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BMJ

RESEARCH

Resting heart rate as a low tech predictor of coronary events in women: prospective cohort study

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ABSTRACT

Objective To evaluate resting heart rate as an independent predictor of cardiovascular risk in women.
Design Prospective cohort study.
Setting The Women's Health Initiative was undertaken at 40 research clinics in the United States.
Participants 129 135 postmenopausal women.
Main outcome measure Clinical cardiovascular events.
Results During a mean of 7.8 (SD 1.6) years of follow up, 2281 women were identified with myocardial infarction or coronary death and 1877 with stroke. We evaluated associations between resting heart rate and cardiovascular events in Cox regression models adjusted for multiple covariates. Higher resting heart rate was independently associated with coronary events (hazard ratio 1.26, 95% confidence interval 1.11 to 1.42 for highest [>76 beats per minute] *v* lowest quintile [≤62 beats per minute]; P=0.001), but not with stroke. The relation between heart rate and coronary events did not differ between white women and women from other ethnic groups (P for interaction=0.45) or between women with and without diabetes (P for interaction=0.31), but it was stronger in women aged 50-64 at baseline than in those aged 65-79 (P for interaction=0.009).
Conclusion Resting heart rate, a low tech and inexpensive measure of autonomic tone, independently predicts myocardial infarction or coronary death, but not stroke, in women.
Trial registration ClinicalTrials.gov NCT00000611.

INTRODUCTION

Resting heart rate, an indicator of autonomic nervous system tone, independently predicts coronary events in men.[1-4] Evidence to date suggests that this relation is weaker or absent in women[2 3 5-8] except for one study that showed a strong association of heart rate with cardiovascular death in African-American women in the National Health And Nutrition Examination Survey.[9] The relation between heart rate and stroke in women is also unclear.

High sympathetic tone might serve as a marker of subclinical cardiovascular disease, or could adversely affect known risk factors such as blood pressure, glucose metabolism, and plasma lipids.[3] Depression and anxiety have been associated with autonomic dysfunction[10 11] and coronary events,[12] but have infrequently been included in analyses of heart rate and cardiovascular risk.

We assessed resting heart rate as an independent predictor of myocardial infarction or coronary death and stroke in a large cohort of women with a broad range of cardiovascular risk, and compared the strength of these associations by age and ethnic group.

METHODS

Study population

The Women's Health Initiative includes 161 808 postmenopausal women enrolled at 40 clinical sites into four randomised trials and an observational study from 1993 to 1998.[13] The present analysis included participants from the observational study and women from the intervention and control groups in the randomised trials. We excluded women with previous myocardial infarction, stroke, or coronary revascularisation at baseline, and those reporting current use of β blockers, digoxin, or non-dihydropyridine calcium channel blockers at baseline, since these agents might affect heart rate. Accordingly the analysis included 129 135 women. The study population and collection of baseline data have been described previously.[14-16]

Measurement of heart rate and covariates

At baseline, women sat quietly for 5 minutes before a trained observer measured heart rate by palpating the radial pulse for 30 seconds. We selected covariates that might be expected to affect heart rate, coronary heart disease, or risk of stroke. Hypertension, smoking, consumption of caffeine and alcohol, diabetes mellitus requiring dietary or drug therapy, and high cholesterol requiring drug treatment were assessed by self-reported questionnaire at baseline. Plasma lipoproteins and glucose were not measured in most women; consequently, hypercholesterolaemia and diabetes were defined exclusively by self-report. Women brought their medications to clinic visits for inventory. Total physical activity was assessed by questions on a

frequency and duration scale for walking and other types of activity.[17] Depression was assessed using six items from the Center for Epidemiological Studies depression scale.[18] Anxiety was assessed by asking "Have you been a very nervous person?" with response categories "all of the time", "most of the time", "a good bit of the time", "some of the time", "a little bit of the time", and "none of the time." We combined the first four categories for analyses, because the first three categories encompassed less than 8% of women. Hormone use reflected blinded treatment assignment in the randomised trials and open label use of oestrogen.

