1.02 to 1.50) compared with an RHR of 62 bpm or lower.[7] The results correspond to ours, although the shape of the association is neither analysed nor described in detail. The authors did not classify stroke, and only included women aged 50 years or older and women of different ethnic groups.

Table 3 Sex-specific HRs and CIs for cardiovascular morbidity and mortality events by selected RHR values; the Tromsø Study 1994–2012

	Men		Women	
	HR (95% CI)*	HR (95% CI)†	HR (95% CI)*	HR (95% CI)†
MI, cases/total	996/11 425		580/12 581	
RHR, bpm				
50	0.59 (0.51 to 0.69)	0.82 (0.70 to 0.95)	0.70 (0.62 to 0.79)	0.81 (0.71 to 0.92)
60	0.80 (0.76 to 0.85)	0.92 (0.86 to 0.98)	0.83 (0.79 to 0.89)	0.90 (0.85 to 0.96)
70 ref	1	1	1	1
80	1.18 (1.13 to 1.23)	1.06 (1.02 to 1.12)	1.20 (1.13 to 1.27)	1.11 (1.04 to 1.18)
90	1.34 (1.23 to 1.45)	1.12 (1.03 to 1.22)	1.43 (1.27 to 1.62)	1.23 (1.09 to 1.40)
100	1.48 (1.33 to 1.65)	1.16 (1.04 to 1.30)	1.72 (1.43 to 2.06)	1.37 (1.13 to 1.66)
p Value‡	<0.001	0.010	<0.001	0.001
AF, cases/total	863/11 661		649/12 630	
RHR, bpm				
50	0.84 (0.76 to 0.94)	0.88 (0.79 to 0.98)	0.81 (0.72 to 0.92)	0.90 (0.79 to 1.02)
60	0.92 (0.87 to 0.97)	0.94 (0.89 to 0.99)	0.90 (0.85 to 0.96)	0.95 (0.89 to 1.01)
70 ref	1	1	1	1
80	1.09 (1.03 to 1.15)	1.07 (1.01 to 1.13)	1.11 (1.04 to 1.18)	1.06 (0.99 to 1.12)
90	1.19 (1.07 to 1.32)	1.14 (1.02 to 1.27)	1.23 (1.09 to 1.39)	1.11 (0.98 to 1.26)
100	1.29 (1.10 to 1.51)	1.21 (1.03 to 1.43)	1.37 (1.14 to 1.65)	1.18 (0.97 to 1.42)
p Value‡	0.001	0.023	<0.001	0.096
Ischaemic stroke, cases/total	549/11 693		417/12 654	
RHR, bpm				
50	0.67 (0.54 to 0.84)	0.81 (0.65 to 1.02)	1.12 (0.78 to 1.60)	1.31 (0.90 to 1.90)
60	0.83 (0.75 to 0.92)	0.91 (0.83 to 1.01)	0.92 (0.83 to 1.02)	1.01 (0.91 to 1.12)
70 ref	1	1	1	1
80	1.14 (1.06 to 1.23)	1.04 (0.96 to 1.12)	1.18 (1.08 to 1.28)	1.08 (0.99 to 1.17)
90	1.17 (1.01 to 1.37)	0.98 (0.84 to 1.16)	1.40 (1.19 to 1.65)	1.19 (1.01 to 1.41)
100	1.05 (0.76 to 1.45)	0.83 (0.60 to 1.15)	1.66 (1.31 to 2.11)	1.32 (1.04 to 1.69)
p Value‡	0.001	0.135	<0.001	0.037
Total mortality, cases/total	1918/11 773		1796/12 716	
RHR, bpm				
50	0.58 (0.53 to 0.64)	0.64 (0.58 to 0.72)	0.70 (0.65 to 0.75)	0.75 (0.69 to 0.80)
60	0.76 (0.72 to 0.79)	0.80 (0.76 to 0.84)	0.84 (0.81 to 0.87)	0.86 (0.83 to 0.90)
70 ref	1	1	1	1
80	1.31 (1.26 to 1.36)	1.24 (1.20 to 1.30)	1.19 (1.15 to 1.24)	1.16 (1.12 to 1.20)
90	1.65 (1.54 to 1.77)	1.50 (1.40 to 1.62)	1.43 (1.33 to 1.53)	1.34 (1.25 to 1.44)
100	1.94 (1.72 to 2.17)	1.72 (1.52 to 1.94)	1.70 (1.53 to 1.89)	1.55 (1.39 to 1.73)
p Value‡	<0.001	<0.001	<0.001	<0.001
Cardiovascular mortality, cases/total	634/11 773		585/12 716	
RHR, bpm				
50	0.62 (0.56 to 0.69)	0.68 (0.61 to 0.76)	1.07 (0.77 to 1.48)	1.17 (0.84 to 1.64)
60	0.79 (0.75 to 0.83)	0.83 (0.78 to 0.87)	0.88 (0.80 to 0.97)	0.94 (0.85 to 1.03)
70 ref	1	1	1	1
80	1.27 (1.20 to 1.34)	1.21 (1.14 to 1.28)	1.24 (1.16 to 1.32)	1.17 (1.09 to 1.25)
90	1.62 (1.45 to 1.80)	1.46 (1.31 to 1.64)	1.55 (1.36 to 1.77)	1.38 (1.21 to 1.59)
100	2.05 (1.75 to 2.41)	1.77 (1.49 to 2.10)	1.92 (1.57 to 2.34)	1.63 (1.33 to 2.00)
p Value‡	<0.001	<0.001	<0.001	<0.001

*Adjusted for age.
†Adjusted for age, systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, triglycerides, body mass index, physical activity and smoking.
‡Likelihood ratio test between a model with and a model without fractional polynomials terms of RHR.
AF, atrial fibrillation; MI, myocardial infarction; RHR, resting heart rate.

