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

Hermann Nabi, PhD[1,*], **Mika Kivimäki, PhD**[2,3], **Jean Phillipe Empana, MD, PhD**[4], **Séverine Sabia, PhD**[1], **Annie Britton, PhD**[2], **Michael G. Marmot, PhD, FFPHM, FRCP**[2], **Martin J Shipley, MSc**[2], and **Archana Singh-Manoux, PhD**[1,2,5]

[1]Centre for Research in Epidemiology & Population Health, INSERM, U1018 [2]Department of Epidemiology and Public Health, University College London, United Kingdom [3]Finnish Institute of Occupational Health and University of Helsinki, Finland [4]INSERM U970, Paris Cardiovascular Research Center (PAARC); University Paris Descartes, Paris, F-75015, France [5]Hôpital Ste Périne, AP-HP, Centre de Gérontologie, Paris, F-75781, France

Abstract

Objective—To examine the combined effects of depressive symptoms and resting heart rate (RHR) on mortality.

Methods—Data come from 5936 participants, aged 61 ± 6 years, from the Whitehall II study. Depressive symptoms were assessed in 2002–2004 using the center-for-epidemiologic-studies-depression-scale (score ≥ 16). RHR was measured at the same study phase via electrocardiogram. Participants were assigned to 1 of 6 risk-factor-groups based on depression status (yes/no) and RHR categories (<60, 60 – 80, >80 bpm). Mean follow-up for mortality was 5.6 years.

Results—In mutually adjusted Cox regression models, depression (hazard ratio = 1.93 $p<0.001$) and RHR>80 bpm (hazard ratio = 1.67, $p<0.001$) were independent predictors of mortality. After adjustment for potential confounding and mediating variables, participants with both depression and high RHR had a 3.0-fold higher ($p<0.001$) risk of death compared to depression-free participants with RHR ranging from 60 to 80 bpm. This risk is particularly marked in participants with prevalent CHD.

Conclusions—This study provides evidence that the coexistence of depressive symptoms and elevated RHR is associated with substantially increased risk of death compared to those without these two factors. This finding raises the possibility that treatments that improve both depression and RHR might improve survival.

Keywords

depression; resting heart rate and mortality

INTRODUCTION

Depression is a major public health issue worldwide [1]. Projections of the Global Burden of Disease by the WHO 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

*Corresponding Author: INSERM Unité 1018, Hôpital Paul Brousse, Bâtiment 15/16, 16 avenue Paul Vaillant Couturier, 94807 Villejuif Cedex, Hermann.Nabi@inserm.fr.

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 non-depressive subjects [8].

Resting heart rate (RHR), 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 of working men without clinically detectable cardiovascular diseases (CVD) at baseline followed up for 23 years, the risk for sudden and non-sudden death from acute myocardial infarction and all-cause mortality increased in a dose-response manner with increasing RHR, after adjustment for biobehavioral risk factors [12]. Another recent study involving a large sample of men and women found elevated RHR to be a long-term predictor for mortality independent of other risk factors in patients with suspected or proven coronary artery disease [13].

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

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

MATERIAL & METHODS

Data are 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 35–55 years in 20 London based departments were invited to participate by letter, 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 ethics committee approved the study.

Measures

Depressive symptoms—Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D, Cronbach's 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 [21]. A score ≥ 16 from a total possible score of 60 has been used extensively to distinguish depressed from nondepressed subjects [21].

Resting Heart Rate—RHR was measured at the phase 7 screening clinic via electrocardiogram (ECG) on participants in the supine position following a standard

protocol. The following classification was used to categorize RHR: RHR<60, 60≤RHR≥80, and RHR>80 beats/minute (bpm), based on current guidelines that have defined adequate rate control as a ventricular response between 60 and 80 bpm at rest [22].

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

Covariates

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

Biobehavioral risk factors: Behavioral risk factors were assessed using response to the phase 7 questionnaire and were categorized as follows: smoking status (never, ex, and current), physical activity (≥1.5 or <1.5 hours of moderate or vigorous exercise/week), alcohol consumption in the previous week was categorized as abstention, moderate (1–14units 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 grams of pure alcohol. The following biological CVD risk factors were measured at 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 (BMI) (<20, 20–24.9, 25–29.9, or ≥30 kg/m^2) and diabetes, assessed via glucose tolerance test at the medical screening or self-report of doctor diagnosis.

