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The association of resting heart rate with cardiovascular, cancer and all-cause mortality

Eight year follow-up of 3527 male Israeli employees (the CORDIS Study)

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Background Resting heart rate has frequently been shown to be a predictor of coronary heart disease mortality. Elevated heart rate could also be a marker for the presence of other risk factors, which have not been taken into consideration in previous studies.

Objective To evaluate the effect of resting heart rate on the risk of all-cause cardiovascular and cancer mortality, taking into consideration haematological variables.

Method The association between resting heart rate and mortality was assessed applying Cox's proportional hazard models to data obtained in an 8 year follow-up of 3527 Israeli male industrial employees. During this period 135 deaths were recorded, 57 from cardiovascular disease and 45 from cancer. Resting heart rate was assessed at entry; potential confounding demographic, anthropometric and socioeconomic variables, haematological data, serum lipid levels and health-related habits were accounted for.

Results We found that the relative risk of all-cause mortality increased with increasing resting heart rate, workers with resting heart rate >90 beats . min^{-1} had an adjusted relative risk of 2·23 (95% CI 1·4–3·6) compared with those with a heart rate <70 beats . min^{-1}. A similar result was achieved for cardiovascular disease mortality (adjusted relative risk 2·02, 95% CI 1·1–4·0). Cancer mortality was not associated with resting heart rate.

Conclusion This study found that resting heart rate is associated with all-cause and cardiovascular disease mortality after controlling (in various statistical models) for platelet counts, haemoglobin concentration, white blood cell counts, total protein, and other recognized risk factors.
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Key Words: Heart rate, mortality, cardiovascular disease, cancer, epidemiology, haematology

See page 97 for the Editorial comment on this article

Introduction

Resting heart rate has consistently been found to be a predictor of coronary heart disease mortality[1–7], but elevated heart rate could also be a marker for the presence of other risk factors. Stress, the amount of regular physical activity, cigarette smoking, blood pressure level, blood viscosity, and plasma catecholamines are among factors that can affect heart rate[8–14]. These factors have also been shown to be associated with blood lipids and lipoproteins[15–18], as well as with haemoglobin, platelet count and leukocyte count[15,19–23]. They are also believed to be cardiovascular disease risk factors[24–33]. To the best of our knowledge these associations and their need for control, have not been appropriately addressed in previous studies of heart rate and cardiovascular disease mortality. Furthermore, the association of heart rate with mortality from non-cardiovascular causes is unclear. In some studies resting heart rate has been found to be a predictor of cancer mortality[34,38]. Physical activity was not always controlled[39] in these studies and we are unaware of studies that controlled for the possible confounders presented above.

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The present study examines the possible association of resting heart rate with cardiovascular disease and cancer mortality among Israeli industrial employees. Our analyses included (in various statistical models) physical activity, anthropometric and socioeconomic factors, blood counts and cholesterol levels, and health habits.

Materials and methods

Study population

In 1985 we collected the names of all Jewish male industrial employees from 21 plants throughout Israel. These included furniture, electronic goods, textile, food, tire and iron product manufacturers. Between 1985 and 1987, the 5547 workers identified through the CORDIS Study[40] were offered, free of charge, an extensive history, physical examination and cardiovascular risk factor evaluation. The screening took place on site, and 3816 (68·8%) of the candidates responded. The mean age of the whole cohort was 43 years, and of the non-responders, 39 years. Nearly all the subjects were present at the workplace 9 h per day, with half-hour breaks for breakfast and lunch. Based on job titles, 76% were blue-collar workers.

