Combined Effects of Depressive Symptoms and Resting Heart Rate on Mortality: The Whitehall II Prospective Cohort Study

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ABSTRACT

Objective: To examine the combined effects of depressive symptoms and resting heart rate on mortality risk.

Method: Analysis was performed on data from 5,936 participants in the Whitehall II study with a mean ± SD age of 61 ± 6 years. Depressive symptoms were assessed from 2002 to 2004 using the Center for Epidemiologic Studies Depression Scale (cutoff score for depression at ≥ 16). Resting heart rate was measured at the same study phase via electrocardiogram. Participants were assigned to 1 of 6 risk-factor groups on the basis of depression status (yes/no) and resting heart rate categories (< 60, 60–80, and > 80 beats/minute [bpm]). All-cause mortality was the main outcome in our analysis. Mean follow-up for mortality was 5.6 years.

Results: In mutually adjusted Cox regression models, depression (hazard ratio = 1.93, $P < .001$) and resting heart rate > 80 bpm (hazard ratio = 1.67, $P < .001$) were independent predictors of mortality. After adjustment for potential confounding and mediating variables, participants with both depression and high resting heart rate had a 3-fold higher ($P < .001$) risk of death compared to depression-free participants with resting heart rates ranging from 60 to 80 bpm. This risk is particularly marked in participants with prevalent coronary heart disease.

Conclusions: This study provides evidence that the coexistence of depressive symptoms and elevated resting heart rate is associated with substantially increased risk of death compared to those without these 2 factors. This finding suggests the possibility that treatments that improve both depression and resting heart rate might improve survival.

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Depression is a major public health issue worldwide.[1] Projections of the Global Burden of Disease project by the World Health Organization suggest that depression will account for 10% of the total disease burden in high-income countries by 2030.[2] There is fairly consistent evidence that depression is independently associated with increased risk of mortality.[3–7] For example, a recent meta-analysis of 25 community studies on a total of 106,628 individuals found a 1.8-fold increased risk for all-cause mortality in depressive compared to nondepressive subjects.[8]

Resting heart rate, an indicator of the autonomic nervous system activity, has also been found to be an independent predictor of mortality.[9–11] In a recent study[12] of working men without clinically detectable cardiovascular disease at baseline who were followed up for 23 years, the risk for sudden and nonsudden death from acute myocardial infarction and all-cause mortality increased in a dose-response manner with increasing resting heart rate, after adjustment for biobehavioral risk factors.[12] Another recent study[13] involving a large sample of men and women found elevated resting heart rate to be a long-term predictor for mortality independent of other risk factors in patients with suspected or proven coronary artery disease.

Despite the large amount of evidence showing depression and resting heart rate to be predictors of mortality, previous studies have not examined the combined impact of depression and resting heart rate. However, in many individuals, depression and elevated resting heart rate are comorbid,[14–16] and it is possible that they exert a combined effect on mortality. Indeed, several studies found clinically depressed psychiatric patients and coronary heart disease patients with depression, as compared with their nondepressed counterparts, to have elevated levels of plasma catecholamines and other markers of altered autonomic nervous system activity, including elevated heart rate, low heart rate variability, exaggerated heart rate responses to physical stressors.[14–20] All these indicators of altered autonomic nervous system function have been found to be associated with increased risks of mortality and cardiac morbidity in patients with coronary heart disease.[14]

We are aware of no published study that has examined mortality risk as a function of both depression status and resting heart rate level. To address this issue, the present study examines the combined effect of depressive symptoms and resting heart rate on mortality in a large cohort of middle-aged British adults.

METHOD

Data were drawn from the Whitehall II study, established in 1985 as a longitudinal cohort study to examine the socioeconomic gradient in health and disease among 10,308 civil servants (6,895 men and 3,413 women). All civil servants aged 35 to 55 years in 20 London-based departments were invited by letter to participate, and 73% agreed. Baseline screening (phase 1) took place during 1985–1988 and involved a clinical examination and a self-administered questionnaire. Subsequent phases of data collection have alternated between postal questionnaire alone (phases 2 [1989–1990], 4 [1995–1996], 6 [2001], and 8 [2006]) and postal questionnaire accompanied

by a clinical examination (phases 3 [1991–1993], 5 [1997–1999], and 7 [2002–2004]). The University College London, United Kingdom, ethics committee approved the study, and patients gave written informed consent.