Ascertainment of outcomes

Participants reported emergency room visits, overnight stays in hospital, and outpatient coronary revascularisation procedures every 6 months. Medical records for all deaths, overnight hospital stays, and outpatient coronary revascularisation procedures were scrutinised for potential outcomes of interest. Centrally trained physician adjudicators classified outcomes by reviewing medical records. Myocardial infarction was categorised using an algorithm that included symptoms, electrocardiographic findings, and cardiac enzyme measurements.[19] Stroke was defined as rapid onset of a persistent neurological deficit not caused by trauma, tumour, infection, or other cause.[20]

Statistical analysis

We divided resting heart rate into quintiles or deciles. For continuous markers, we evaluated differences in baseline characteristics by modelling the covariate of interest by a continuous term of heart rate category in a linear model. Categorical models were evaluated using a χ^2 test comparing the marker of interest and the categories of heart rate. For multivariable analysis, we calculated hazard ratios with 95% confidence intervals from Cox regression models adjusted for all the covariates shown in the tables; age, body mass index, caffeine, and saturated fat consumption were included as continuous variables. We assessed interactions between heart rate or change in heart rate quintile and coronary heart disease or risk of stroke by age, ethnic origin, and presence of diabetes mellitus at baseline; P values were calculated from likelihood ratio tests by comparing models with and

Table 1 | Characteristics of study population by quintile of resting heart rate at baseline

	≤62 bpm (n=32195)	63-66 bpm (n=23213)	67-70 bpm (n=24235)	71-76 bpm (n=25453)	>76 bpm (n=24039)	P value
Age, years	62.4 (7.2)	62.6 (7.2)	62.7 (7.2)	62.8 (7.2)	63.0 (7.1)	<0.001
Ethnic origin, %	—	—	—	—	—	<0.001
White	84	83	84	84	83	—
Black	7	7	7	8	10	—
Hispanic	5	5	4	4	4	—
American Indian	0.4	0.4	0.5	0.4	0.4	—
Asian/Pacific Islander	3	3	3	2	2	—
Unknown	1	1	1	1	1	—
Hypertension, %	25	27	28	31	36	<0.001
Diabetes mellitus ever, %	3	3	4	5	8	<0.001
Current smoking, %	6	6	7	8	9	<0.001
High cholesterol requiring drugs, %	9	10	11	11	12	<0.001
Depressive symptoms score, points	2.2 (2.5)	2.2 (2.5)	2.3 (2.5)	2.3 (2.6)	2.5 (2.6)	<0.001
Nervousness, %	—	—	—	—	—	<0.001
At least some of the time	19	20	20	20	22	—
A little bit of the time	35	35	35	35	35	—
None of the time	46	45	45	44	43	—
Body mass index, kg/m^2	27 (5)	27 (5)	28 (6)	28 (6)	29 (6)	<0.001
Physical activity, metabolic equivalent-h/week	16 (16)	13 (14)	13 (14)	12 (13)	11 (12)	<0.001
Alcohol use	—	—	—	—	—	<0.001
Current	73.6	72.5	72.8	71.2	68.8	—
Past	15.7	16.4	16.3	17.6	19.4	—
Never	9.9	10.4	10.3	10.5	11.0	—
Dietary caffeine, mg/day	170 (135)	171 (136)	173 (137)	173 (135)	171 (136)	0.22
Dietary % energy from saturated fat	10.5 (3.3)	10.8 (3.3)	10.9 (3.3)	11.1 (3.3)	11.3 (3.3)	<0.001
Hormone use at baseline	—	—	—	—	—	<0.001
None	59	60	62	63	66	—
Unopposed oestrogen	23	21	20	19	17	—
Oestrogen with progestogen	19	19	18	17	17	—
Statin use, %	4.7	5.2	5.4	5.6	6.2	<0.001

bpm=beats per minute.Values are mean (SD) or percentage. Diabetes mellitus ever excludes gestational diabetes.

Table 2 | Resting heart rate by quintile as a predictor of coronary events and stroke in univariable analysis

	Myocardial infarction or coronary death	Stroke
≤62 bpm (referent)	1.00	1.00
63-66 bpm	1.07 (0.94 to 1.23)	1.07 (0.93 to 1.24)
67-70 bpm	1.19 (1.04 to 1.36)	1.02 (0.88 to 1.18)
71-76 bpm	1.21 (1.06 to 1.38)	1.21 (1.06 to 1.38)
>76 bpm	1.68 (1.49 to 1.89)	1.23 (1.07 to 1.41)
P value	<0.001	0.07

bpm=beats per minute. Values are hazard ratio (95% CI) unless otherwise indicated. Stratified for participation in hormone trial, dietary modification trial, and observational study.

without the interaction terms. All reported P values are two-sided. Analyses were done by the statistics unit at the Fred Hutchinson Cancer Research Center using the SAS System for Windows version 9 (SAS Institute, Cary, NC).