Data collection at entry

Employees from one or two factories were screened each month. Blood samples were taken on the same day for all responders in a given factory; on a different day, physical examinations were performed and questionnaires completed. Venous blood samples were taken in vacuum tubes without additives and with EDTA (for blood counts) with the subjects sitting at the beginning of a regular workday (0700–0900 h) after a fast of 8–10 h. The tourniquet was released immediately after blood began to enter the tube, to avoid venous stasis. Serum was separated from the whole blood in the tubes without additive within 2 h of being drawn. Blood tests (for lipids) were carried out on fresh sera (in groups sampled on the same day) on an Abbott VP automated chemical analyser. The enzymatic colour method using CEH Mas Cholesterol reagent, Lancer[41], determined cholesterol. Blood with EDTA was stored (3–4 h) at 4°C until blood counts were carried out on a Sequoia 3000 automated haematology system. Albumin was determined by the Bron-Cresol-Green (BCG) method (Sigma U.S.A.). Total protein was estimated by the Biuret method (Sigma U.S.A.). In addition to internal and external quality control of the laboratory, blinded serum samples were received periodically from the lipid reference laboratory of the WHO MONICA project for regular checking of the lipid measurements. The coefficients of variation for cholesterol were as follows: (1) intra-assay: 1·0%; (2) inter-assay: 1·9%. The average bias compared with the WHO reference serum was − 2%.

Physical examinations were carried out by trained technicians one subject at a time in the non-fasting state between 0700 and 1600 h in a quiet air-conditioned room allocated by factory management. Trained technicians took all of the measurements. The examination included weight and height measurements. Blood pressure was measured with a standard mercury sphygmomanometer, once with the subject supine and twice with the subject seated (1 min apart). The systolic blood pressure corresponded to the first Korotkoff sound. The average of the second and third measurements was included in the analysis. Quetelet's index = weight (kg)/height $(m)^2$ was used as an index of body mass. After at least 5 min supine rest, blood pressure and resting ECG were measured in a lying position. From a 12-channel resting electrocardiogram (ECG), cardiac cycles over a 20 s period were used to estimate heart rate. This value was validated with the automatic output of the ECG device (Cardiograph Hewlett Packard Model 4760AM). Additional data on resting heart rate standing and sitting were also obtained[42].

Information was collected for each subject in a personal computerized interview and included demographic data, country of origin, education, personal habits, medical history, and detailed data on smoking, coffee and alcohol consumption. Engagement in sport activities at leisure time was included in the analysis as: physically active (regular training at least once a week) or not physically active. A past history of cardiovascular disease was based on answers to questions concerning whether the subjects' physician had ever diagnosed a heart attack or stroke.

Exclusions

Subjects who were younger than 25 years (n = 119), had diagnosed cardiovascular disease or were receiving chronic medication capable of affecting heart rate (such as beta-blockers) (n = 116), were working only part time (n = 33), or were missing data (n = 21) were excluded from the analyses. Complete data were available for 3527 subjects.

Mortality data

Follow-up data on mortality were obtained from the National Death Registry (NDR) for the years 1987 through 1994, and all death certificates were re-examined. Further information was obtained from the National Cancer Registry. We verified the deaths identified by the National Death Register by contacting the households of 2690 of the workers over the 2 years following the 8-year follow-up period. The mortality data were found to be reliable in that no additional deaths to those recorded during the follow-up period were identified; this assured us that there were no losses to follow-up. We also corrected the cause of death

reported by the National Death Register by reviewing the death certificates and compared the cause of death on the death certificates to those recorded in the National Death Register and confirmed the cancer deaths with the Cancer Registry. We divided the deaths into three groups by cause: cardiovascular disease (ICD-9-401-459·9), cancer (IDC-9-140-239) and other. Although there were numerous classification errors in the type of cancer, 45 of the 48 cancer cases were identified correctly as cancer deaths by the National Death Register; the remainder were misclassified under other causes (two cases) or cardiovascular causes (one case). Cardiovascular disease was identified by the National Death Register as the cause of 65 deaths, but six were misclassified: one cancer, two chronic lung disease, two valvular heart disease, and one motor vehicle accident. Furthermore, there were five cases of cardiovascular disease that were misclassified as other causes by the National Death Register. Thus the overall accuracy of the National Death Register was 91%.