Medications: Data on antidepressant medications was drawn from the phase 7 questionnaire where participants were asked whether in the last 14 days they had taken antidepressants drugs prescribed by a doctor (yes/no). CVD medications at phase 7 were also drawn from questions on whether in the last 14 days the participant had taken CVD drugs, including diuretics, beta blockers, ACE inhibitors, calcium channel blockers, nitrates, 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 (CHD): CHD status at phase 7 was defined as non-fatal myocardial infarction (MI) or 'definite' angina and was based on clinical examinations at phases 1, 3, 5, and 7 and records obtained from general practitioners and hospitals. Potential non-fatal myocardial infarction was ascertained by questionnaire items on chest pain (the World Health Organisation Rose questionnaire [23]) and the physician's diagnosis of heart attack. Confirmation of myocardial infarction according to MONICA[24] criteria (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) was based on electrocardiograms, markers of myocardial necrosis, and chest pain history from medical records. Angina was assessed based on 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 RHR categories as a function of the sample characteristics were assessed using a chi-square test. The associations of depression and RHR with mortality were examined separately using Cox regressions in 4 serially adjusted models. A resting heart rate between 60–80 bpm was used as the reference category so that the hazard ratios (HRs) of lower RHR (< 60 bpm) and higher RHR (above 80 bpm) were

estimated. In model 1, HRs were adjusted for the following socio-demographic characteristics: sex, age, ethnicity and SEP. Model 2 additionally adjusted the hazard of mortality for smoking, BMI, alcohol consumption, physical activity, hypertension, total blood cholesterol and diabetes. Model 3 was model 1 additionally adjusted for CVD medication (diuretics, beta blockers, ACE inhibitors, calcium channel blockers, nitrates, antiplatelets), antidepressant medication, lipid lowering medication, and history of CHD. Model 4 included all aforementioned variables, depression and RHR categories, in order to estimate their independent effect on mortality.

To examine the combined effect of depression and RHR on mortality, we divided the study sample into six groups based on the cross classification of depression status (depression, CES-D ≥16 vs. no depression, CES-D < 16) and RHR categories (<60, 60 – 80, >80 bpm) with non-depressive participants with RHR between 60 and 80 bpm taken as the reference group.

Cox regressions 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 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 RHR as defined by Rothman [25] by calculating the relative excess risk due to interaction (RERI) [26] using the methods outlined by Andersson et al. [27]. For example, a RERI of 4.0 would mean that the relative risk of death from all-causes in depressive participants with elevated RHR is increased by 4.0 compared to the relative risk that one would expect if there were no interaction between these two factors. In the absence of an interaction between depressive symptoms and RHR, the RERI will be 0. Probability values and 95% CIs for the RERI were computed by the delta method [28].

RESULTS

A total of 5936 participants were included in the analyses. Of them, 170 died during the mean follow-up period of 5.6 years (SD 0.7, range 0.03–6.6). 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 ≥16) was 14.9%. 24% of participants had RHR<60 bpm, 61 % were in the normal range with RHR between 60 and 80 bpm and 15% had RHR >80 bpm. Compared to participants included in this study, those who did not respond to the CES-D questionnaire or did not have data on RHR were more likely to be: women (39.8% vs. 29.1%, $p<0.001$), non-white (15.2% vs. 8.4%, $p <0.001$), older (19.5% vs. 9.3%, $p<0.001$), and from lower SEP (34.1% vs. 15.9%, $p<0.001$).

Table 1 shows the sample characteristics as a function of depression status and RHR categories at phase 7. Participants with depressive symptoms were more likely to be female, younger, from lower SEP, non-white, on medication (antidepressants, nitrates and antiplatelets), current smokers, less physically active, and to have lower BMI and higher prevalence of diabetes and CHD (all $p ≤ 0.04$). Men were more likely to have low RHR (<60 bpm, $p<0.001$). Participants with higher RHR (>80 bpm) were more likely to be from lower SEP, less physically active, hypertensive, obese, diabetic, on CVD medication (beta blockers, nitrates, antiplatelets) and lipid-lowering medication, and to have depressive symptoms (all $p ≤ 0.032$).

Table 2 presents estimates from Cox regression models for the associations between depressive symptoms, RHR and mortality. In model 1 adjusted for socio-demographic

characteristics, depressive participants (CES-D ≥ 16) were at increased risk of death (HR = 2.46, 95% CI 1.74–3.48), when compared to nondepressive participants (CES-D < 16). Using the same adjustments, but with RHR as the predictor, participants with RHR >80 bpm were at increased risk of death from any cause (HR = 1.70, 95% CI 1.18–2.44) compared to those with RHR between 60 and 80 bpm. In model 2 adjusted for CVD biobehavioral risk, the magnitude of the associations was reduced, but participants with depressive symptoms remained at greater risk of mortality. Participants with RHR > 80 bpm were also at greater risk of mortality. In model 3, adjustments for CVD, antidepressant and lipids lowering medication and prevalent CHD did not alter the associations observed in model 1. Inclusion of all of these variables and both depression and RHR in model 4 did not substantially affect these associations; both depressive symptoms (HR=1.93, 95% CI 1.35–2.76) and high RHR (HR=1.67, 95% CI 1.14–2.45) remained independently associated with an increased risk of mortality.