Measures

Depressive symptoms. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D)[21] (Cronbach $\alpha = 0.83$) at phase 7 of the Whitehall II study (2002–2004). The CES-D, a widely used and validated instrument, is a 20-item self-report questionnaire designed to measure depressive symptomatology in community studies. A score ≥ 16 from a total possible score of 60 has been used extensively to distinguish depressed from nondepressed subjects.[21]

Resting heart rate. Resting heart rate was measured at the phase 7 screening clinic via electrocardiogram with participants in the supine position and following a standard protocol. The following classification was used to categorize resting heart rate: < 60, 60–80, and > 80 beats/minute (bpm), based on current guidelines[22] that have defined adequate rate control as a ventricular response between 60 and 80 bpm at rest.

Vital status. Mortality follow-up was available through the British National Health Services Central Registry until April 30, 2009. Death certificates were coded using the *International Classification of Diseases, Tenth Revision (ICD-10)*. All-cause mortality was the main outcome in our analysis.

Covariates. Sociodemographic measures. Sociodemographic measures included age, sex, ethnicity, and socioeconomic position assessed by the British civil service grade of employment taken from the phase 7 questionnaire.

Biobehavioral risk factors. Behavioral risk factors were assessed using responses to the phase 7 questionnaire and were categorized as follows: smoking status (never smoked, ex-smoker, and current smoker), physical activity (≥ 1.5 or < 1.5 hours of moderate or vigorous exercise per week), and alcohol consumption in the previous week (abstention, moderate consumption [1–14 units for women; 1–21 units for men], and high consumption [> 14 units for women; > 21 units for men]). A unit is 10 mL or 8 g of pure alcohol. The following biological cardiovascular disease risk factors were measured at the phase 7 clinical examination: hypertension (systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg or antihypertensive medications), high total blood cholesterol (≥ 6.2 mmol/L), body mass index (kg/m^2) (< 20, 20–24.9, 25–29.9, or ≥ 30), and diabetes, assessed via glucose tolerance test at the medical screening or self-report of doctor diagnosis.

Medications. Data on antidepressant medications were drawn from the phase 7 questionnaire in which participants were asked whether in the last 14 days they had taken antidepressant drugs prescribed by a doctor (yes/no). Cardiovascular disease medications at phase 7 were also drawn from questions on whether in the last 14 days the participant had taken cardiovascular disease drugs, including diuretics, β-blockers, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, nitrates, or antiplatelets prescribed by a doctor (yes/no). The same question was used to assess whether participants had taken lipid-lowering medications.

Prevalent coronary heart disease. Coronary heart disease status at phase 7 was defined as nonfatal myocardial infarction or "definite" angina and was based on clinical examinations at phases 1, 3, 5, and 7 and on records obtained from general practitioners and hospitals. Potential nonfatal myocardial infarction was ascertained by questionnaire items on chest pain (the World Health Organization Rose questionnaire[23]) and the physician's diagnosis of heart attack. Confirmation of myocardial infarction according to Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA)[24] criteria was based on electrocardiograms, markers of myocardial necrosis, and chest pain history from medical records. Angina was assessed on the basis of the participant's reports of symptoms with corroboration in medical records or abnormalities on a resting electrocardiogram, an exercise electrocardiogram, or a coronary angiogram.

Statistical Analysis

Differences in depression status and resting heart rate categories as a function of the sample characteristics were assessed using a χ^2 test. The associations of depression and resting heart rate with mortality were examined separately using Cox regressions in 4 serially adjusted models. A resting heart rate between 60 and 80 bpm was used as the reference category so that the hazard ratios (HRs) of the lower resting heart rate (< 60 bpm) and the higher resting heart rate (> 80 bpm) were estimated. In model 1, HRs were adjusted for the following sociodemographic characteristics: sex, age, ethnicity, and socioeconomic position. Model 2 additionally adjusted the hazard of mortality for smoking status, body mass index, alcohol consumption, physical activity, hypertension, total blood cholesterol, and diabetes. Model 3 was model 1 additionally adjusted for cardiovascular disease medication (diuretics, β-blockers, ACE inhibitors, calcium channel blockers, nitrates, antiplatelets), antidepressant medication, lipid-lowering medication, and history of coronary heart disease. Model 4 was adjusted for all aforementioned variables and depression status or resting heart rate categories in order to estimate their independent effect on mortality.

