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The relationship between resting heart rate and all-cause, cardiovascular and cancer mortality

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Aims The association between resting heart rate and changes in heart rate with all-cause, cardiovascular and cancer mortality was studied among 1827 men and 2929 women, aged 40–80 years, followed for 12 years.

Methods and results After adjustment for initial age, serum cholesterol, body mass index, systolic blood pressure, smoking and diabetes, the all-cause mortality hazard ratio was 1·7 (95% confidence interval 1·4–2·2) for heart rate increments of 20 beats . min^{-1} for men and 1·4 (confidence interval 1·1–1·8) for women. For cardiovascular mortality, the risk estimates were 1·7 (confidence interval 1·2–2·6) for men and 1·3 (confidence interval 0·9–2·0) for women. We observed no significant association between heart rate and cancer mortality. For women, stronger predictive information for all-cause mortality was provided if changes in heart rate were evident at the 2-year review.

Conclusion The resting heart rate is a predictor of mortality, independent of major cardiovascular risk factors. **(Eur Heart J 1997; 18: 1404–1410)**

Key Words: Heart rate, all-cause mortality, cardiovascular mortality, cardiovascular risk factors, change, cancer.

Introduction

Feeling the pulse has a long tradition in medicine as a non-invasive, easily obtained indicator of illness. The heart rate changes dramatically during fever, physical exercise and in stressful situations. However, its use as a predictor of survival was emphasized only recently. An elevated resting heart rate has been associated with cardiovascular[1–3] and all-cause mortality[5,6] independent of major cardiovascular risk factors, and with cancer mortality[7]. It partly reflects physical inactivity, which has been shown to increase the cardiovascular disease risk[8,9]. It is suspected that the resting heart rate has an effect on atherosclerosis because it has been positively related to the occurrence of atherosclerotic plaques in primates[10].

Few reports exist on the association between heart rate and mortality among women[2,4,5]. We present the relationship between resting heart rate for both men and women with all-cause, cardiovascular and cancer mortality, adjusted for other risk factors. We analysed longitudinal data from 1827 men and 2929 women, aged 40–80 at initial survey. These were followed for 12 years, during which time there were health examinations at 2-year intervals. In addition, effects of changes in heart rate on survival time were studied.

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Materials and methods

The first survey of the Spandau Health Test was conducted on a voluntary basis in 1982/83 among citizens of Berlin–Spandau aged 16 and older. Participants were recruited by local newspaper advertisements. Every 2 years (1984/85; 1986/87; 1988/89; 1990/91) the participants were re-invited for follow-up surveys. Additionally, a small number of new participants was allowed to enter the study after the first survey (see Table 1). For all 6410 subjects (2502 men and 3908 women) at least one primary medical record and a follow-up were assessed. From these subjects we selected 40–80 year olds (at initial survey) for the present analyses.

Medical assistants, using computerized questionnaires, interviewed the participants regarding their education, profession, drinking and smoking habits, and medical history. The medical examination included assessment of height and weight, blood pressure and resting heart rate. Blood pressure and resting heart rate were measured twice, after 5 min rest, at the start of the medical examination and about 1 h later at the end of the examination. Korotkoff sounds were recorded at a paper speed of 25 mm . s^{-1} during blood pressure readings. The heart rate was calculated from five consecutive cardiac cycles. The average of both heart rate measurements during one visit was used in the present analyses. Additionally, blood and urine samples were obtained. In the blood samples, serum cholesterol, HDL-cholesterol (since second survey), serum triglycerides, and several other parameters were analysed. Subjects were coded as

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Table 1 Sample characteristics for persons aged 40–80 years at initial survey

