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Resting Heart Rate is a Risk Factor for Cardiovascular and Noncardiovascular Mortality

The Chicago Heart Association Detection Project in Industry

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In a prospective cohort study, associations of resting heart rate with risk of coronary, cardiovascular disease, cancer, and all-cause mortality in age-specific cohorts of black and white men and women were examined over 22 years of follow-up. Participants were employees from 84 companies and organizations in the Chicago, Illinois, area who volunteered for a screening examination. Participants included 9,706 men aged 18–39 years, 7,760 men aged 40–59 years, 1,321 men aged 60–74 years, 6,928 women aged 18–39 years, 6,915 women aged 40–59 years, and 1,151 women aged 60–74 years at the baseline examination in 1967–1973. Vital status was ascertained through 1992. For fatal coronary disease, multivariate-adjusted relative risks associated with a 12 beats per minute higher heart rate (one standard deviation) were as follows: for men aged 18–39 years, relative risk (RR) = 1.27 (95% confidence interval (CI) 1.08–1.48); for men aged 40–59 years, RR = 1.13 (95% CI 1.05–1.21); for men aged 60–74 years, RR = 1.00 (95% CI 0.89–1.12); for women aged 40–59 years, RR = 1.21 (95% CI 1.07–1.36); and for women aged 60–74 years, RR = 1.16 (95% CI 0.99–1.37). Corresponding risks for all fatal cardiovascular diseases were similar to those for coronary death alone. Deaths from cancer were significantly associated with heart rate in men and women aged 40–59 years. All-cause mortality was associated with higher heart rate in men aged 18–39 years (RR = 1.11, 95% CI 1.01–1.20), men aged 40–59 years (RR = 1.16, 95% CI 1.11–1.21), and women aged 40–59 years (RR = 1.20, 95% CI 1.13–1.27). Heart rate was not associated with mortality in women aged 18–39 years. In summary, heart rate was a risk factor for mortality from coronary disease, all cardiovascular diseases, and all causes in younger men and in middle-aged men and women, and for cancer mortality in middle-aged men and women. *Am J Epidemiol* 1999;149:853–62.

cardiovascular diseases; coronary disease; heart rate; mortality; neoplasms; prospective studies; risk factors

In humans, several long term cohort studies have found resting heart rate to be a risk factor for mortality from coronary heart disease, cardiovascular diseases, cancer, or all causes (1–8). Some prior reports have been limited to men (1, 2, 4, 5, 8), and most were restricted to specific age groups, typically persons who were middle-aged at baseline examination. In a few reports, heart rate was not found to be a risk factor for mortality after adjustment for multiple covariates (3, 7, 8). Thus, the role of resting heart rate as a risk factor in humans remains incompletely examined in a wide range of ages and in both sexes.

Heart rate as an independent risk factor for mortality was investigated with use of data from the Chicago Heart Association Detection Project in Industry, a large prospective study providing mortality data for age-specific cohorts of both women and men. In this set of analyses, we stratified the data by sex and age to determine the relation of resting heart rate to mortality in women and men aged 18–39, 40–59, and 60–74 years at baseline, and we controlled for multiple possible confounding variables.

MATERIALS AND METHODS

Population

Between November 1967 and January 1973, the Chicago Heart Association Detection Project in Industry screened 39,573 women and men of varied ethnicities in 84 cooperating companies and organizations in the Chicago, Illinois, area. All employees in

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Abbreviations: CI, confidence interval; ICD-8, *International Classification of Diseases*, Eighth Revision; NHANES I, First National Health and Nutrition Examination Survey.

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the labor force, totaling approximately 75,000 people, were invited to participate regardless of type of job or shift worked. The volunteer rate for this screening effort was 53 percent.

Survey methods

Details on the standardized methods used in the Chicago Heart Association field examination have been given elsewhere (9). In brief, trained staff (nurses and technicians) measured height, weight, supine blood pressure (a single casual reading using a standard mercury sphygmomanometer), serum total cholesterol (nonfasting blood sample), plasma glucose level (1 hour after a 50-g oral glucose load), and serum uric acid level, and took a resting electrocardiogram. A self-administered questionnaire was used to collect demographic data, smoking history, and information on previous medical diagnoses and treatments (e.g., clinical diagnosis of hypertension or diabetes mellitus).

Resting electrocardiograms were recorded with the participant lying supine following a minimum rest period of 5 minutes. All electrocardiograms were read by one cardiologist using the criteria and forms of the 1960–1962 National Health Examination Survey (10). Tracings with any abnormality were later identified and reclassified according to the Minnesota code (11). Electrocardiographic abnormalities were classified as major or minor based on the criteria of the Pooling Project Research Group (12).

During the first years of screening, resting heart rate was determined to the nearest beat per minute by measuring the interval between R waves for three consecutive QRS complexes recorded on the electrocardiogram. In the later years of screening, a heart rate meter attached to skin electrodes performed the same measurement electronically and provided a digital reading. During a brief middle phase, heart rate was not systematically measured. Participants screened during this interim phase were excluded from these analyses.