Statistical analysis

Two-sample t-test and non-parametric test were applied to test inter-group differences in quantitive parameters, and Pearson, chi-square and Fisher's exact test for inter-group differences in categorical parameters. Mortality rates per 1000 person-years of follow-up were computed for each of the categories of resting heart rate. Age-adjusted relative risk (RR) and 95% confidence intervals (CI) were determined with Cox's proportional hazard models. Both logistic regression and Cox's proportional hazard models with and without age as a time-dependent covariant were used to analyse the relationship between heart rate and subsequent mortality, with adjustment for potential confounders. Cox's proportional hazard models were performed with the PHREG procedure in SAS[43] version 6·09 on a Sun station. In further analyses, resting heart rate from ECG was substituted by sitting and standing resting measures. Since results were similar for all the methods (logistic regression and Cox's proportional hazard models), only Cox's proportional hazard models without age as a time-dependent covariant are presented. The possible interaction of resting heart rate with all minor independent variables was tested. No significant interactions were found. The chi-square test for trend was used to check the hypothesis of increasing mortality with increasing heart rate. All tests were two-tailed, and a P value of 5% or less was considered statistically significant. The data were analysed with the SAS software (SAS Institute, Cary, North Carolina, U.S.A.)[43].

Results

Table 1 shows the characteristics at entry of the 3527 subjects, distributed by outcome at follow-up. During the follow-up period, 135 deaths were recorded, 57 from cardiovascular disease and 45 from cancer. Statistically significant differences between the alive and dead subjects were found in the following variables at entry: age, sport engagement at leisure time, cigarette smoking habits, resting systolic blood pressure, serum cholesterol level, haemoglobin concentration, total protein concentration and, blue or white-collar work. There were 14 subjects in the cohort unaware of their cardiovascular disease but having major changes in ECG at entry. In univariate analyses, age, smoking status, sports activities, total protein, haemoglobin concentration, cholesterol level, LDL-cholesterol, systolic blood pressure and years of formal education were all predictors of all-cause mortality ($P<0·05$ for all variables).

Categorization of the subjects was as follows: <60 beats . min^{-1}, 60–69 beats . min^{-1}, 70–79 beats . min^{-1}, 80–89 beats . min^{-1}, and ≥ 90 beats . min^{-1}. This was in order to allow comparability with previous studies. According to this classification 4% of the subjects had heart rates lower than 60 beats . min^{-1}, 19% between 60 and 69 beats . min^{-1}, 38% between 70 and 79, 26% between 80 and 89, and 13% had heart rate equal to or higher than 90 beats . min^{-1}. Table 2 shows the baseline characteristics of the subjects by heart rate group. There were clear differences between the groups; statistically significantly positive correlations were found between heart rate and age, body mass index, cigarette smoking, systolic blood pressure, serum cholesterol, platelets and white blood cell counts, and blue collar work ($P<0·05$ for all variables). Subjects who participated in sports activities had lower heart rate. An inverse relationship was found between the years of formal education and heart rate. More subjects with lower heart rates were of European origin. There were no differences between heart rate groups in the subjects' family history of cardiovascular disease, in alcohol consumption and HDL levels. The statistical significance of some findings in both Tables 1 and 2 might be chance findings due to multiple testing.

Table 3 describes the 8-year follow-up findings for numbers of deaths, person-years of exposure to heart rate, and crude mortality rate per 1000 person-years for all causes, and for causes of cardiovascular disease and cancer, by resting heart rate category. Mortality rates for all-cause and cardiovascular disease increased with increases in heart rate. This trend was not seen for cancer mortality rates. Age-adjusted relative risks are also given in Table 3 and demonstrate a significant increase in risk of all-cause mortality in subjects with heart rates of 80 beats . min^{-1} or higher, and an increase in risk of cardiovascular disease mortality in subjects with heart rates of 90 beats . min^{-1} or more. No statistically significantly trend was found for cancer mortality.