	Men	Women
Participants*	1827	2929
40–60 years	1281	1853
60–80 years	546	1076
Initial survey 1982–1983	1102	1763
Initial survey 1984–1985	200	334
Initial survey 1985–1986	380	589
Initial survey 1987–1988	145	243
Total person years follow-up	15 250	25 106
Average person years	8·4	8·6
Average survey participation	3·0	2·9
Initial risk factor levels:		
Heart rate (beats . min^{-1})	70·0 (11·6)‡	73·3 (10·6)
Cholesterol (mmol . l^{-1})	6·2 (1·1)	6·4 (1·2)
HDL-cholesterol (mmol . l^{-1})†	1·3 (0·4)	1·6 (0·4)
Systolic blood pressure (mmHg)	146·1 (19·6)	139·5 (21·0)
Diastolic blood pressure (mmHg)	84·2 (11·4)	83·1 (10·9)
Body mass index (kg . m^{-2})	26·0 (2·9)	25·2 (10·6)
Smoker (%)	26·9	16·6
Ex-smoker (%)	41·0	16·3

*Valid heart rates were obtained for 1798 men and 2908 women.
†HDL, high density lipoprotein.
‡Mean (standard deviation).

diabetic if they were receiving medical treatment or if their blood glucose level exceeded 180 mg . dl^{-1}.

In March 1994, all participants were followed-up for mortality. Sixty-seven subjects had moved and eight were lost to follow-up for other reasons. Their data were removed from the study. A total of 430 (214 men and 216 women) deaths were reported. Causes of death were obtained from death certificates from the regional health office (27%), or from hospital records (26%). If these sources were not available, the cause of death was obtained by a physician from interviews with relatives or neighbours of the deceased (47%). Information was gained about the primary cause of death, the underlying illness and up to three accompanying diseases, the death location and the information source. For the presented analyses, mortality causes were coded as cardiovascular disease (International Classification of Diseases, 9th revision, codes 390–459·9), cancer (codes 140–208·9) or other, using the information of the underlying illness.

Analyses were conducted for men and women separately. We calculated the age-standardized mortality rates for four heart rate groups (<60, 60–70, 70–80, >80 beats . min^{-1}) using the German population of 1987 as standard. With use of proportional hazard models[11], the risk ratios for initial heart rate expressed in units of 20 beats . min^{-1} (two standard deviations), adjusted for age (in years), serum cholesterol (mmol . l^{-1}), body mass index (kg . m^{-2}), systolic blood pressure (mmHg), smoking (yes/no) and diabetes (yes/no) were estimated. We inspected smoothed Schoenfeld's residuals plots[12,13] of all covariates to check for violations of the proportional hazard assumption. Similar analyses were performed excluding deaths occurring during the first 2 years of follow-up. We tested for effect modification by other risk factors using log likelihood ratio tests[14] and calculated the risk ratios for relevant subgroups. Furthermore, we estimated the impact of the 2-year change in resting heart rate on all-cause mortality stratified by initial level.

Results

The presented analyses are based on a total of 15 250 person years of follow-up for men and 25 106 person years for women. On average, the participants were examined three times in this period (see Table 1). The mean heart rate level was 70 beats . min^{-1} for men and 73 beats . min^{-1} for women. Initial resting heart rate levels above 90 beats . min^{-1} were observed for 99 men and 212 women. Among them, 29 men and 54 women had heart rates above 100 beats . min^{-1}. For 41 men and 18 women we observed heart rates below 50 beats . min^{-1}. The age structure differed from the German population due to a slight over-representation of the 40–49-year age groups.

An almost linear increase in all-cause mortality with initial heart rate level is seen among men (Fig. 1). The age-standardized all-cause and cardiovascular mortality rates according to initial resting heart rate are presented in Table 2. An increase in all-cause and cardiovascular mortality with higher heart rate is observed for men in both age groups. For women a similar trend is observed only in the 60–80-year age group. Among younger women with heart rates below 70 beats . min^{-1} no cardiovascular mortality was observed.