To examine the combined effect of depression and resting heart rate on mortality, we divided the study sample into 6 groups based on the cross-classification of depression status (depression [CES-D score ≥ 16] versus no depression [CES-D score < 16]) and resting heart rate categories (< 60, 60–80, > 80 bpm), with nondepressive participants with resting heart rate between 60 and 80 bpm taken as the reference group.

Cox regression models were used to calculate multivariable-adjusted risk of death for each group compared with the reference group using the adjustment specified in models 1 and 2 above. The proportional hazards assumption was checked graphically by plotting the log of the negative

Table 1. Sample Characteristics as a Function of Depression and Resting Heart Rate at Phase 7 (N = 5,936)

		Depressive Symptoms (CES-D Score ≥ 16)		Resting Heart Rate			
Characteristic	n	n (%)	*P* Value	< 60 bpm, n (%)	60–80 bpm, n (%)	> 80 bpm, n (%)	*P* Value
Sex			< .001				< .001
Male	4,268	559 (13.1)		1,124 (79.2)	2,498 (68.8)	646 (73.0)	
Female	1,668	326 (19.5)		296 (20.8)	1,133 (31.2)	239 (27.0)	
Age, y			< .001				.703
< 54	1,110	212 (19.1)		250 (17.6)	721 (19.9)	139 (15.7)	
54–59	1,822	272 (14.9)		421 (29.6)	1,139 (31.4)	262 (29.6)	
60–64	1,259	163 (12.9)		321 (22.6)	746 (20.5)	192 (21.7)	
65–69	1,196	163 (13.6)		275 (19.4)	717 (19.7)	204 (23.1)	
70–74	549	75 (13.7)		153 (10.8)	308 (8.5)	88 (9.9)	
Socioeconomic position			< .001				< .001
High	2,040	201 (9.9)		546 (38.5)	1,221 (33.6)	273 (30.8)	
Middle	3,032	469 (15.5)		717 (50.5)	1,831 (50.4)	484 (54.7)	
Low	864	215 (24.9)		157 (11.1)	579 (15.9)	128 (14.5)	
Ethnicity/race			< .001				.543
White	5,485	743 (13.5)		1,320 (93.0)	3,347 (92.2)	818 (92.4)	
Other	451	142 (31.5)		100 (7.0)	284 (7.8)	67 (7.6)	
Smoking status			< .001				.479
Never a smoker	2,678	377 (14.1)		639 (45.0)	1,637 (45.1)	402 (45.4)	
Ex-smoker	2,282	297 (13.0)		556 (39.2)	1,364 (37.6)	362 (40.9)	
Current smoker	680	145 (21.3)		157 (11.1)	437 (12.0)	86 (9.7)	
Missing	296	66 (22.3)		68 (4.8)	193 (5.3)	35 (4.0)	
Alcohol consumption			.514				.755
Abstainers	973	220 (22.9)		206 (14.5)	604 (16.6)	163 (18.4)	
Moderate consumption	3,725	484 (13.0)		9,439 (66.1)	2,286 (63.0)	500 (56.5)	
High consumption	1,158	153 (13.2)		254 (17.9)	691 (19.0)	213 (24.1)	
Missing	80	28 (35.0)		21 (1.5)	50 (1.5)	9 (1.0)	
Exercise			< .001				< .001
≥ 1.5 hours/wk	5,152	699 (13.6)		1,277 (89.9)	3,134 (86.3)	741 (83.7)	
< 1.5 hours/wk	784	186 (23.7)		143 (10.1)	497 (13.7)	144 (16.3)	
Hypertension			.315				.032
No	3,585	521 (14.5)		811 (57.1)	2,336 (64.3)	438 (49.5)	
Yes	2,351	364 (15.5)		609 (42.9)	1,295 (35.7)	447 (50.5)	
Body mass index (kg/m^2)			.002				< .001
< 20	179	38 (21.2)		53 (3.7)	108 (3.0)	18 (2.0)	
20–24.9	2,028	263 (13.0)		570 (40.1)	1,242 (34.2)	216 (24.4)	
25–29.9	2,606	365 (14.0)		588 (41.4)	1,627 (44.8)	391 (44.2)	
≥ 30	1,099	214 (19.5)		206 (14.5)	638 (17.6)	255 (28.8)	
Missing	24	5 (20.8)		3 (0.2)	16 (0.4)	5 (0.6)	
Diabetes			< .001				< .001
No	5,655	816 (14.4)		1,371 (96.5)	3,469 (95.5)	815 (92.1)	
Yes	281	69 (24.6)		49 (3.5)	162 (4.5)	70 (7.9)	
High blood cholesterol			.266				< .174
No	3,940	599 (15.2)		991 (69.2)	2,401 (66.1)	548 (61.9)	
Yes	1,886	263 (13.9)		396 (27.9)	1,174 (32.2)	316 (35.7)	
Missing	110	23 (20.9)		33 (2.3)	56 (1.5)	21 (2.4)	
Antidepressant drugs			< .001				.842
No	5,728	786 (13.7)		1,366 (96.2)	3,514 (96.8)	848 (95.8)	
Yes	208	99 (47.9)		54 (3.8)	117 (3.2)	37 (4.2)	
Cardiovascular disease medications (yes)							
Diuretics	494	76 (15.4)	.757	135 (9.5)	277 (7.6)	82 (9.3)	.518
β-Blockers	584	91 (15.6)	.631	345 (24.3)	223 (6.1)	16 (1.8)	< .001
ACE inhibitors	649	110 (16.9)	.122	164 (11.5)	356 (9.8)	129 (14.6)	.113
Calcium channel blockers	420	67 (16.0)	.533	118 (8.3)	228 (6.3)	74 (8.4)	.614
Nitrates	62	18 (29.0)	.002	27 (1.9)	33 (0.9)	2 (0.2)	< .001
Antiplatelets	584	104 (17.8)	.038	199 (14.0)	310 (8.5)	75 (8.5)	< .001
Lipid-lowering medications			.242				.001
No	5,247	772 (14.7)		1,207 (85.0)	3,253 (89.6)	787 (88.9)	
Yes	689	113 (16.4)		213 (15.0)	378 (10.4)	98 (11.1)	
History of coronary heart disease			.001				< .001
No	5,385	777 (14.4)		1,229 (86.5)	3,348 (92.2)	808 (91.3)	
Yes	551	108 (19.7)		191 (13.5)	283 (7.8)	77 (8.7)	
Depressive symptoms (CES-D ≥ 16)							.007
No	5,051			1,239 (87.3)	3,074 (84.7)	738 (83.4)	
Yes	885			181 (12.7)	557 (15.3)	147 (16.6)	