RESULTS

During a mean of 7.8 (SD 1.6) years of follow-up, 2281 coronary events (myocardial infarction or coronary death) and 1877 strokes were identified among 129 135 postmenopausal women who at baseline did not have cardiovascular disease and were not taking bradycardiogenic drugs. Table 1 shows baseline characteristics by quintile of resting heart rate. In general, age, body mass index, and saturated fat consumption were higher and cardiovascular risk factors such as hypertension, diabetes, smoking, hypercholesterolaemia, and depressive symptoms more prevalent in women with higher resting heart rate, as was self reported nervousness. Physical activity and alcohol use were inversely related to heart rate (both P<0.001), and heart rate was lower in women who used postmenopausal hormone therapy than in those who did not (P<0.001).

In univariate analysis, resting heart rate predicted myocardial infarction or coronary death, with a hazard ratio of 1.68 (95% confidence interval 1.49 to 1.89) for the highest (>76 beats per minute) versus lowest (≤62 beats per minute) quintile (p<0.001; table 2). In multivariable analysis, higher resting heart rate was independently associated with increased coronary risk, with a hazard ratio of 1.26 (95% confidence interval 1.11 to 1.42) for the highest versus lowest quintile (P=0.001). For the highest (>80 beats per minute) versus lowest decile (≤60 beats per minute) of resting heart rate, the hazard ratio was 1.33 (95% confidence interval 1.14 to 1.55; P=0.002; data not shown).

In univariate analysis, resting heart rate also predicted stroke (table 2), with hazard ratio 1.23 (95% confidence interval 1.07 to 1.41) for the highest versus lowest quintile (P=0.007). In multivariable analysis, however, heart rate was not independently associated with stroke (P=0.64; table 3). When the multivariable analysis was limited to ischaemic stroke (n=1084), hazard ratios with 95% confidence intervals for heart rate quintiles were 1.00, 1.22 (1.00 to 1.49), 1.16 (0.96 to 1.41), 1.16 (0.96 to 1.40), and 1.24 (1.02 to 1.50), with a P value of 0.197. When the analysis was limited to haemorrhagic stroke (n=366), hazard ratios with 95% confidence intervals for heart rate quintiles were 1.00, 1.06 (0.75 to 1.49), 1.09 (0.76 to 1.56), 1.14 (0.82 to 1.59) and 0.94 (0.65 to 1.35), with a P value of 0.849.

Coronary events and stroke were independently associated with age, hypertension, diabetes, smoking, and consumption of saturated fat (table 3). Greater physical activity and consumption of alcohol and caffeine were associated with lower risk of coronary events, but not with stroke. Black and Asian ethnic origins were associated with lower risk of coronary events than other ethnic groups; Hispanic ethnic origin was associated with lower risk of coronary events and stroke. Use of oestrogen with progestogen was associated with a reduced risk of coronary events and stroke, compared with no oestrogen use, whereas unopposed oestrogen use was associated with a lower risk of coronary events and higher risk of stroke.

In formal interaction testing, we found that the relation between resting heart rate and coronary events or stroke did not differ between white women and those from other ethnic groups (P for interaction=0.45 for coronary events and 0.85 for stroke), and between women with and without diabetes mellitus at baseline (P for interaction =0.31 for coronary events and 0.92 for stroke). The relation with resting heart rate differed by age for coronary events (P for interaction=0.009; table 4). The association of higher heart rate with coronary events was stronger in women aged 50-64 years than in those aged 65-79 years at baseline. We noted no such interaction between heart rate and age for stroke (P for interaction=0.14).

DISCUSSION

Principal findings

In a large, diverse cohort of postmenopausal women, resting heart rate was an independent predictor of coronary events, with higher heart rate associated with greater risk. The relation between resting heart rate and risk of coronary events was stronger in younger postmenopausal women than in older ones. Resting heart rate did not independently predict stroke.

Strengths and limitations

Strengths of this analysis include the size and diversity of the cohort, the use of prospective ascertainment and adjudication of outcomes, the large number of clinical events, and the range of covariates available for analysis, including physical activity and depression. A limitation is that since electrocardiograms were not done for most of the participants, they were not used for this analysis; consequently, some women included in the analysis may have had atrial fibrillation or permanent pacemakers. We excluded individuals taking digoxin, β blockers, and calcium channel blockers, which should have covered most women with atrial fibrillation. Another limitation is that the cohort included no women younger than 50 and no men.