With proportional hazard models, the effect of heart rate on survival time was modelled with adjustment for initial age, serum cholesterol, body mass index, systolic blood pressure, smoking and diabetes. The

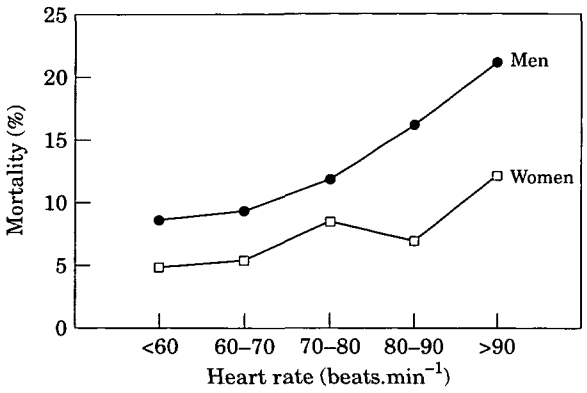

Figure 1 **All-cause mortality for 12 years against resting heart rate levels, men and women, aged 40–80 years.**

proportional hazard assumption was appropriate for all covariates. For persons with a 20 beats . min^{-1} higher heart rate level (about two standard deviations), an all-cause mortality hazard ratio of 1·7 with confidence interval of 1·4–2·2 for men and of 1·4 (confidence interval 1·1–1·8) for women was calculated. For cardiovascular mortality the hazard ratios were of the same magnitude although not significant for women (see Table 3). We repeated the analyses with the first 2 years of observation excluded. Among men and women, the cardiovascular mortality hazard ratios were slightly smaller, for all-cause mortality the risk remained the same. For cancer mortality, we observed no significant higher risk for elevated resting heart rate levels. We repeated the analyses, excluding those who had been taking medical treatment for cardiovascular disease (427 men and 1018 women) or hypertension (364 men and 646 women) within 6 months prior to the initial survey. For all-cause mortality the hazard ratio was 1·4 (confidence interval 1·0–2·0) for men and 1·3 (confidence interval 0·9–1·9) for women, when persons under treatment for cardiovascular diseases were excluded. A similar reduction was observed for cardiovascular disease, cancer and other mortality causes. When persons under treatment for hypertension were excluded, the all-cause mortality hazard ratio was 1·9 (confidence interval 1·5–2·5) for men and 1·7 (confidence interval 1·2–2·3) for women. We observed similar increases for cardiovascular disease, cancer and other mortality causes.

Serum cholesterol level for men and body mass index for women affected the relationship between heart rate and mortality. In Table 4, we present the risk ratios for all-cause and cardiovascular mortality for heart rate levels above and below 80 beats . min^{-1} and divided in tertiles of cholesterol level for men and of body mass index for women. Persons with heart rate levels below 80 beats . min^{-1} in the lowest risk factor tertiles were used as reference. For men, the increased risk associated with elevated heart rate is highest for persons with cholesterol levels below 5·7 mmol . l^{-1} (hazard ratio 2·6, confidence interval 1·6–4·3). The association of heart rate and survival disappears when cholesterol levels are above or equal to 6·7 mmol . l^{-1}. For cardiovascular mortality, the hazard ratio for both elevated cholesterol and heart rate is less than one would expect from the separate risks for one risk factor. For all-cause mortality, a less than additive effect of smoking and elevated heart rate was observed. This was not observed for cardiovascular mortality but for mortality from cancer and other causes among male smokers with an elevated pulse rate at baseline (non-significant). Effect modification was observed for body mass index among women. Only

*Table 2 Age standardized mortality rates and mean risk factor levels (95% confidence interval) according to initial heart rate**

	Heart rates (beats . min^{-1})			
	<60	60–70	70–80	>80
Mortality men				
Ages 40–60: Persons at risk	234	452	344	239
Events (total/cardiovascular disease)	7/3	19/11	21/8	18/9
All-cause	34·0	48·0	65·2	80·0
Cardiovascular disease mortality	10·8	18·4	22·7	32·3
Ages 60–80: Persons at risk	94	176	159	100
Events (total/cardiovascular disease)	21/12	40/26	39/19	42/23
All-cause	220·8	246·6	277·5	462·8
Cardiovascular disease mortality	107·1	146·1	102·3	216·0
Mortality women				
Ages 40–60: Persons at risk	127	631	640	449
Events (total/cardiovascular disease)	0/0	5/1	20/7	6/1
All-cause	0	9·1	35·2	18·2
Cardiovascular disease mortality	0	0	6·1	0
Ages 60–80: Persons at risk	84	340	386	251
Events (total/cardiovascular disease)	10/4	47/31	67/33	54/28
All-cause	120·6	159·2	186·1	222·4
Cardiovascular disease mortality	24·7	75·4	63·9	70·0

*Total and cardiovascular mortality rates per 1000 persons from 1982 till 1994.