The evaluation of the relationship of resting heart rate (beats . min^{-1}) as a continuous variable with all-cause mortality, with adjustment for statistically significant risk factors in univariate analyses, showed that resting heart rate was positively associated with all-cause

Table 1 Characteristics at entry of the 3527 male subjects, distributed by outcome at follow-up

Variable	Alive	All-cause deaths	CVD deaths	Cancer deaths
Sample size	3,392	135	57	45
Age at entry (years)	44·8 (11)	56·7* (8)	58·6* (7)	55·6* (9)
Weight (kg)	75·1 (12)	74·4 (12)	74·7 (14)	75·3 (11)
BMI (kg . m^{-2})	25·9 (0·4)	26·5 (4)	26·7 (4)	26·4 (3)
Alcohol consumption (3 drinks . week^{-1}) (%)	13	8	9	9
Sports (%)	24	13*	15*	9*
Smoking status (%)				
Past smoker	20	27	30	22
Current smoker	38	45*	42	49*
Cigs/day among smokers	20·6 (11)	22·2 (14)	18 (9)	27* (16)
Family history of CVD (%)	6	4	5	2
Formal education (%)				
<12 years	60	76	77	75
12 years	20	16	12	16
>12 years	20	8	11	6
Resting SBP (mmHg)	125·3 (16)	137·1* (21)	142·1* (20)	133* (21)
Serum cholesterol (mg . dl^{-1})	205·4 (47)	217* (74)	225·8* (85)	206·7 (72)
Triglycerides (mg . dl^{-1})	156 (103)	161·3 (89)	160·8 (96)	155·1 (79)
HDL (mg . dl^{-1})	43·4 (12)	42·6 (12·9)	42·7 (16)	41·3 (17)
LDL (mg . dl^{-1})	131·8 (40)	143·6 (63)	152·8* (73)	134·4 (57)
HDL/cholesterol	0·21 (0·07)	0·19* (0·07)	0·20 (0·07)	0·21 (0·06)
Hemoglobin (g . dl^{-1})	15·4 (1·7)	15·0 (2·2)	15·2 (1·1)	14·5* (3·4)
Platelet (10^3 . mm^{-1})	224·3 (65)	224 (84)	228·1 (94)	220·1 (81)
Tot. protein (g . dl^{-1})	7·16 (0·83)	6·9 (1·5)	6·95 (1·74)	6·64* (1·80)
WBC (cells . µl^{-1})	7026 (2440)	7235 (2051)	7262 (1487)	7135 (2750)
Country of origin (%)				
Africa	28	25	28	20
Asia	15	18	21	11
Europe	48	52	46	61
Israel	1	1	0	3
Yemen	7	34	4	5
Blue-collar (%)	75	84	82	86*
Resting heart rate (beats . min^{-1})	76·9 (10)	81·1 (12)	81·1 (14)	79·1 (9)

Figures are mean (standard deviation), $^{**}P<0.01$; $^{*}P<0.05$, as compared with the alive group. CVD=cardiovascular disease; BMI=body mass index; cigs.=cigarettes, SBP=systolic blood pressure; HDL=high density lipoproteins; LDL=low density lipoproteins.