Exclusions

A total of 5,792 participants were excluded, for the following reasons: data were missing upon follow-up (n = 100); the participants were outside of the age range of the study, i.e., they were not aged 18–74 years (n = 190); information on heart rate was missing, as described above (n = 4,971); data on other relevant variables were missing (n = 435); and there was electrocardiographic evidence of prior myocardial infarction at baseline (n = 96). Thus, this report is based on 33,781 persons (18,787 men and 14,994 women) aged 18–74 years who were free of electrocardiographic evidence of prior myocardial infarction at baseline, with the following age breakdown: 9,706 men aged 18–39 years, 7,760 men aged 40–59 years, 1,321 men aged 60–74 years, 6,928 women aged 18–39 years, 6,915 women aged 40–59 years, and 1,151 women aged 60–74 years.

Mortality endpoints

Vital status was ascertained through 1992, with a mean follow-up of 22 years. Deaths among cohort members were determined by several methods: before 1979, by direct mail, telephone, contact with the original employer, or matching of cohort records against Social Security Administration files; after 1979, by matching of study records against National Death Index records. Death certificates were obtained for known decedents, and multiple causes of death were coded by a physician according to the Eighth Revision of the *International Classification of Diseases* (ICD-8), adapted for use in the United States (13). All coding decisions were cross-checked by study team members blinded to baseline data. For this report, only underlying cause of death was used. Coronary heart disease mortality was defined as ICD-8 codes 410.0–414.9, cardiovascular disease mortality as ICD-8 codes 400.0–445.9, and cancer mortality as ICD-8 codes 140.0–209.9.

Statistical analyses

Two types of analyses were conducted. In the first type, participants were subdivided into four strata based on heart rate (<70, 70–79, 80–89, and ≥90 beats per minute). For each of the six age/sex groups, age-adjusted mortality rates per 10,000 person-years of follow-up were computed for coronary heart disease, cardiovascular disease, cancer, and all-cause mortality. Mortality rates for the four heart rate strata were age-adjusted by the direct method for each age/sex cohort based on the overall age distribution for each age/sex cohort. In the second type of analysis, three proportional hazards (Cox) regression models were used to calculate relative risks of death associated with a difference of 12 beats per minute (approximately one standard deviation) in heart rate. Model 1 adjusted only for baseline age. Model 2 adjusted for age, education (years), race (black and nonblack), serum total cholesterol (mg/dl), cigarette smoking (cigarettes/day), body mass index (weight (kg)/height (m)^2), body mass index squared, clinical diagnosis of diabetes mellitus, and major and minor electrocardiographic abnormalities. Because heart rate can contribute directly to the pathogenesis of hypertension (14, 15), blood pressure may be in the pathway of the relation between heart rate and mortality; therefore, model 2 analyses were

performed without inclusion of blood pressure, to take into consideration the possibility of overadjustment. In a third model (model 3), all variables in model 2 were included plus systolic blood pressure (mmHg).

To determine whether the heart rate-mortality association was consistent over time, we fitted separate Cox regression analyses for all men and all women aged 18–74 years for the 1- to 11-year and ≥12-year segments of follow-up time. This analysis could not be performed meaningfully for the six separate age/sex cohorts because of small numbers of deaths in several of these subgroups during the first 11 years of follow-up.

RESULTS

Baseline descriptive statistics

Table 1 presents data on baseline variables for the six age-/sex-specific cohorts. Mean heart rate was similar across the three age groups in men and was lower with age in women. Blood pressure was higher with age in both men and women; as expected, serum cholesterol was higher with age in women only. The proportion of current smokers was lower in men and women aged 60–74 years than in persons aged 18–39 years and 49–59 years. On average, male smokers used more than one package of cigarettes per day, female smokers fewer. Proportions of men and women with electrocardiographic abnormalities, diabetes, and antihypertensive drug treatment increased with age.

Correlations of heart rate with other baseline variables are shown by age and sex in table 2. Heart rate was positively and significantly correlated with systolic and diastolic blood pressures and cigarette smoking in all age groups ($p < 0.01$). Education was inversely correlated with heart rate in men and women aged 18–39 years and 40–59 years ($p < 0.01$); this association could have been due to greater cigarette smoking by less educated persons. Correlations of heart rate with age, serum cholesterol, and body mass index were small and/or inconsistent.

Baseline heart rate and 22-year mortality

Age-adjusted mortality rates for coronary heart disease, cardiovascular disease, all cancers, and all causes were generally higher with higher heart rate in younger men and in middle-aged and older men and women (tables 3 and 4). With only eight coronary heart disease deaths and 17 cardiovascular disease deaths in women aged 18–39 years, rates in this age/sex group were unstable across the four heart rate strata.

Tables 5–7 show the relation of a heart rate higher by 12 beats per minute to 22-year relative risks of death from coronary heart disease, cardiovascular disease, cancer, and all causes for age-specific cohorts of men and women, with adjustment for age only (model 1) and adjustment for age and other major risk factors and potentially confounding factors (models 2 and 3). Because of concern about overadjustment (see

TABLE 1. Baseline characteristics of men and women in the Chicago Heart Association Detection Project in Industry, by age group, 1967–1973