Table 3 All-cause, cardiovascular and cancer mortality hazard ratios* for initial heart rate (per 20 beats . min^{-1}) and with exclusion of first 2 years of follow-up

	Events	Hazard ratio (95% CI)†	Excluding first two years	
			Events	Hazard ratio (95% CI)
All-cause				
Men	205	1·7 (1·4–2·2)	175	1·7 (1·3–2·3)
Women	207	1·4 (1·1–1·8)	183	1·4 (1·1–1·8)
Cardiovascular disease				
Men	85	1·7 (1·2–2·6)	69	1·6 (1·0–2·5)
Women	68	1·3 (0·9–2·0)	61	1·3 (0·8–2·0)
Cancer				
Men	60	1·5 (1·0–2·5)	48	1·3 (0·8–2·2)
Women	66	1·1 (0·7–1·7)	56	1·1 (0·7–1·8)
Other				
Men	60	2·5 (1·7–3·9)	58	2·6 (1·7–4·0)
Women	73	2·1 (1·5–3·2)	66	2·1 (1·4–3·2)

*Adjusted for initial age, serum cholesterol, body mass index, systolic blood pressure, smoking and diabetes. Number of events are lower as stated earlier due to missing values for these covariates.
†CI=confidence interval.

Table 4 All-cause and cardiovascular mortality hazard ratios* for heart rates above and below 80 beats . min^{-1} for different levels of other risk factors

	All-cause mortality			Cardiovascular mortality	
Men	<80 beats . min^{-1}	≥80 beats . min^{-1}		<80 beats . min^{-1}	≥80 beats . min^{-1}
Cholesterol			Cholesterol		
<5·7 mmol . l^{-1}	1	2·6 (1·6–4·3)	<5·7 mmol . l^{-1}	1	2·4 (0·9–6·6)
5·7–6·7 mmol . l^{-1}	0·9 (0·6–1·4)	2·1 (1·3–3·5)	5·7–6·7 mmol . l^{-1}	0·8 (0·4–1·7)	3·7 (1·7–7·9)
≥6·7 mmol . l^{-1}	1·2 (0·8–1·8)	1·2 (0·7–2·2)	≥6·7 mmol . l^{-1}	1·9 (1·0–3·4)	2·3 (1·0–5·2)
	P†=0·034			*P*=0·073	
Non-smokers	1	2·5 (1·7–3·7)	Non-smokers	1	2·3 (1·3–4·2)
Smokers	2·8 (2·0–4·0)	3·1 (1·9–5·2)	Smokers	2·2 (1·3–3·9)	4·5 (2·2–9·1)
	P=0·010			*P*=0·790	

	All-cause mortality			Cardiovascular mortality	
Women	<80 beats . min^{-1}	≥80 beats . min^{-1}		<80 beats . min^{-1}	≥80 beats . min^{-1}
BMI			BMI		
<24 kg . m^{-2}	1	1·8 (1·1–2·8)	<24 kg . m^{-2}	1	1·9 (0·8–4·6)
24–26·5 kg . m^{-2}	0·8 (0·5–1·1)	0·9 (0·5–1·7)	24–26·5 kg . m^{-2}	0·5 (0·2–1·1)	0·9 (0·3–2·5)
≥26·5 kg . m^{-2}	0·9 (0·6–1·4)	0·6 (0·4–1·1)	≥26·5 kg . m^{-2}	1·0 (0·5–1·9)	0·6 (0·2–1·4)
	P=0·024			*P*=0·096	

*Adjusted for initial age, serum cholesterol, body mass index, systolic blood pressure, smoking and diabetes.
BMI=body mass index.
†*P*-value of the likelihood ratio test for significant contribution of the interaction term.

among women with a body mass index below 24 kg . m^{-2}, was the hazard ratio for heart rate levels above or equal to 80 beats . min^{-1} significantly higher than the reference (hazard ratio 1·8, confidence interval 1·1–2·8).