mortality (adjusted RR, 1·03; 95% CI, 1·01–1·04). Age, smoking status, and cholesterol were all significant confounders in this relationship. Multivariate analyses of the association between heart rate and cardiovascular disease mortality showed similar results (adjusted RR, 1·03; 95% CI, 1·01 to 1·05); no statistically significant association was found with cancer mortality (adjusted RR 1·01; 95% CI, 0·98 to 1·04 (data not shown in tables). Multivariate analyses with heart rate as a categorical variable showed positive associations with all-cause mortality (adjusted RR, 1·35; 95% CI, 1·34–1·59) and cardiovascular disease mortality (adjusted RR, 1·39; 95% CI, 1·07–1·80), and a trend for cancer mortality (adjusted RR, 1·11; 95% CI, 0·82–1·51 data not shown in tables). Exclusion of subjects with ECG abnormalities at entry did not affect significantly the association of heart rate with cardiovascular disease mortality (adjusted RR, 1·44; 95% CI, 1·10–1·90). When the analyses were repeated to include age as a time-dependent variable and logistic regression was performed, there were essentially no differences in the results (data not shown). There were 51 diabetic subjects in the entire cohort at entry; their inclusion or exclusion from the statistical models did not affect the results. Dividing the follow-up into two periods had no effect on the results. Table 4 shows the results of the relative risk and 95% confidence interval for all-cause, cardiovascular disease and cancer mortality of the different heart rates categories after adjustment for statistically significant risk factors in univariate analyses, with additional adjusting for sports activities and for haemoglobin level. These models show that the association of resting heart rate with all-cause and cardiovascular mortality is independent. Due to the small number of cancer deaths, statistical models were repeated comparing only two categories of resting heart rate. Analyses of cancer data with heart rate divided into two categories [<79 beats . min^{-1} (reference group) and >80 beats . min^{-1}] did not affect the results: RR adjusted for age, smoking and education 1·44, 95% CI 0·77 to 2·71; RR also adjusted for sport 1·40, 95% CI 0·75 to 2·60; RR also adjusted for haemoglobin 1·48, 95% CI 0·79–2·78.

Discussion

Previous studies have reported an association between resting heart rate and all-cause mortality and mortality

Table 2 Baseline characteristics of the study groups

	Resting heart rate (beats . min^{-1})					
Variable	<60	60–69	70–79	80–89	≥90	*P**
Sample size	132	678	1349	909	459	
Age (years)	43·7 (12)	45·9 (11)	44·6 (11)	45·3 (10)	46·7 (11)	0·003
Weight (kg)	74·9 (11)	74·7 (12)	74·7 (12)	75·8 (12)	75·5 (12)	0·278
BMI (kg . m^{-2})	25·6 (3)	25·6 (4)	25·6 (3)	25·7 (3)	26·1 (4)	0·001
Alcohol consumption (3 drinks . week^{-1}) (%)	9	12	14	13	13	0·547
Sports (%)	45	29	25	20	16	0·001
Smoking status (%)						0·001
Never smoked	58	49	42	36	37	
Past smoker	27	22	21	18	16	
Current smoker	15	29	37	46	47	
Cigs/day among smokers	16 (10)	18 (12)	20 (11)	23 (12)	21 (11)	0·0001
Family history of CVD (%)	4·2	6·1	7·3	6·1	5·8	0·540
Formal education (%)						0·001
<12 years	47	59	59	64	68	
12 years	23	20	21	20	19	
>12 years	28	21	20	16	13	
Resting SBP (mmHg)	126 (17)	125 (18)	124 (16)	127 (16)	131 (18)	0·0001
Serum cholesterol (mg . dl^{-1})	203 (44)	204 (47)	204 (47)	208 (52)	212 (53)	0·028
HDL (mg . dl^{-1})	47 (13)	44 (12)	43 (12)	43 (13)	43 (13)	0·129
Triglycerides (mg . dl^{-1})	117 (64)	144 (94)	153 (99)	166 (111)	169 (167)	0·001
LDL (mg . dl^{-1})	127 (36)	131 (40)	131 (40)	132 (42)	135 (47)	0·346
HDL/cholesterol	0·24 (0·07)	0·22 (0·07)	0·22 (0·07)	0·22 (0·07)	0·22 (0·07)	0·048
Haemoglobin (g . dl^{-1})	15 (1)	15 (20)	15 (2)	15 (2)	16 (1)	0·0002
Haematocrit (%)	44·6 (2·8)	44·7 (4·4)	45·1 (2)	45·2 (5·3)	46·0 (2·8)	0·001
Platelet (10^3 . mm^{-3})	217 (55)	219 (55)	222 (66)	229 (66)	232 (62)	0·0004
WBC (cells . µl^{-1})	6803 (1481)	6822 (3954)	6882 (1766)	7215 (2056)	7510 (1931)	0·0001
Tot. protein (g . dl^{-1})	7·2 (0·4)	7·2 (0·8)	7·2 (0·8)	7·1 (1·1)	7·2 (0·8)	0·010
Ethnic origin (%)						
Africa	21	25	29	30	31	
Asia	19	14	16	15	18	0·024
Europe	58	54	47	47	46	
Israel	0	1	1	1	0	
Yemen	1	6	7	6	5	
Blue-collar (%)	66	73	76	77	80	0·01