Abbreviations: ACE = angiotensin converting enzyme, bpm = beats/minute, CES-D = Center for Epidemiologic Studies Depression Scale.

log of the survival function. These curves were essentially parallel, suggesting therefore that the proportional hazard was not violated.

We also examined the additive interaction between depressive symptoms and elevated resting heart rate, as defined by Rothman,[25] by calculating the relative excess risk due to interaction (RERI) using the methods outlined by Andersson et al.[26] For example, a RERI of 4.0 would mean that the relative risk of death from all causes in depressive participants with elevated resting heart rate is increased by 4.0 compared to the relative risk that one would expect if there were no interaction between these 2 factors. In the absence of an interaction between depressive symptoms and resting heart rate, the RERI will be 0. Probability values and 95% CIs for the RERI were computed by the delta method.[27]

RESULTS

A total of 5,936 participants were included in the analyses. Of these, 170 died during the mean follow-up period of 5.6 years (SD = 0.7; range, 0.03–6.6 years). The mean age of the participants at phase 7, the start of the follow-up for our analysis, was 61 years (SD = 6.0). The prevalence of depression (CES-D score ≥ 16) was 14.9%. Almost one-quarter of participants (24%) had resting heart rates < 60 bpm, 61% were in the normal range with resting heart rates between 60 and 80 bpm, and 15% had resting heart rates > 80 bpm. Compared to participants included in this study, those individuals who did not respond to the CES-D questionnaire or who did not have data on resting heart rate were more likely to be women (39.8% vs 29.1%; $P < .001$), nonwhite (15.2% vs 8.4%; $P < .001$), older (19.5% vs 9.3%; $P < .001$), and from lower socioeconomic position (34.1% vs 15.9%; $P < .001$).