Relation to other studies

The association of depression with coronary heart disease has been attributed to behaviours induced by

Table 3 | Resting heart rate as an independent predictor of coronary events and stroke in multivariable analysis

	Myocardial infarction or coronary death		Stroke	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Resting heart rate, beats per minute	—	0.001	—	0.64
≤62 (referent)	1.00		1.00	—
63-66	1.02 (0.89 to 1.17)		1.04 (0.90 to 1.20)	—
67-70	1.08 (0.95 to 1.23)		0.96 (0.83 to 1.11)	—
71-76	1.02 (0.89 to 1.16)		1.07 (0.94 to 1.23)	—
>76	1.26 (1.11 to 1.42)		1.01 (0.87 to 1.16)	—
Age, per 5 year increase	1.53 (1.48 to 1.58)	<0.001	1.69 (1.63 to 1.76)	<0.001
Ethnic origin	—	<0.001	—	0.02
White (referent)	1.00	—	1.00	—
Black	0.68 (0.57 to 0.80)	—	1.18 (1.00 to 1.40)	—
Hispanic	0.54 (0.40 to 0.74)	—	0.71 (0.51 to 0.99)	—
American Indian/Alaskan native	1.11 (0.63 to 1.96)	—	0.56 (0.21 to 1.48)	—
Asian/Pacific Islander	0.60 (0.43 to 0.85)	—	0.94 (0.70 to 1.27)	—
Unknown	0.91 (0.64 to 1.31)	—	1.36 (0.98 to 1.91)	—
Hypertension	1.69 (1.55 to 1.84)	<0.001	1.87 (1.70 to 2.06)	<0.001
Diabetes mellitus ever	2.68 (2.36 to 3.03)	<0.001	1.94 (1.66 to 2.27)	<0.001
Current smoking	2.32 (2.03 to 2.65)	<0.001	1.95 (1.67 to 2.28)	<0.001
High cholesterol requiring drugs	1.14 (0.98 to 1.33)	0.057	1.18 (1.00 to 1.40)	0.15
Depression construct >5	1.08 (0.94 to 1.24)	0.29	1.14 (0.98 to 1.33)	0.09
Nervousness	—	0.09	—	0.67
None of the time (referent)	1.00	—	1.00	—
A little bit of the time	1.09 (0.99 to 1.20)	—	0.96 (0.86 to 1.06)	—
At least some of the time	1.12 (1.00 to 1.25)	—	1.00 (0.89 to 1.14)	—
Body mass index, per 5 kg/m^2 increase	1.08 (1.04 to 1.12)	<0.001	1.00 (0.96 to 1.05)	0.98
Physical activity, per 5 metabolic equivalent-h/week increase	0.97 (0.95 to 0.99)	<0.001	0.98 (0.97 to 1.00)	0.08
Alcohol use	—	0.007	—	0.21
Never (referent)	1.00	—	1.00	—
Past	1.07 (0.92 to 1.24)	—	1.02 (0.86 to 1.20)	—
Current	0.91 (0.79 to 1.04)	—	0.92 (0.80 to 1.07)	—
Dietary caffeine, per 50 mg increase	0.98 (0.97 to 1.00)	0.048	0.99 (0.97 to 1.01)	0.36
Dietary saturated fat, per 5% increase	1.13 (1.05 to 1.20)	<0.001	1.11 (1.03 to 1.19)	0.008
Hormone use at baseline	—	0.002	—	<0.001
None (referent)	1.00	—	1.00	—
Unopposed oestrogen	0.86 (0.77 to 0.97)	—	1.19 (1.06 to 1.34)	—
Oestrogen with progestogen	0.81 (0.71 to 0.94)	—	0.85 (0.72 to 0.99)	—
Statin use	1.06 (0.87 to 1.30)	0.57	0.81 (0.64 to 1.03)	0.08

depression, such as poor diet and physical inactivity, and its physiological consequences, including adverse effects on inflammation and on endothelial and platelet function.[11 18 21 22] Depression has been associated with autonomic dysregulation, leading to increased heart rate and reduced heart rate variability.[23 24] In our analysis, depressive symptoms were not associated with coronary events or stroke with or without adjustment for heart rate (data not shown), so we are unable to confirm that the relation between depressive symptoms and clinical events is mediated through autonomic effects. This limitation might be attributable to the fact that this subsample of the Women's Health Initiative cohort had quite low scores for depressive symptoms—that is, was not very depressed.