Variable	Men			Women		
	Ages 18–39 years (n = 9,706)	Ages 40–59 years (n = 7,760)	Ages 60–74 years (n = 1,321)	Ages 18–39 years (n = 6,928)	Ages 40–59 years (n = 6,915)	Ages 60–74 years (n = 1,151)
Mean heart rate (beats/minute)	75.4 (12.2)*	76.5 (12.2)	75.1 (12.2)	79.5 (12.3)	76.8 (11.7)	74.9 (11.4)
Mean age (years)	29.6 (5.5)	48.7 (5.6)	63.1 (3.0)	26.8 (6.1)	49.5 (5.4)	63.2 (3.2)
Mean serum cholesterol level (mg/dl)	189.7 (36.2)	212.5 (37.2)	210.9 (35.0)	180.8 (33.3)	218.8 (40.4)	233.0 (39.7)
Mean systolic blood pressure (mmHg)	134.2 (10.7)	141.5 (20.2)	152.8 (22.3)	123.3 (13.8)	136.4 (20.2)	149.0 (21.9)
Mean diastolic blood pressure (mmHg)	77.9 (10.7)	84.2 (12.2)	86.7 (12.4)	72.6 (10.5)	80.3 (11.8)	83.1 (11.9)
Antihypertensive treatment (%)	1.1	5.6	11.6	0.7	7.7	17.5
Cigarette smoking						
Current smokers (%)	48.3	42.1	28.6	44.0	36.0	23.7
Ex-smokers (%)	23.4	34.2	41.9	16.7	15.1	14.1
Mean no. of cigarettes smoked per day (among smokers only)	21.1 (10.7)	23.7 (11.6)	21.1 (11.0)	16.7 (9.9)	6.4 (10.1)	7.0 (9.7)
Mean body mass index†	26.0 (3.7)	27.3 (3.7)	27.3 (3.6)	22.8 (4.0)	25.2 (4.5)	26.8 (4.3)
Electrocardiographic abnormality						
Major (%)	3.3	8.5	20.2	5.3	12.3	20.1
Minor only (%)	5.4	7.6	10.8	3.3	4.9	5.0
Diagnosis of diabetes mellitus (%)	1.0	3.4	6.7	0.8	2.3	3.2
Mean years of education	13.8 (2.6)	12.8 (2.8)	11.9 (3.1)	13.0 (2.1)	11.9 (2.2)	11.4 (2.6)
Black race (%)	8.6	5.6	4.2	23.7	5.3	2.1

* Numbers in parentheses, standard deviation.
† Weight (kg)/height $(m)^2$.

TABLE 2. Simple correlations of baseline heart rate with other variables among men and women in the Chicago Heart Association Detection Project in Industry, by age group, 1967–1973

Variable	Men			Women		
	Ages 18–39 years	Ages 40–59 years	Ages 60–74 years	Ages 18–39 years	Ages 40–59 years	Ages 60–74 years
Age (years)	0.034*	−0.028	−0.024	−0.038*	−0.094*	−0.038
Serum cholesterol level (mg/dl)	0.088*	0.078	0.013	0.024	−0.024*	−0.017
Systolic blood pressure (mmHg)	0.295*	0.267*	0.255*	0.293*	0.226*	0.264*
Diastolic blood pressure (mmHg)	0.191*	0.206*	0.244*	0.189*	0.197*	0.195*
Cigarette smoking (no./day)	0.190*	0.212*	0.149*	0.123*	0.142*	0.154*
Body mass index†	0.041*	0.039*	−0.029	0.010	0.023	−0.059*
Education (years)	−0.140*	−0.121*	−0.042	−0.064*	−0.042*	−0.037

* $p < 0.01$.
† Weight (kg)/height (m)^2.

"Statistical analyses" above), results from model 2 are emphasized below.

Coronary heart disease mortality. Significant independent positive associations of heart rate and 22-year coronary heart disease mortality were found in men aged 18–39 years and in men and women aged 40–59 years, with relative risks (model 2) of 1.27, 1.13, and 1.21, respectively, per 12 beats/minute higher heart rate. Women aged 60–74 years had a relative risk of 1.16 per 12 beats/minute difference in heart rate for fatal coronary disease. This increased risk, although similar to that for women aged 40–59 years, was—with the smaller sample size—of borderline statistical significance.

Cardiovascular disease mortality. For all cardiovascular disease mortality, significantly greater risk with higher heart rate was also found in younger men and in middle-aged men and women. Relative risks for fatal cardiovascular disease were 1.23, 1.10, and 1.22, respectively, in these three cohorts.

Cancer mortality. For cancer mortality, associations were significant for middle-aged men and women (relative risks were 1.20 and 1.15, respectively). Heart rate was not associated with risk of mortality due to cancer among younger or older men or women.

All-cause mortality. An increased risk of death from all causes with higher heart rate was observed in five of the six age/sex groups—i.e., for all groups except women aged 18–39 years (relative risks of 1.05–1.20). Results were significant for younger men and middle-aged men and women and were borderline significant for older men.

Relations of heart rate to risks of coronary heart disease mortality, all cardiovascular disease mortality, and all-cause mortality tended to be stronger in middle-

TABLE 3. Age-adjusted cause-specific mortality rates over 22 years in men, by heart rate (beats per minute), Chicago Heart Association Detection Project in Industry

Age group and heart rate (beats/minute)	No. of men	Person-years of follow-up	No. of coronary heart disease deaths	Age-adjusted rate/10,000 person-years	No. of cardiovascular disease deaths	Age-adjusted rate/10,000 person-years	No. of cancer deaths	Age-adjusted rate/10,000 person-years	No. of deaths from all causes	Age-adjusted rate/10,000 person-years
Ages 18–39 years										
<70	3,100	65,535	22	3.4	28	4.4	34	5.4	114	17.6
70–79	3,018	63,776	28	4.4	39	6.1	42	6.5	147	23.0
80–89	2,282	47,852	50	10.3	61	12.6	46	9.6	146	30.4
≥90	1,306	27,442	35	12.1	43	14.9	23	8.0	101	35.3
Ages 40–59 years										
<70	2,225	44,390	149	32.7	214	46.9	153	33.5	452	99.2
70–79	2,474	48,052	234	47.9	298	60.9	221	45.3	643	131.6
80–89	1,844	35,248	187	54.5	251	73.6	186	53.9	540	157.8
≥90	1,217	22,160	157	74.1	193	90.6	148	68.8	444	207.2
Ages 60–74 years										
<70	442	7,273	106	145.8	145	199.3	72	99.0	256	352.0
70–79	419	6,730	85	126.1	122	181.7	82	122.7	254	378.7
80–89	272	4,332	56	127.9	82	189.3	44	103.2	155	360.8
≥90	188	2,670	47	179.7	61	233.4	35	133.0	132	501.5