Table 1 shows the sample characteristics as a function of depression status and resting heart rate category at phase 7. Participants with depressive symptoms were more likely to be female, younger, from lower socioeconomic position, nonwhite, taking medication (antidepressants, nitrates, and antiplatelets), current smokers, and less physically active and to have lower body mass index and higher prevalence of diabetes and coronary heart disease (all $P \leq .04$). Men were more likely to have a low resting heart rate (< 60 bpm, $P < .001$). Participants with a higher resting heart rate (> 80 bpm) were more likely to be from lower socioeconomic position, less physically active, hypertensive, obese, diabetic, and taking cardiovascular disease medication (β-blockers, nitrates, antiplatelets) and lipid-lowering medication and to have depressive symptoms (all $P \leq .032$).

Table 2 presents estimates from Cox regression models for the associations between depressive symptoms, resting heart rate, and mortality. In model 1, adjusted for sociodemographic characteristics, depressive participants (CES-D score ≥ 16) were at increased risk of death (HR = 2.46; 95% CI, 1.74–3.48) when compared to nondepressive participants (CES-D score < 16). When the same adjustments were used, but with resting heart rate as the predictor, participants with a resting heart rate > 80 bpm were at increased risk of death from any cause (HR = 1.70; 95% CI, 1.18–2.44) compared to those with a resting heart rate between 60 and 80 bpm. In model 2, adjusted for cardiovascular disease biobehavioral risk, the magnitude of the associations was reduced, but participants with depressive symptoms remained at greater risk of mortality. Participants with a resting heart rate > 80 bpm were also at greater risk of mortality. In model 3, adjustments for cardiovascular disease medications, antidepressants, lipid-lowering medications, and prevalent coronary heart disease did not alter the associations observed in model 1. Inclusion of all these variables and both depression and resting heart rate in model 4 did not substantially affect these associations; both depressive symptoms (HR = 1.93; 95% CI, 1.35–2.76) and high resting heart rate (HR = 1.67; 95% CI, 1.14–2.45) remained independently associated with an increased risk of mortality.

Table 2. Associations Between Depression and Mortality and Between Resting Heart Rate and Mortality

Predictor	No. of Events/ Total N	Mortality Risk Hazard Ratio	95% CI
Model 1[a]			
Depressive symptoms	170/5,936		
CES-D score ≤ 15	123/5,051	1.00	reference
CES-D score ≥ 16	47/885	2.46	1.74–3.48***
Resting heart rate, bpm	170/5,936		
< 60	33/1,420	0.85	0.57–1.26
60–80	95/3,631	1.00	reference
> 80	42/885	1.70	1.18–2.44**
Model 2[b]			
Depressive symptoms	170/5,936		
CES-D score ≤ 15	123/5,051	1.00	reference
CES-D score ≥ 16	47/885	1.98	1.39–2.82***
Resting heart rate, bpm	170/5,936		
< 60	33/1,420	0.85	0.57–1.27
60–80	95/3,631	1.00	reference
> 80	42/885	1.54	1.06–2.23*
Model 3[c]			
Depressive symptoms	170/5,936		
CES-D score ≤ 15	123/5,051	1.00	reference
CES-D score ≥ 16	47/885	2.42	1.70–3.45***
Resting heart rate, bpm	170/5,936		
< 60	33/1,420	0.69	0.45–1.06
60–80	95/3,631	1.00	reference
> 80	42/885	1.74	1.21–2.52**
Model 4[d]			
Depressive symptoms	170/5,936		
CES-D score ≤ 15	123/5,051	1.00	reference
CES-D score ≥ 16	47/885	1.93	1.35–2.76***
Resting heart rate, bpm	170/5,936		
< 60	33/1,420	0.75	0.49–1.15
60–80	95/3,631	1.00	reference
> 80	42/885	1.67	1.14–2.45**