In Table 5, we present the estimated all-cause mortality hazard ratios of heart rate changes between first and second visit of more than 10 beats . min^{-1}, between 0 and 10 beats . min^{-1}, and negative changes (<0 beats . min^{-1}) for persons with initial levels above and below the population mean (72 beats . min^{-1}). A total of 119 men and 208 women showed an increase above 10 beats . min^{-1} between first and second measurement, of which 18 men and 25 women showed increases above 20 beats . min^{-1}. For both men and women the risk estimates are highest for those with a positive change and initial levels above the population mean. A similar trend was seen for those with initial

Table 5 Total mortality hazard ratios for 2 year changes in resting heart rate stratified by initial levels above and below the population mean*

Change	Men Initial level		Women Initial level	
	<72 beats . min^{-1}	≥72 beats . min^{-1}	<72 beats . min^{-1}	≥72 beats . min^{-1}
≥10 beats . min^{-1}	1·5 (0·7–3·3) n=99	2·3 (0·9–6·4) n=20	2·2 (1·1–4·7) n=154	2·9 (1·2–7·2) n=54
0–10 beats . min^{-1}	1·3 (0·7–2·3) n=363	1·9 (0·9–3·6) n=124	1·1 (0·6–2·3) n=451	1·9 (1·0–3·7) n=272
<0 beats . min^{-1}	1 n=361	1·3 (0·7–2·3) n=367	1 n=431	1·6 (0·9–2·9) n=772
(n events/at risk)	(110/1334)		(120/2134)	

*Adjusted for initial age, serum cholesterol, body mass index, systolic blood pressure, smoking and diabetes.

levels below 72, but this could partly reflect reaching their true level (regression to the mean).

Discussion

The study population has a higher proportion of 40 to 50 year-olds than the German population as a whole. This, however, has no influence on the presented risk estimates. Several cardiovascular risk factors are related to resting heart rate level, as observed by others[15]. Smoking was observed to elevate catecholamine levels and heart rate[16]. In our study, age shows almost no association with resting heart rate. A similar lack of association with age was observed in a representative sample of the German population[9], so it is unlikely that this indicates a selection bias. Small sex differences in heart rate were observed, but women had much lower mortality rates than men. We observed almost no cardiovascular mortality among the 40–60 year-old women, and only a few events among women with initial heart rates above 70 beats . min^{-1}. These low mortality rates are probably responsible for the absence of a significant association between heart rate and cardiovascular mortality among women.

Our analyses show a positive association between heart rate and total and cardiovascular mortality, even after adjustment for major cardiovascular risk factors. Several studies reported a similar association[1,2,5]. To the extent that heart rate is positively associated with unspecific mortality causes, it could be argued that it is an indicator of general poor health. Persons with known cardiovascular diseases were excluded in additional analyses, but there was still a positive association between heart rate and mortality. When the first 2 years of follow-up are excluded (excluding early mortality cases) the risk estimates remain almost the same. This indicates that the association between heart rate and mortality cannot be subscribed to the role of heart rate as an indicator of pre-existing illnesses. Although there is a tendency for a positive association between cancer mortality and heart rate, this does not reach statistical significance. A positive association between cancer and heart rate was observed by Persky *et al.*[7]. They assumed that excessive alcohol intake could be an important confounder. Correction for alcohol intake in our study does not, however, change the magnitude of association.

The effect of heart rate on mortality is somewhat modified by other risk factors. We observed the largest hazard ratio for elevated heart rates among men with a low cholesterol level and among women with low body mass index. In both cases, the estimated hazard ratio for the combined presence of risk factors was lower than expected from the isolated risks. This could possibly indicate that elevated levels of these risk factors, as well as elevated heart rate, result from the same atherogenic process which increases the mortality risk. For men, we observed a stronger association between heart rate and all-cause mortality among non-smokers. This was not observed for cardiovascular mortality and appeared to be due to a less than additive effect for cancer and other mortality causes.