TABLE 4. Age-adjusted cause-specific mortality rates over 22 years in women, by heart rate (beats per minute), Chicago Heart Association Detection Project in Industry

Age group and heart rate (beats/minute)	No. of women	Person-years of follow-up	No. of coronary heart disease deaths	Age-adjusted rate/10,000 person-years	No. of cardiovascular disease deaths	Age-adjusted rate/10,000 person-years	No. of cancer deaths	Age-adjusted rate/10,000 person-years	No. of deaths from all causes	Age-adjusted rate/10,000 person-years
Ages 18–39 years										
<70	1,350	27,972	4	1.4	5	1.8	15	5.4	34	12.1
70–79	2,145	44,966	1	0.2	1	0.2	31	6.7	47	10.3
80–89	2,014	41,963	2	0.5	6	1.4	22	5.2	49	11.6
≥90	1,419	29,725	1	0.4	5	1.8	15	5.4	36	12.8
Ages 40–59 years										
<70	1,776	36,558	53	13.3	80	20.0	107	28.1	227	58.1
70–79	2,323	47,957	63	13.1	100	20.8	143	29.8	303	63.1
80–89	1,810	36,749	88	25.1	121	34.4	149	41.8	317	89.4
≥90	1,006	20,227	50	26.4	75	39.1	86	43.9	210	108.1
Ages 60–74 years										
<70	360	6,679	36	52.8	62	90.6	57	84.8	137	202.2
70–79	407	7,362	59	79.7	86	116.0	55	74.5	165	222.6
80–89	258	4,748	31	63.3	53	110.9	24	57.0	109	236.0
≥90	126	2,194	22	104.3	32	147.8	20	92.4	59	271.4

TABLE 5. Adjusted relative risk* of mortality over 22 years in men and women aged 18–39 years, by baseline heart rate, Chicago Heart Association Detection Project in Industry

Cause of death	Men						Women					
	Model 1†		Model 2§		Model 3¶		Model 1†		Model 2§		Model 3¶	
	RR‡	95% CI‡	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Coronary heart disease	1.51	1.31–1.75	1.27	1.08–1.48	1.20	1.02–1 42	—#		—#		—#	
Cardiovascular disease	1.57	1.29–1.68	1.23	1.07–1.42	1.14	0.99–1.32	1.18	0.74–1.87	1.02	0.62–1.68	0.91	0.54–1.52
Cancer	1.23	1.05–1.43	1.10	0.94–1.29	1.09	0.92–1.29	1.02	0.82–1.26	1.02	0.81–1.27	0.99	0.78–1.25
All causes	1.26	1.16–1.36	1.11	1.01–1.20	1.04	0.95–1.14	1.05	0.90–1.22	1.01	0.86–1.18	0.97	0.82–1.14

* *Relative risk associated with a 12 beats/minute higher heart rate.*
† Age-adjusted model.
‡ RR, relative risk; CI, confidence interval.
§ Multivariate proportional hazards (Cox) model adjusted for baseline age and education (years), serum cholesterol (mg/dl), smoking (cigarettes/day), body mass index, body mass index^2, major and minor electrocardiographic abnormalities (no/yes), race (black/nonblack), and diabetes (no/yes).
¶ Adjusted for variables listed in model 2 plus systolic blood pressure (mmHg).
# There were too few deaths in this category for estimation of the relative risk.

TABLE 6. Adjusted relative risk* of mortality over 22 years in men and women aged 40–59 years, by baseline heart rate, Chicago Heart Association Detection Project in Industry

Cause of death	Men						Women					
	Model 1†		Model 2§		Model 3¶		Model 1†		Model 2§		Model 3¶	
	RR‡	95% CI‡	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Coronary heart disease	1.33	1.24–1.41	1.13	1.05–1.21	1.06	0.99–1.14	1.35	1.20–1.51	1.21	1.07–1.36	1.13	1.01–1.28
Cardiovascular disease	1.28	1.21–1.36	1.10	1.04–1.17	1.03	0.97–1.09	1.34	1.22–1.47	1.22	1.10–1.35	1.13	1.02–1.25
Cancer	1.30	1.22–1.39	1.20	1.11–1.28	1.17	1.09–1.26	1.19	1.09–1.30	1.15	1.05–1.26	1.13	1.03–1.24
All causes	1.31	1.26–1.36	1.16	1.11–1.21	1.11	1.06–1.15	1.28	1.21–1.36	1.20	1.13–1.27	1.15	1.08–1.22

* Relative risk associated with a 12 beats/minute higher heart rate.
† *Age-adjusted model.*
‡ RR, relative risk; CI, confidence interval.
§ Multivariate proportional hazards (Cox) model adjusted for baseline age and education (years), serum cholesterol (mg/dl), smoking (cigarettes/day), body mass index, body mass index^2, major and minor electrocardiographic abnormalities (no/yes), race (black/nonblack), and diabetes (no/yes).
¶ Adjusted for variables listed in model 2 plus systolic blood pressure (mmHg).