[a]Model 1 is adjusted for sex, age, ethnicity, and socioeconomic position.
[b]Model 2 is model 1 additionally adjusted for body mass index, alcohol consumption, smoking status, exercise, hypertension, total blood cholesterol, and diabetes.
[c]Model 3 is model 1 additionally adjusted for cardiovascular disease medication (diuretics, β-blockers, ACE inhibitors, calcium channel blockers, nitrates, antiplatelets), antidepressant medication, lipid-lowering medication, and history of coronary heart disease.
[d]Model 4 is adjusted for all aforementioned variables and depression (for the association between resting heart rate and mortality) or resting heart rate (for the association between depression and mortality).
*$P < .05$, **$P < .01$, ***$P < .001$.
Abbreviations: ACE = angiotensin converting enzyme, bpm = beats/minute, CES-D = Center for Epidemiologic Studies Depression Scale.

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Table 3. Hazard Ratios for Mortality as a Function of Combinations of Depression and Resting Heart Rate[a]

	Resting Heart Rate <60 bpm, Hazard Ratio (95% CI)	Resting Heart Rate 60–80 bpm, Hazard Ratio (95% CI)	Resting Heart Rate >80 bpm, Hazard Ratio (95% CI)
Model 1[b]			
Depressive symptoms			
No	0.92 (0.58–1.45)	1.00 (reference)	1.80 (1.17–2.76)**
Yes	1.88 (0.86–4.13)	2.71 (1.73–4.23)***	3.85 (2.03–7.31)***
Model 2[c]			
Depressive symptoms			
No	0.92 (0.58–1.46)	1.00 (reference)	1.66 (1.08–2.56)*
Yes	1.55 (0.70–3.42)	2.21 (1.41–3.49)***	2.81 (1.46–5.56)**
Model 3[d]			
Depressive symptoms			
No	0.75 (0.46–1.21)	1.00 (reference)	1.84 (1.20–2.83)**
Yes	1.67 (0.76–3.70)	2.55 (1.62–4.04)***	3.67 (1.92–7.02)***
Model 4[e]			
Depressive symptoms			
No	0.79 (0.48–1.28)	1.00 (reference)	1.77 (1.14–2.75)**
Yes	1.40 (0.63–3.13)	2.10 (1.32–3.32)***	2.99 (1.53–5.81)***

[a]No. of events/total n is the same in all 4 models:

	Resting Heart Rate <60 bpm	Resting Heart Rate 60–80 bpm	Resting Heart Rate >80 bpm
No	26/1,239	66/3,074	29/738
Yes	7/181	29/557	11/147

[b]Model 1 hazard ratios are adjusted for sex, age, ethnicity, and socioeconomic position.
[c]Model 2 is model 1 additionally adjusted for body mass index, alcohol consumption, smoking status, exercise, hypertension, total blood cholesterol, and diabetes.
[d]Model 3 is model 1 additionally adjusted for cardiovascular disease medication (diuretics, β-blockers, ACE inhibitors, calcium channel blockers, nitrates, antiplatelets), antidepressant medication, lipid-lowering medication, and history of coronary heart disease.
[e]Model 4 hazard ratios are adjusted for all aforementioned variables.
*P < .05, **P < .01, ***P < .001.
Abbreviations: ACE = angiotensin converting enzyme, bpm = beats/minute.

Table 3 shows the associations of combinations of depression status and resting heart rate categories with mortality as the outcome. Model 1, adjusted for sociodemographic characteristics, shows that compared with the reference group (participants without depression and with resting heart rate between 60 and 80 bpm), the hazard of death was higher for depressive participants with a resting heart rate between 60 and 80 bpm (HR = 2.71; 95% CI, 1.73–4.23), for those without depression but with a resting heart rate >80 bpm (HR = 1.80; 95% CI, 1.17–2.76), and for those with both depression and resting heart rate >80 bpm (HR = 3.85; 95% CI, 2.03–7.31). After further multivariate adjustment for biobehavioral risk factors in model 2, the magnitude of the associations was reduced, but the associations persisted. In model 3, adjustment for cardiovascular disease medications, antidepressants, lipid-lowering medications, and prevalent coronary heart disease did not substantially alter the associations observed in model 1. Finally, after inclusion of all these variables in model 4, the hazard for death was 2.1-fold (P < .001) higher for participants with depression but with a resting heart rate between 60 and 80 bpm, 1.8-fold (P < .01) higher for those without depression but with a resting heart rate >80 bpm, and 3-fold (P < .001) higher for those with both depression and a resting heart rate >80 bpm. The RERI between depressive symptoms and elevated resting heart rate was 0.20 (95% CI, −2.17 to 2.50).