* ANOVA tests were used for quantitative parameters and chi-square and Fisher's exact test for differences in categorical parameters.

from cardiovascular disease. The present results confirm that these associations are independent of haematological factors that may have confounded previous studies. However, due to the limited number of end-points we were unable to control for all the haematological and other risk factors simultaneously. No statistically significant association was found between resting heart rate and cancer mortality, but the confidence intervals were wide due to a small number of end-points. One of the criticisms of previous studies was the fact that the majority used resting heart rate from ECGs, and this could be the source of discrepancy with negative studies[44]. For our sample three different measures were available in different body postures[42], and when the analyses were repeated using these measures there were essentially no differences in the results. Further follow-up of our cohort is needed to increase the sensitivity of our analysis regarding the association of resting heart rate with cancer mortality.

Possible explanations for the associations between resting heart rate with serum lipids and haematological factors were discussed elsewhere[23,45]. Among others, it was suggested that elevated heart rate may be a result of increased sympathetic activity, reduced vagal activity, or both (this may at least partly explain the association of resting heart rate with haematological factors)[46,47]. Several underlying mechanisms have been indicated as possibly responsible for the association between elevated heart rate and cardiovascular disease mortality. A rapid heart rate may intensify the pulsatile nature of the arterial blood flow (altering velocity and direction), which may favour the occurrence of injury to the endothelium[48,49] with consequent initiation or exacerbation of the arteriosclerosis process[50,51]. Furthermore, a rapid heart rate resulting from autonomic imbalance, with reduced heart rate variability, has consistently been shown to promote the occurrence of life-threatening ventricular arrhythmias, whereas increased vagal tone exerts a protective and antifibrillatory effect[52]. Therefore a study on the association of heart rate with cardiovascular disease mortality controlled for heart rate variability would be beneficial. In older subjects and

Table 3 Crude mortality rates and age-adjusted relative risk for all-cause, cardiovascular disease and cancer mortality by resting heart rate, Israeli CORDIS study 1987–1996

Resting heart rate beats . min $^{-1}$	All-cause mortality				CVD mortality			Cancer mortality		
	Person-years	No. of deaths	CMR/1000 person-years	Age-adjusted RR (95% CI)	No. of deaths	CMR/1000 person-years	Age-adjusted RR (95% CI)	No. of deaths	CMR/1000 person-years	Age-adjusted RR (95% CI)
<70	6402	23	3·59	1·0	13	2·03	1·0	8	1·24	1·0
70–79	10658	38	3·56	1·17 (0·7–2·0)	12	1·12	0·68 (0·3–1·5)	14	1·31	1·21 (0·5–2·9)
80–89	7142	40	5·60	1·79 (1·1–3·0)	15	2·10	1·24 (0·6–2·6)	16	2·24	2·01 (0·9–4·7)
≥90	3548	34	9·58	2·67 (1·5–4·5)	17	4·79	2·42 (1·2–5·0)	7	1·97	1·57 (0·6–4·3)
Tests for trend				P=0·0001			P=0·0006			P=0·3719

CVD=cardiovascular disease; CMR=crude mortality rate; RR=relative risk; CI=confidence interval.