Table 3 shows the associations of combinations of depression status and RHR categories with mortality as the outcome. Model 1, adjusted for sociodemographic characteristics, shows that compared with the reference group (participants without depression and with RHR between 60 and 80 bpm), the hazard of death was higher for depressive participants with RHR between 60 and 80 bpm (2.71, 95% CI 1.73–4.23), for those without depression but with RHR >80 bpm (1.80, 95% CI 1.17–2.76), and for those with both depression and RHR >80 bpm (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 CVD, antidepressant and lipid lowering medications, and prevalent CHD 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 ($p<0.001$) higher for participants with depression but with RHR between 60 and 80 bpm, 1.8-fold ($p<0.001$) higher for those without depression but with RHR >80 bpm, and 3-fold ($p<0.001$) higher for those with both depression and RHR >80 bpm. The RERI between depressive symptoms and elevated RHR was 0.20 (95% CI, −2.17–2.5).

Sensitivity analyses

In order to assess the robustness of the present findings, we repeated the analyses excluding participants with a personal history of CHD. The number of deaths was reduced by 22% (n deaths=133). In fully mutually-adjusted model, depressive symptoms (HR=1.82, $p=0.005$) and elevated RHR (>80 bpm, HR= 1.63, $p=0.03$) remained independent predictors of death. The corresponding fully adjusted risk of death was 2.5-fold ($p=0.04$) higher for participants with both depressive symptoms and RHR > 80 bpm when compared to those without depressive symptoms and with RHR between 60 and 80 bpm. The corresponding RERI was −0.60 (95% CI, −2.90–1.71). Similar patterns of association were observed when the analyses were restricted to participants with prevalent CHD (n deaths = 37). The corresponding fully mutually adjusted HRs were 2.97 ($p=0.006$) for depressive symptoms and 2.00 (p=0.17) for those with RHR > 80 bpm. Finally, participants with both depressive symptoms and RHR >80 bpm had a 7.5-fold ($p=0.005$) higher risk of death relative to those without depressive symptoms and with RHR between 60 and 80 bpm. The corresponding RERI was 2.39 (95% CI, −4.13–8.90).

In addition, we repeated the analysis in subgroups of beta blockers users and non-users. In fully mutually-adjusted model, depressive symptoms (HR=2.14, $p<0.001$) and elevated RHR (>80 bpm, HR= 1.57, $p=0.025$) remained independent predictors of death (n=142) among non beta blockers users. The corresponding fully adjusted risk of death was 3.22-fold ($p≤0.001$) higher for participants with both depressive symptoms and RHR > 80 bpm when compared to those without depressive symptoms and with RHR between 60 and 80 bpm. Among beta blockers users (n deaths= 28) the corresponding HRs were 0.99 ($p=0.99$) for

depressive symptoms and 2.48 (*p*=0.26) for elevated RHR. Only two beta blocker users had depressive symptoms and RHR > 80 bpm thus preventing further analysis of this group. Although the risk of death seems to be lower among beta 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 RHR on mortality in a large cohort of British adults. We found that depressive symptoms and elevated RHR were independent predictors for death from all-causes over 5 years of follow up. Concurrently, the study also shows that the coexistence of depression and higher RHR is associated with substantially elevated risk of death from all-causes beyond the effect of having either depression or elevated RHR alone. For instance, after adjustment for relevant biobehavioral risk factors, participants with both depression and RHR >80 bpm were at a 3-fold higher risk of death when compared to those without depression and with RHR ranging from 60 to 80 bpm. This risk is particularly marked in participants with prevalent CHD where there was some evidence of an additive interaction between depressive symptoms and elevated RHR.