Sensitivity Analyses

In order to assess the robustness of the present findings, we repeated the analyses excluding participants with a personal history of coronary heart disease. The number of deaths was reduced by 22% (no. of deaths = 133). In the fully mutually adjusted model, depressive symptoms (HR = 1.82, P = .005) and elevated resting heart rate (>80 bpm; HR = 1.63, P = .03) remained independent predictors of death. The corresponding fully adjusted risk of death was 2.5-fold (P = .04) higher for participants with both depressive symptoms and a resting heart rate >80 bpm when compared to those without depressive symptoms and with a resting heart rate between 60 and 80 bpm. The corresponding RERI was −0.60 (95% CI, −2.90 to 1.71). Similar patterns of association were observed when the analyses were restricted to participants with prevalent coronary heart disease (no. of deaths = 37). The corresponding fully mutually adjusted HRs were 2.97 (P = .006) for depressive symptoms and 2.00 (P = .17) for those with a resting heart rate >80 bpm. Finally, participants with both depressive symptoms and resting heart rate >80 bpm had a 7.5-fold (P = .005) higher risk of death relative to those without depressive symptoms and with a resting heart rate between 60 and 80 bpm. The corresponding RERI was 2.39 (95% CI, −4.13 to 8.90).

In addition, we repeated the analysis in subgroups of β-blocker users and nonusers. In a fully mutually adjusted model, depressive symptoms (HR = 2.14, P < .001) and elevated resting heart rate (>80 bpm; HR = 1.57, P = .025) remained independent predictors of death (no. of deaths = 142) among nonusers of β-blockers. The corresponding fully adjusted risk of death was 3.22-fold ($P \leq .001$) higher for participants with both depressive symptoms and a resting heart rate >80 bpm when compared to those without depressive symptoms and with a resting heart rate between 60 and 80 bpm. Among β-blocker users (no. of deaths = 28), the corresponding HRs were 0.99 (P = .99) for depressive symptoms and 2.48 (P = .26) for elevated resting heart rate. Only 2 β-blocker users had depressive symptoms and a resting heart rate >80 bpm, thus preventing further analysis of this group. Although the risk of death seems to be lower among β-blocker users, the small number of deaths among this group precludes any definite conclusions regarding these observations.

DISCUSSION

In this study, we sought to examine the combined effect of depressive symptoms and resting heart rate on mortality in a large cohort of British adults. We found that depressive symptoms and elevated resting heart rate were independent predictors for death from all causes over 5 years of follow-up. Concurrently, the study also showed that the coexistence of

depression and higher resting heart rate is associated with substantially elevated risk of death from all causes beyond the effect of having either depression or elevated resting heart rate alone. For instance, after adjustment for relevant biobehavioral risk factors, participants with both depression and a resting heart rate > 80 bpm were at a 3-fold higher risk of death when compared to those without depression and with a resting heart rate ranging from 60 to 80 bpm. This risk is particularly marked in participants with prevalent coronary heart disease, in which there was some evidence of an additive interaction between depressive symptoms and elevated resting heart rate.

Findings in the Context of the Literature and Possible Mechanisms

To our knowledge, this is the first prospective cohort study to compare the effects of depressive symptoms on mortality in individuals as a function of their resting heart rate. Our findings are based on a large well-characterized cohort with depression symptomatology assessed by a validated scale and biological risk factors assessed by clinical examination. We found that both depression and resting heart rate were strong predictors of death independently of biobehavioral risk factors and of each other. This finding is consistent with previous studies,[3–5,9–11] even though these studies usually considered depression and resting heart rate as individual predictors and rarely showed mutually adjusted analyses. In comparisons across the 6 exposure categories, we also found that participants with coexisting depression and elevated resting heart rate (> 80 bpm) were more likely to die than were participants in any of the other 5 combinations. Moreover, participants with depression but with a resting heart rate ranging from 60 to 80 bpm were at increased risk of mortality compared to those without depression and with a resting heart rate > 80 bpm, a resting heart rate considered to be elevated. These results suggest that the effect of depression on mortality is strong, and it is perhaps a stronger predictor of death than resting heart rate in this cohort of middle-aged men and women.