The resting heart rate level is sensitive to such things as infections, recent physical activity, anxiety, and stress[17–19]. Intra-individual fluctuations will partly be a result of measurement error and of daily variations. Therefore changes in resting heart rate, as an independent predictor of mortality should be treated with caution[20]. It may not be possible to separate an observed effect of measured changes from effects due to regression to the mean, or effects of true changes. We tried to avoid such misinterpretations by stratification for the initial level. For persons with an initial level above the population average there was an additional predictive value of a 2 year change on survival. Without stratification by initial level, the higher risk for a change above 10 beats . min^{-1} will be diluted due to regression to the mean, and the positive risk for negative changes could be misinterpreted.

Several mechanisms on the relationship between heart rate and cardiovascular mortality have been proposed. The beneficial effects of beta-blockers on survival were partly associated with their heart rate lowering capabilities[21]. We did not have sufficient information on the use of beta-blockers at baseline, but conducted

analyses, excluding persons who reported they were in medical treatment prior to initial survey for cardiovascular disease as well as for hypertension. The initial heart rate distributions in these groups are not significantly different. Nevertheless, because of differences in mortality risks in these groups, differences in magnitude of the association between heart rate and mortality are observed. The hazard ratios for all-cause, cardiovascular disease, cancer and other mortality causes are lower when excluding persons under treatment for cardiovascular disease. This is expected because high risk persons are excluded. The hazard ratios, when excluding persons under treatment for hypertension, however, were higher than the ratios in Table 3. In the 1980s, hypertension was often treated with beta-blockers. Such persons will have a higher mortality risk but lower heart rates compared to non-hypertensives, which will dilute the observed relationship.

Heart rate is an indicator of physical fitness and can be modified by physical exercise[8,22]. Both physical fitness and physical activity are associated with cardiovascular mortality, which could explain a part of the association between heart rate and mortality. However, the association between heart rate and mortality among hypertensives remained after correction for physical activity levels[5].

The resting heart rate is also a marker of haemodynamic and autonomic nervous system states that could promote cardiovascular mortality by inducing atherosclerosis and by producing rhythm disturbances[23]. A chronic predominance of sympathetic over parasympathetic activity could promote atherosclerosis. An elevated heart rate level was associated with atherogenic serum lipid fractions[24] and a faster progression of atherosclerosis in clinical experiments with primates[10,25]. Higher heart rates were associated with progression of diffuse atherosclerosis and of distinct coronary stenosis[26]. It was suggested that local haemodynamic effects of heart rate contribute to faster plaque formation in the coronary arteries. Other mechanisms could also be involved. A low heart rate will result in longer diastolic filling time; this will, to a certain degree, increase stroke volume[27] and improve the oxygen supply of the heart muscle. Haemodynamic disturbances could predispose persons to sudden death[23] or to lower survival chance after myocardial infarction[6]. The inability to reduce heart rate during sleep could also be a damaging factor[28]. An inverse relationship of heart rate with heart rate variability was observed and lower variability, indicating lower adaptability (sympathetic predominance), was associated with increased mortality after myocardial infarction[29].

An elevated heart rate could also be a result of increased insulin resistance induced by high carbohydrate and/or fat intake, physical inactivity and obesity. As a consequence, chronic high insulin levels will increase sympathetic activity[30,31]. The observed lower impact of elevated heart rate among men with high cholesterol levels and women with high body mass index would fit in this hypothesis, because these elevated risk factors and elevated heart rate could be indicators of the insulin resistance syndrome. The strong effect of heart rate among men with low levels of cholesterol and women with low body mass index, however, suggests that other mechanisms could also be important. Overall, the resting heart rate (favourably based on repeated measurements) seems to be an important predictor of survival and can be used to select persons at higher risk. Recently, we observed a difference of about 3–5 beats . min^{-1} between former East and West Germany. This may partly explain the discrepancy in life expectancy between the two parts of Germany[32].

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