TABLE 7. Adjusted relative risk* of mortality over 22 years in men and women aged 60–74 years, by baseline heart rate, Chicago Heart Association Detection Project in Industry

Cause of death	Men						Women					
	Model 1†		Model 2§		Model 3¶		Model 1†		Model 2§		Model 3¶	
	RR‡	95% CI‡	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Coronary heart disease	1.05	0.94–1.17	1.00	0.89–1.12	0.95	0.85–1.07	1.22	1.04–1.44	1.16	0.99–1.37	1.01	0.85–1.19
Cardiovascular disease	1.05	0.95–1.15	1.00	0.90–1.09	0.94	0.85–1.04	1.15	1.01–1.31	1.10	0.96–1.25	0.99	0.86–1.13
Cancer	1.11	0.97–1.26	1.06	0.93–1.20	1.04	0.91–1.19	1.01	0.85–1.19	0.86	0.81–1.14	0.94	0.78–1.11
All causes	1.12	1.05–1.20	1.07	1.00–1.15	1.03	0.96–1.11	1.10	1.00–1.21	1.05	0.95–1.15	0.97	0.88–1.07

* Relative risk associated with a 12 beats/minute higher heart rate.
† Age-adjusted model.
‡ RR, relative risk; CI, confidence interval.
§ Multivariate proportional hazards (Cox) model adjusted for baseline age and education (years), serum cholesterol (mg/dl), smoking (cigarettes/day), body mass index, body mass index², major and minor electrocardiographic abnormalities (no/yes), race (black/nonblack), and diabetes (no/yes).
¶ Adjusted for variables listed in model 2 plus systolic blood pressure (mmHg).

aged women than in men (table 6). However, the small differences in Cox coefficients between men and women were not statistically significant (t = 0.86–1.63; p = 0.39–0.10).

In general, associations were weaker with the inclusion of systolic blood pressure in the Cox model (i.e., model 3 as compared with model 2). Increased mortality risk for all endpoints with higher heart rate remained significant among women aged 40–59 years (table 6, model 3); results were significant for cancer and all-cause mortality in middle-aged men. Further adjustment for baseline plasma glucose and uric acid levels did not change the relative risks (data not shown).

Cox regression analyses were conducted separately for all men and all women aged 18–74 years for the first 11 years of follow-up and the subsequent 11 years of follow-up. In the two follow-up periods, respectively, there were 426 and 730 deaths from coronary disease, 541 and 996 deaths from all cardiovascular diseases, 335 and 751 deaths from cancer, and 1,149 and 2,235 deaths from all causes in men; there were 103 and 307 deaths from coronary disease, 145 and 481 deaths from all cardiovascular diseases, 240 and 484 deaths from cancer, and 487 and 1,206 deaths from all causes in women. Findings were consistent across the two time periods, with no evidence of weakening of the associations over time.

DISCUSSION

In this 22-year mortality follow-up study of six age-/sex-specific cohorts of Chicago-area employed adults, a 12 beats/minute higher heart rate was significantly associated with increased risk of coronary heart disease and cardiovascular disease mortality in younger (aged 18–39 years) and middle-aged (aged 40–59 years) men and in middle-aged women. Higher resting heart rate was also an independent risk factor for cancer mortality in middle-aged men and women and for all-cause mortality in younger and middle-aged men and in middle-aged women. Heart rate was not found to be a significant independent risk factor for any of the causes of mortality analyzed here in older (aged 60–74 years) men or women. In addition, higher heart rate was not found to be a risk factor in the younger female cohort. Finally, risk relations were present in both the earlier (first 11 years) and the later (second 11 years) portions of the 22-year follow-up period. The findings extend observations on associations of resting heart rate to cardiovascular and noncardiovascular mortality that were previously reported from this cohort (1, 4, 8) and from other prospective studies (2, 3, 5–7).

A previous report based on three male Chicago cohorts, including the largest of those cohorts reassessed here with longer follow-up (8), demonstrated that resting heart rate was associated with increased risk of all cardiovascular and coronary disease mortality. In the prior report (8), which was based on only 5 years of follow-up in 5,784 Chicago Heart Association men aged 45–64 years at baseline, positive associations between heart rate and mortality were attenuated or became nonsignificant after adjustment for covariates including age, systolic blood pressure, cigarette smoking, cholesterol, and body weight. A similar effect, whereby the risk association was attenuated after adjustment for major covariates, was observed in a Kaiser Permanente study (16) and in an Israeli cohort (17). While the association between increased heart rate and cardiovascular disease endpoints weakened after multivariate adjustment in a Framingham Study report (3), the positive association of heart rate with death from coronary heart disease or all-cause mortality remained significant. A 1993 paper

based on 7,735 men from the British Regional Heart Study (18) who were followed for 8 years reported results similar to those for Framingham men.