Although this study did not aim to examine the mechanisms that could explain the current observations, several hypotheses seem possible. The finding showing depression to be associated with increased risk of all-cause mortality suggests that depression may act as an exacerbating factor in the progression of other medical illnesses.[28] Although depression is thought to be implicated in the development of certain physical illnesses such as cardiovascular disease,[29] secondary depression, in which a diagnosed or undiagnosed medical illness precedes depression, is also possible. In this case, depression may appear to be a marker of the severity of physical illnesses.[30,31] The coexistence of depression with other medical illnesses may impair recovery and increase the risk of mortality by impeding treatment-seeking, adherence to pharmacologic and behavioral regimens, and adoption of healthy lifestyles.[32]

The association between resting heart rate and mortality is plausible because resting heart rate is a marker of both autonomic nervous system and cardiorespiratory fitness, both of which, when impaired, are associated with the risk of death.[33,34] Although an elevated resting heart rate might be the reflection of poor underlying health status,[10] it is primarily an indicator of cardiorespiratory fitness, which is related to physical fitness.[33] Indeed, exercise capacity is a powerful predictor of mortality,[33] and resting heart rate is lower in individuals who undertake vigorous physical activity.[35] Depression has been shown to be associated with decreased cardiorespiratory fitness,[36] which may be the consequence of a lower engagement of individuals in physical activity. Data from the Established Populations Epidemiologic Studies of the Elderly[32] cohort provide some evidence that physical activity is one of the mechanisms underlying the link between depression and physical decline, as those who were depressed undertook less walking, gardening, and vigorous physical activities.[32] This fact may explain why depression has been found to be associated with high resting heart rate, although depression itself could also affect physical fitness and, subsequently, resting heart rate levels by directly modulating central nervous system pathways.[14,37] Furthermore, despite the independent effects observed in this study, high resting heart rate and depression may be associated due to partially shared biological processes. Increased resting heart rate in depressive participants could reflect deficits in cardiac vagal control. It is known that cardiac vagal activity, when unaltered, decreases cardiac activity by reducing resting heart rate and contractility.[38] However, there is also some evidence showing an increased resting heart rate in the absence of reduced vagal tone in depressed patients.[39] Recent studies[40,41] have shown depression to be associated with low heart rate variability, an index of reduced cardiac vagal activity, which has been found to be a risk factor for all cause and cardiac mortality.[42,43]

Considering the plausibility of the influence of depression on resting heart rate via behavioral and pathophysiological mechanisms and their independent link with mortality, it is highly possible that they exert a combined effect on mortality risk. However, the underlying mechanisms, including the vagal mechanism, behind this association need to be examined in future studies.

Study Limitations

In interpreting the present results, it is important to note some limitations. First, this cohort of civil servants did not include blue-collar workers, unemployed individuals, or younger adults; thus, the sample is not representative of the general population of working age, which may limit the generalizability of our findings. Second, we assessed depressive symptoms rather than clinical depression. However, it has been suggested that significant depressive symptomatology could be a risk factor for clinical depression.[21] Finally, we did not have the power to examine cause-specific mortality, but the results for all-cause mortality are robust. The lack of power may also explain why the confidence interval around the RERI estimating the interaction between depressive symptoms and elevated resting heart rate was large among

participants with coronary heart disease but did not reach statistical significance. Although this finding is consistent with the idea that depression and resting heart rate are general rather that specific risk factors of any disease,[10,44] further studies should examine whether depression and elevated resting heart rate exert a combined effect on cardiovascular disease, cancer, and non–cardiovascular disease mortality.

Conclusions and Implications of These Findings

Despite these potential limitations, depression is increasingly recognized to have an important predictive and prognostic value, and this study provides additional evidence that the coexistence of depressive symptoms and elevated resting heart rate is associated with substantially increased risk of death. Our findings suggest the possibility that treatments that improve both depression and resting heart rate might improve survival.

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