Table 4 Adjusted* relative risk of all-cause, cardiovascular disease, and cancer death, by resting heart rate at baseline; CORDIS study, 1987–1994

Heart rate (beats . min^{-1})	Adjusted		Also adjusted for sport		Also adjusted for haemoglobin	
All cause death*	RR	95% CI	RR	95% CI	RR	95% CI
70–79	0·94	0·6–1·5	0·94	0·6–1·5	0·95	0·6–1·6
80–89	1·42	0·8–2·3	1·40	0·8–2·3	1·45	0·9–2·4
≥90	2·11	1·3–3·4	2·08	1·2–3·9	2·23	1·4–3·6
Test for trend	P=0·001		P=0·001		P=0·001	
CVD death*						
70–79	0·53	0·2–1·2	0·53	0·2–1·2	0·54	0·2–1·2
80–89	0·82	0·4–1·8	0·83	0·4–1·8	0·83	0·4–1·9
≥90	1·95	1·1–3·8	1·95	1·1–3·8	2·02	1·1–4·0
Test for trend	P=0·017		P=0·011		P=0·001	
Cancer death**						
70–79	0·85	0·4–2·0	0·85	0·4–1·9	0·86	0·3–2·0
80–89	1·53	0·7–3·4	1·49	0·6–3·3	1·55	0·7–3·5
≥90	1·08	0·4–2·9	1·04	0·4–2·8	1·13	0·4–3·0
Test for trend	P=0·398		P=0·445		P=0·353	

Reference group resting heart rate <70 beats . min^{-1}.
*Adjusted for age, education, body mass index, cholesterol, and smoking.
**Adjusted for age, smoking, and education.
When haemoglobin was replaced in different models by platelets, white blood cells and total protein; the results of all models were essentially the same (data not shown).

in patients with pre-existing disease, a rapid heart rate might indicate merely low physical fitness that is associated with increased mortality. While we controlled for sport engagement in leisure time, we cannot conclude on the fitness of our subjects. In subjects with subclinical forms of cardiovascular disease, a fast heart rate may reflect loss of cardiac reserve as a result of impaired myocardial function. An elevated heart rate could enhance ischaemia by increasing myocardial oxygen consumption. Finally, a rapid heart rate may reflect a faster metabolism and the accompanying faster production of harmful free radicals. However, in the latter case we would expect an association of heart rate with cancer mortality that was not observed in this study.

There are several possible biases in this study. First, the study population was restricted to industrial male employees. Although the healthy worker effect would probably lead to an under-estimation of the magnitude of the association of heart rate with mortality, it would not be prudent to extrapolate them to the general population. Second, subjects in the high heart rate group may have had undiagnosed diseases or disabilities that could lead to early all-cause mortality. We attempted to correct for this bias by carefully excluding from our analysis all subjects with known cardiovascular disease and those receiving chronic medication. Exclusion of subjects with major ECG changes at entry did not change the results. We also evaluated the relationship between heart rate and mortality at both early and late follow-up intervals, and no significant changes were observed. Furthermore, risk factor adjustment partly corrects for subclinical illness. Third, heart rate was assessed at entry, and there was no information on possible changes in this and other risk factors over the study period. However, time and age adjustments were done. Finally, there was possible information bias in the study, since death certificates are prone to misclassification. We verified the deaths identified by the National Death Registry by contacting the households of 2690 of the workers. Since no additional deaths took place during the follow-up period, we assumed that the mortality data were reliable and that there was no loss to follow-up. Causes of death on the death certificates were compared to the National Death Register records, and the cancer deaths were confirmed with the Cancer Registry; the overall accuracy of the data was 91%. However, it is unclear what effect the inclusion of cancer morbidity would have had on our results.

We conclude that among industrial employees, all-cause and cardiovascular disease mortality rates are independently associated with resting heart rate, whereas there is no association of resting heart rate with cancer mortality. A fast resting heart rate should not be considered an essentially benign condition, merely reflecting a temporary state of anxiety[44]. The effect of interventions to reduce heart rate on mortality rates should be investigated.

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