Few previous studies have examined the relation between heart rate and mortality in women. In two reports from the Framingham Study (3, 19), heart rate was associated with total coronary disease death and sudden coronary disease death after adjustment for multiple coronary disease risk factors in men, but these relations were not confirmed in women. In the NHANES I Epidemiologic Follow-up Study (6) cohort, higher heart rate was associated with increased risk of cardiovascular and noncardiovascular mortality in both black men and white men. In that study, for black women, a resting heart rate of >84 beats per minute was associated with a threefold increase in risk of cardiovascular disease death. However, no significant increased risk with higher heart rate was observed in white women in the NHANES I Epidemiologic Follow-up Study. Thus, in the few previous studies that have included women, risks associated with higher heart rate in women have been uncertain because of variable results within and between studies. The variable results may be attributable to fundamental differences in the cohorts under study or to other undetermined factors, but a likely factor underlying the lack of association in several studies was smaller numbers of events due to shorter follow-up and/or smaller cohorts. This report from the Chicago Heart Association cohort included relatively large numbers of men and women. Thus, to our knowledge, this is the first long term cohort study to show similar multivariate-adjusted independent relations of increased heart rate to coronary, all cardiovascular disease, cancer, and all-cause mortality in middle-aged women and men.

As was shown here and elsewhere (20–23), heart rate is correlated with other cardiovascular disease risk factors, including systolic blood pressure, cigarette smoking, physical inactivity (18), levels of cholesterol (in other studies) and of important lipid fractions such as high density lipoprotein cholesterol (23), diabetes, insulin, uric acid, and general health status (2). In this study and in some others (2, 5), associations of higher heart rate with mortality risks, both cardiovascular and noncardiovascular, remained significant after adjustment for multiple covariates. Indeed, adjustment for some covariates, particularly blood pressure, may represent overadjustment, since heart rate is a known risk factor for high blood pressure (14, 15, 21) and a common underlying mechanism may account for elevation of both measures (24). Therefore, for the primary analyses here, we adjusted for age and other major covariates, but because of concern about possible overadjustment for blood pressure, our main conclusions are based on the model without adjustment for systolic blood pressure (model 2).

Several mechanisms for the coronary and cardiovascular disease findings are plausible. Animal studies have demonstrated that higher heart rate may be a causal factor in promoting atherosclerosis independent of blood pressure or blood lipids, presumably via a hemodynamic mechanism (25–27). Nabel et al. (28) showed that elevated heart rate induced by pacing can cause coronary artery vasoconstriction in humans with atherosclerotic coronary disease, suggesting a means by which elevated heart rate can cause myocardial ischemia independent of its effect on myocardial oxygen demand. Thus, higher heart rate could increase cardiovascular mortality risk by accelerating atherosclerosis or, in coronary disease patients, both by increasing oxygen demand and by directly reducing myocardial blood flow (28).

A limitation of some other reports on the role of heart rate in mortality risk has been short follow-up (8, 16, 17). If higher resting heart rate represents a surrogate for poor cardiovascular health or poor general health, then associations seen in short term follow-up might disappear in later follow-up. On the other hand, if higher heart rate is causal, cardiovascular damage may accrue over many years, requiring long term follow-up to uncover adverse effects. Owing to the lengthy follow-up available in this large Chicago cohort, we were able to examine the impact of heart rate on mortality in two successive 11-year intervals. Positive associations seen in the overall 22-year follow-up period were found to occur in the first 11 years after the baseline examination, and they persisted in the second 11-year period (years 12–22). Thus, these data, in contrast to those from shorter-term studies, provide increased confidence that the associations between elevated heart rate and mortality are not merely related to underlying poor health undetected by other means.

Because of the inability in this study (and in all observational research) to adjust for some plausible confounding variables, it is possible that higher resting heart rate is a surrogate for one or more unmeasured variables that may be causally linked to cardiovascular or noncardiovascular death. For example, Williams et al. (23) demonstrated associations between heart rate and certain lipoprotein subfractions that were not measured here. These included triglycerides, high density lipoprotein cholesterol, high density lipoprotein 3 mass, very low density lipoprotein mass, and low density lipoprotein mass (23). Wannamethee and Shaper (2) also found correlations of resting heart rate with potential confounders that we did not measure, including forced expiratory volume (inverse relation), physical

activity (inverse relation), and nonfasting triglyceride level. In the Williams et al. report (23), approximately 30 percent of the variance in resting heart rate was attributed to the lipid subfractions listed above. Thus, it is conceivable that higher heart rate could be partly due to covariates, such as those listed, which we did not measure and could not adjust for in our analyses.

Higher heart rate was also associated with total cancer mortality, although the association was significant only in middle-aged men and women. An association between higher resting heart rate and total cancer mortality has been shown previously in all-male cohorts, including the Chicago Heart Association cohort reported on here in longer follow-up (1), two other Chicago cohorts (1), and a British cohort (5, 29). Higher resting heart rate has been associated with prostate cancer mortality in men in a previous Chicago cohort report (4), but the association of higher heart rate with prostate cancer incidence and mortality was not confirmed in a recent report from a large cohort of men examined in multiphasic checkups in the Kaiser Permanente system in California (30). Higher heart rate has also been associated with colon cancer mortality in a male Hawaiian cohort (31). Recently, Dekker et al. (32) found an association, also only in men, between total cancer mortality and reduced heart rate variability, a factor that is correlated with both higher resting heart rate and abnormal autonomic function. There do not appear to have been any prior reports linking higher resting heart rate with cancer mortality in women, as described here. Because of limited data on women outside of this report, inconsistency of the association of heart rate with cancer in different age groups in this study, and the conflicting results in men concerning prostate cancer, further study of the relation between heart rate and cancer is warranted.