The gender differences in the association between RHR and ischaemic stroke and the J-shaped association in women that we found have not been described before. Whether an increased risk of ischaemic stroke (although not significant) in women with low RHR levels is real or due to chance is debateable, given that a small number of events occurred in this group. However, we have conducted different types of sensitivity analysis excluding those people who had ever been on blood pressure medication, adjusting for blood pressure medication and comorbidities such as self-reported diabetes, angina pectoris and heart attack. None of these had an effect on the shape of the association between RHR and ischaemic stroke.

Total death and cardiovascular death

Many studies from different settings have concluded that elevated RHR is strongly and independently associated with total

death and cardiovascular death in the general population,[2 9 10 25] which corresponds to our findings. A Norwegian study of 379 843 middle-aged men and women followed up for 12 years demonstrated a continuous positive association between RHR and both total death and cardiovascular death.[8] After adjustment for other cardiovascular risk factors, the association with cardiovascular death in women became negative. Save this negative association, the findings are in accordance with ours.

Strengths and limitations

This study presents associations of RHR with a range of incident cardiovascular events and total mortality. RHR was measured by an automated device following a standardised protocol. Other strengths of this study include a large cohort based on a general population including both sexes and wide age ranges. We had a high attendance rate, a prospective study design with 18 years of follow-up, a large number of cardiovascular events and information on a lot of other cardiovascular risk factors, which meant we were able to adjust for these in our models. Another major strength was our method for identifying cardiovascular events, which included registry data from hospital and outpatient clinics, as well as a manual text search and adjudication of diagnoses discovered by an independent end point committee. We used fractional polynomials to reveal possible non-linear associations, and Cox proportional hazards analysis with time-dependent covariates to update RHR and other risk factors whenever possible. By introducing fractional polynomials, we were able to fit the association into linear as well as non-linear relationships, whichever best fit the data. This method also provided the possibility to derive risk estimates for extreme low and high RHR values.

At the same time, 18 years of follow-up makes the associations between baseline RHR and the events fairly remote. Lots of factors, such as medical therapies and comorbidities, could change during the period. However, we updated baseline information for those who attended two later surveys (37.1% of the study sample). We had no detailed information on treatment, such as type of drugs interacting with RHR or doses, but we excluded from the analysis all participants taking blood pressure medications at baseline. We did not update information for those who started to take blood pressure medications at later surveys in the main analysis, as their RHR as well as some of the other covariates could be affected. However, a sensitivity analysis excluding all the people who ever took blood pressure medications only strengthened most of the associations.

We had no information on fasting glucose level nor on diabetes treatment, although diabetes has an impact on the autonomous nervous system and thus the regulation of RHR. However, adjustment for self-reported diabetes at baseline or at later surveys in a sensitivity analysis had virtually no effect on the results. This was also the case when adjusting for self-reported history of other comorbidities such as angina pectoris, heart attack and stroke.

Information on smoking and physical activity was self-reported. Although a large proportion of incident MI, AF and ischaemic stroke were detected, there still may be undiagnosed participants in the study. The associations were not adjusted for markers of inflammation, heart rate variability, cardiorespiratory fitness, depression and diet.

Conclusions

In summary, we found an independent positive association between RHR and the risk of incident MI and AF, and both total death and cardiovascular death in men from a general population in Norway. The risk increased gradually from the lowest to the highest RHR values. In women, the associations were similar for MI and total death. For ischaemic stroke and cardiovascular death in women, the associations were J-shaped, with the highest risk in those with high RHR, and no protective effect of low RHR values. These findings suggest that RHR should be considered as a main risk factor for cardiovascular disease. RHR monitoring as well as modification of RHR with lifestyle changes and/or medications may be beneficial for cardiovascular health and the prevention of cardiovascular disease.

What is already known on this subject

During the last decades elevated resting heart rate has been considered to be a risk factor for cardiovascular death although it is still unclear whether this association is independent. Studies on cardiovascular morbidity and especially atrial fibrillation are scarce and results have been inconsistent. A number of methodological limitations are among the reasons behind this inconsistency.

What this study adds

Using a large cohort based on the general population, completing 18 years of follow-up and applying methodologies that have the potential to overcome previous limitations, this study showed that with increasing resting heart rate the risk of incident myocardial infarction and total death increased gradually in men as well as in women. A positive association with incident atrial fibrillation and cardiovascular death was also found in men. Resting heart rate was associated with incident ischaemic stroke in women only, and this association as well as the association with cardiovascular death in women was J-shaped. Monitoring and modification of resting heart rate with lifestyle changes and/or medications may be beneficial for cardiovascular health and the prevention of cardiovascular disease.

Contributors ES participated in the design of this study, carried out statistical analysis and interpretation of data, and drafted the manuscript. TW participated in the design of this study, helped with statistical analysis, helped to draft the manuscript and revised it critically. EBM participated in data collection and validation of diagnoses, helped to draft the manuscript and revised it critically. M-LL participated in data collection and validation of diagnoses, helped to draft the manuscript and revised it critically. IN participated in data collection and validation of diagnoses, helped to draft the manuscript and revised it critically. TB participated in the design of the study, helped with statistical analysis, coordinated and helped to draft the manuscript, and revised it critically. All the authors have read and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Approval was granted by the Data Inspectorate and by the Regional Committee for Medical and Health Research Ethics, North Norway.

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