Heart rate was higher in women with self reported nervousness than in less nervous women, but nervousness was not independently associated with either coronary events or stroke in our analysis. This finding contrasts with reports identifying anxiety as a predictor of coronary events or of poor outcome after coronary artery bypass surgery.[21 22] Possible explanations are that our dataset did not include a true anxiety scale, or that adjustment for heart rate and several other variables weakened the association of coronary events with anxiety. The latter explanation might also account for the absence of an association between alcohol consumption and coronary events in the multivariable analysis.

We know from the Women's Health Initiative randomised hormone trials that unopposed oestrogen and oestrogen with progestogen are associated with increased risk of stroke, and that oestrogen with progestogen increases coronary events.[20 25 26]

Table 4 | Interaction of resting heart rate and coronary events by age group and heart rate quintile

	Number of events (% of participants with event per year)	Hazard ratio (95% CI)
Age 50-64		
≤62 bpm	163 (0.12)	1.00
63-66 bpm	125 (0.13)	1.02 (0.81 to 1.29)
67-70 bpm	142 (0.14)	1.08 (0.86 to 1.35)
71-76 bpm	147 (0.14)	1.01 (0.81 to 1.27)
>76 bpm	222 (0.24)	1.47 (1.20 to 1.80)
Age 65-79		
≤62 bpm	312 (0.37)	1.00
63-66 bpm	240 (0.39)	1.02 (0.86 to 1.20)
67-70 bpm	279 (0.43)	1.08 (0.92 to 1.27)
71-76 bpm	299 (0.43)	1.03 (0.88 to 1.21)
>76 bpm	352 (0.54)	1.14 (0.98 to 1.33)

bpm=beats per minute. P for interaction=0.009; determined by comparing Cox models that included all the variables in table 1 with and without an interaction term (age*heart rate).

Nonetheless, analyses from non-randomised cohorts, including the Women's Health Initiative observational study, have consistently shown lower cardiovascular risk in women taking hormones, for reasons that have been extensively discussed.[27 28] Hormone use in the current analysis includes randomised treatment assignment in the hormone trials, as well as open label use by women not participating in those trials. Unsurprisingly, the associations with cardiovascular disease present a mixed picture.

We did not confirm the previously reported increased predictive value of resting heart rate for cardiovascular death in African-American women.[9] In fact, the hazard ratio for coronary events was lower in black, Hispanic, and Asian women than in white women. Our models included 149 coronary events among black women, somewhat more than the 92 in the National Health and Nutrition Examination survey analysis. In addition to the difference in sample size, disparities between ethnic groups in identification and management of risk factors have changed since the 1970s and early 1980s when that analysis was undertaken.

We found a stronger association between increased heart rate and coronary events in women aged 50-64 than in those aged 65-79 (P for interaction=0.009). A possible explanation for this finding is that chronotropic insufficiency is more frequent in the older women, reducing the reliability of heart rate as a predictor of coronary events.

Coronary risk was consistent across the lower four quintiles of heart rate; the hazard ratio increased only in the highest quintile. This apparent threshold potentially increases the clinical usefulness of the association; individuals with heart rates in the highest quintile or decile for age could be readily identified and targeted for aggressive management of risk factors.

Conclusion

Although more elaborate, time consuming, and expensive methods are available to assess autonomic tone, we have found that simple measurement of resting pulse independently predicts coronary events, but not stroke, in postmenopausal women. The strength of this association, from lowest to highest quintile, is less than the association with cigarette smoking or diabetes mellitus, but might be large enough to be clinically meaningful, and is independent of physical activity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Resting heart rate predicts coronary events in men

For women, the relation between heart rate and coronary events or stroke has been uncertain

WHAT THIS STUDY ADDS

Resting heart rate predicts coronary events in women

This relation is independent of physical activity and conventional risk factors

This association appears stronger in women aged 50-64 than in those aged 65 or older

Resting heart rate does not predict stroke in women

Women's Health Initiative investigators are listed at www.whiscience.org/publications/WHI_investigators_shortlist.pdf.

Contributors: JH was responsible for conception and design of this analysis and drafted the manuscript. JCL analysed and interpreted the data, JKO, GES, MAA, SLH, JGR, AZL, JEM interpreted the data and critically reviewed the manuscript. The final version was approved by all authors. JH is the guarantor.

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Competing interests: None declared.

Ethical approval: The protocol and consent forms were approved by institutional review boards of the participating institutions; all trial participants provided written informed consent.

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