Several mechanisms might link mortality from various cancers to higher resting heart rate. For example, some cancers are believed to be directly under the influence of local neurotrophic factors associated with sympathetic nervous system activity. Prostate cancer is an example, and the prior report by Gann et al. (4) discusses this possibility at length. Frequent or regular exercise, which can reduce resting heart rate, has been linked to improved monocyte function (33), which could protect against the development or spread of various cancers by improving cancer phagocytosis and killing. In some but not all studies (34), regular exercise has been linked to a reduced risk of breast cancer (35), possibly via suppression of endogenous estrogen secretion. Since exercise training can also lower resting heart rate, the association of regular exercise with reduced breast cancer risk could also be related to lower heart rate. Conversely, if higher heart rate is a marker of underlying "stress," then a putative association between stress and cancer mortality (36) could manifest itself through an elevated heart rate. Associations between cancer and heart rate may be worthy of further exploration, including the relation of resting heart rate to specific cancers (those already mentioned and others).

While the results presented here were positive, significant, and concordant for middle-aged men and women, findings in older men and women did not retain significance after multivariate adjustment. It is unclear from these data whether heart rate associations attenuate with age because of changes in biology or simply because of smaller numbers of older people in the cohorts, resulting in loss of statistical power. Moreover, the meaning of resting heart rate in older people is complex, since elevated resting heart rate can be a marker for underlying diseases of various types (37). On the other hand, slow heart rate can also be a marker for cardiovascular disease, especially sinus node dysfunction in older people, and a cardiac risk factor in the elderly (38).

Results of this study, along with those of some others published previously, lend strong support to the concept that higher heart rate within the "normal" range in humans is a risk factor for coronary, cardiovascular, cancer, and all-cause mortality in both middle-aged women and men and younger men. Associations remained significant after adjustment for multiple covariates and were present in both shorter- and longer-term follow-up. The data are consistent with studies in both animals and humans suggesting that a causal role for increased heart rate in cardiovascular disease is biologically plausible (25–27).

In terms of therapeutic or preventive implications, these observations might help explain a protective effect of regular exercise (39, 40) and of heart rate-slowing medications in the primary and/or secondary prevention of cardiovascular disease (41–45). Aerobic exercise training can be advocated for a multitude of reasons as a preventive approach to cardiovascular disease, cancer, and all-cause mortality (39, 40). On the other hand, a possible preventive role for drugs that reduce heart rate in apparently healthy people requires further study before this practice can be advocated. These data from humans, combined with observations in mammalian species suggesting that resting heart rate correlates with life expectancy (46), raise the provocative idea that various means of slowing heart rate might be useful in prolonging life.

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REFERENCES

1. Persky V, Dyer AR, Leonas J, et al. Heart rate: a risk factor for cancer? Am J Epidemiol 1981;114:477–87.
2. Wannamethee G, Shaper AG. The association between heart rate and blood pressure, blood lipids and other cardiovascular risk factors. J Cardiovasc Risk 1994;1:223–30.
3. Kannel WB, Kannel C, Paffenbarger RS Jr, et al. Heart rate and cardiovascular mortality: The Framingham Study. Am Heart J 1987;113:1489–94.
4. Gann PH, Daviglus ML, Dyer AR, et al. Heart rate and prostate cancer mortality: results of a prospective analysis. Cancer Epidemiol Biomarkers Prev 1995;4:611–16.
5. Wannamethee G, Shaper AG, Macfarlane PW. Heart rate, physical activity, and mortality from cancer and other noncardiovascular diseases. Am J Epidemiol 1993;137:735–48.
6. Gillum RF, Makuc DM, Feldman JJ. Pulse rate, coronary heart disease, and death: The NHANES I Epidemiologic Follow-up Study. Am Heart J 1991;121:172–7.
7. Gillman MW, Kannel WB, Belanger A, et al. Influence of heart rate on mortality among persons with hypertension: The Framingham Study. Am Heart J 1993;125:1148–54.
8. Dyer AR, Persky V, Stamler J, et al. Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. Am J Epidemiol 1980; 112:736–49.
9. Stamler J, Dyer AR, Shekelle RB, et al. Relationship of baseline major risk factors to coronary and all-cause mortality, and to longevity: findings from long-term follow-up of Chicago cohorts. Cardiology 1993;82:191–222.
10. Gordon T. Disease in adults: United States, 1960–1962. (National Health Survey, series 11, no. 6). (Report no. PC A03 MF A01). Washington, DC: National Center for Health Statistics, 1964:28. (Available from the US GPO, Washington, DC (publication no. PB-260416)).
11. Blackburn H, Keys A, Simonson E, et al. The electrocardiogram in population studies: a classification system. Circulation 1960;21:1160–75.
12. The Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. J Chronic Dis 1978;31:201–306.
13. World Health Organization. International classification of diseases, eighth revision, adapted for use in the United States. Vol 1. Washington, DC: National Center for Health Statistics, 1967:49–522. (PHS publication no. 1693).
14. Lund-Johansen P, Omvik P. Hemodynamic patterns of untreated hypertensive disease. In: Laragh JH, Brenner BM, eds. Hypertension: pathophysiology, diagnosis, and management. New York, NY: Raven Press Ltd, 1995:323–41.
15. Falkner B. Cardiovascular characteristics of the young with borderline hypertension. J Cardiovasc Pharmacol 1986: 8(suppl 5):S44–7.
16. Friedman GD, Klatsky AL, Siegelaub AB. Predictors of sudden cardiac death. Circulation 1975;52(suppl):III164–9.
17. Medalie JH, Kahn HA, Neufeld HN, et al. Five-year myocardial infarction incidence. II. Association of single variables to age and birthplace. J Chronic Dis 1973;26:325–49.
18. Shaper AG, Wannamethee G, Macfarlane PW, et al. Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men. Br Heart J 1993;70:49–55.
19. Stokes J III, Kannel WB, Wolf PA, et al. The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years of follow-up in the Framingham Study. Circulation 1987;75:V65–73.
20. Gillum RF. The epidemiology of resting heart rate in a national sample of men and women: associations with hypertension, coronary heart disease, blood pressure, and other cardiovascular risk factors. Am Heart J 1988;116:163–74.
21. Filipovsky J, Ducimetiere P, Eschwege E, et al. The relationship of blood pressure with glucose, insulin, heart rate, free fatty acids and plasma cortisol levels according to degree of obesity in middle-aged men. J Hypertens 1996;14:229–35.
22. Kristal-Boneh E, Harari G, Green MS. Serum lipids and haematological factors associated with resting heart rate: The CORDIS Study. Cardiovascular Occupational Risk Factors Detection in Israeli Industries. J Cardiovasc Risk 1994;1: 59–67.
23. Williams PT, Haskell WL, Vranizan KM, et al. Associations of resting heart rate with concentrations of lipoprotein subfractions in sedentary men. Circulation 1985;71:441–9.
24. Kreutz R, Struk B, Stock P, et al. Evidence for primary genetic determination of heart rate regulation: chromosomal mapping of a genetic locus in the rat. Circulation 1997;96:1078–81.
25. Bassiouny HS, Zarins CK, Kadowaki MH, et al. Hemodynamic stress and experimental aortoiliac atherosclerosis. J Vasc Surg 1994;19:426–34.
26. Beere PA, Glagov S, Zarins CK. Retarding effect of lowered heart rate on coronary atherosclerosis. Science 1984;226: 180–2.
27. Kaplan JR, Manuck SB, Clarkson TB. Heart rate, social behavior and coronary artery atherosclerosis. Curr Opin Cardiol 1988;3(suppl):S23–8.
28. Nabel EG, Selwyn AP, Ganz P. Paradoxical narrowing of atherosclerotic coronary arteries induced by increases in heart rate. Circulation 1990;81:850–9.
29. Wannamethee G, Shaper AG. Blood pressure and cancer in middle-aged British men. Int J Epidemiol 1996;25:22–31.
30. Friedman GD. Blood pressure and heart rate: no evidence for a positive association with prostate cancer. Ann Epidemiol 1997;7:486–9.
31. Severson RK, Nomura AM, Grove JS, et al. A prospective analysis of physical activity and cancer. Am J Epidemiol 1989:130:522–9.
32. Dekker JM, Schouten EG, Klootwijk P, et al. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men: The Zutphen Study. Am J Epidemiol 1997;145:899–908.
33. Peters C, Lotzerich H, Niemeir B, et al. Exercise, cancer and the immune response of monocytes. Anticancer Res 1995; 15:175–9.
34. Gammon MD, John EM, Britton JA. Recreational and occupational physical activities and risk of breast cancer. J Natl Cancer Inst 1998;90:100–17.
35. Thune I, Brenn T, Lund E, et al. Physical activity and the risk of breast cancer. N Engl J Med 1997;336:1269–75.
36. Cohen S, Herbert TB. Health psychology: psychological factors and physical disease from the perspective of human psychoneuroimmunology. Annu Rev Psychol 1996;47:113–42.
37. Nul DR, Doval HC, Grancelli HO, et al. Heart rate is a mark-

er of amiodarone mortality reduction in severe heart failure. The GESICA-GEMA Investigators. Grupo de Estudios de la Sobrevida en la Insuficiencia Cardiaca en Argentina-Grupo de Estudios Multicentricos en Argentina. J Am Coll Cardiol 1997:29:1199–205.
38. Hinkle LE Jr, Carver ST, Plakun A. Slow heart rates and increased risk of cardiac death in middle-aged men. Arch Intern Med 1972;129:732–48.
39. Sandvik L, Erikssen J, Thaulow E, et al. Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. N Engl J Med 1993;328:533–7.
40. Lee IM, Paffenbarger RS Jr, Hennekens CH. Physical activity, physical fitness and longevity. Aging (Milano) 1997;9:2–11.
41. Kaplan JR, Manuck SB. Antiatherogenic effects of beta-adrenergic blocking agents: theoretical, experimental, and epidemiologic considerations. Am Heart J 1994;128:1316–28.
42. Hjalmarson A, Gilpin EA, Kjekshus J, et al. Influence of heart rate on mortality after acute myocardial infarction. Am J Cardiol 1990;65:547–53.
43. Gundersen T, Grottum P, Pedersen T, et al. Effect of timolol on mortality and reinfarction after acute myocardial infarction: prognostic importance of heart rate at rest. Am J Cardiol 1986;58:20–4.
44. Kjekshus JK. Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. Am J Cardiol 1986;57:43F–9F.
45. Kaplan JR, Manuck SB, Adams MR, et al. Inhibition of coronary atherosclerosis by propranolol in behaviorally predisposed monkeys fed an atherogenic diet. Circulation 1987; 76:1364–72.
46. Levine HJ. Rest heart rate and life expectancy. J Am Coll Cardiol 1997;30:1104–6.