Findings in 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 RHR. 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 RHR were strong predictors of death independently of biobehavioral risk factors and of each other. This is consistent with previous studies [3–5, 9–11], even though these studies usually considered depression and RHR as individual predictors and rarely showed mutually adjusted analyses. In comparisons across the six exposure categories, we also found that participants with co-existing depression and elevated RHR (>80 bpm) were more likely to die than were participants in any of the other five combinations. Moreover, participants with depression but with RHR ranging from 60 to 80 bpm were at increased risk of mortality compared to those without depression and RHR > 80 bpm, RHR 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 RHR 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 [29]. Although depression is thought to be implicated in the development of certain physical illnesses such as CVD [30], secondary depression, where 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 [31, 32]. The coexistence of depression with other medical illnesses may impair recovery and increase the risk of mortality by impeding treatment seeking, adherence to pharmacological and behavioral regimens, and adoption of healthy life-styles [33]. The association between RHR and mortality is plausible because RHR is a marker of both autonomic nervous system and cardiorespiratory fitness, both of which, when impaired, are associated with the risk of death [34, 35]. Although an elevated RHR might be the reflection of poor underlying health status [10], it is primarily an indicator of cardiorespiratory fitness which is related to physical fitness [34]. Indeed, exercise capacity is a powerful predictor of mortality [34] and RHR is lower in individuals who undertake vigorous physical activity [36]. Depression has been shown to be associated with decreased

cardiorespiratory fitness [37] which may be the consequence of a lower engagement of individuals in physical activity. Data from the Established Populations Epidemiologic Studies of the Elderly 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 [33]. This may explain why depression has been found to be associated with high RHR, although depression itself could also affect physical fitness and subsequently RHR levels by directly modulating central nervous system pathways [14, 38]. Furthermore, despite the independent effects observed in this study, high RHR and depression may be associated due to partially shared biological processes. Increased RHR in depressive participants could reflect deficits in cardiac vagal control. It is known that cardiac vagal activity when unaltered decreases cardiac activity by reducing RHR and contractility.[39] However, there is also some evidence showing an increased RHR in the absence of reduced vagal tone in depressed patients [40]. Recent studies have shown depression to be associated with low heart rate variability [41, 42], an index of reduced cardiac vagal activity, which has been found to be a risk factor for all cause and cardiac mortality [43, 44].

Considering the plausibility of the influence of depression on RHR 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 or younger adults; thus it is not representative of the general population of working age, which may limit the generalisability 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 clinicaldepression [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 RHR was large among participants with CHD, but did not reach statistical significance. Although this finding is consistent with the idea that depression and RHR are general rather that specific risk factors of any disease, [10, 45] further studies should examine whether depression and elevated RHR exert a combined effect on CVD, cancer, and non CVD mortality.

Conclusions and implications of this finding

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 RHR is associated with substantially increased risk of death. Our findings raise the possibility that treatments that improve both depression and RHR might improve survival.

Acknowledgments

References

1. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007 Sep 8; 370(9590):851–858. [PubMed: 17826170]

2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006 Nov.3(11):e442. [PubMed: 17132052]

3. Michaud CM, Murray CJ, Bloom BR. Burden of disease--implications for future research. Jama. 2001 Feb 7; 285(5):535–539. [PubMed: 11176854]

4. Zheng D, Macera CA, Croft JB, Giles WH, Davis D, Scott WK. Major depression and all-cause mortality among white adults in the United States. Ann Epidemiol. 1997 Apr; 7(3):213–218. [PubMed: 9141645]

5. Abas M, Hotopf M, Prince M. Depression and mortality in a high-risk population. 11-Year follow-up of the Medical Research Council Elderly Hypertension Trial. Br J Psychiatry. 2002 Aug. 181:123–128. [PubMed: 12151282]

6. Surtees PG, Wainwright NW, Luben RN, Wareham NJ, Bingham SA, Khaw KT. Depression and ischemic heart disease mortality: evidence from the EPIC-Norfolk United Kingdom prospective cohort study. Am J Psychiatry. 2008 Apr; 165(4):515–523. [PubMed: 18245176]

7. Schiffer AA, Pelle AJ, Smith OR, Widdershoven JW, Hendriks EH, Pedersen SS. Somatic versus cognitive symptoms of depression as predictors of all-cause mortality and health status in chronic heart failure. J Clin Psychiatry. 2009 Jul 28.

8. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. J Affect Disord. 2002 Dec; 72(3):227–236. [PubMed: 12450639]

9. 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 Dec; 112(6):736–749. [PubMed: 7457467]

10. Greenland P, Daviglus ML, Dyer AR, et al. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. Am J Epidemiol. 1999 May 1; 149(9):853–862. [PubMed: 10221322]

11. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. Am Heart J. 1987 Jun; 113(6):1489–1494. [PubMed: 3591616]

12. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med. 2005 May 12; 352(19):1951–1958. [PubMed: 15888695]

13. Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J. 2005 May; 26(10):967–974. [PubMed: 15774493]

14. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. Psychosom Med. 2005 May-Jun; 67(Suppl 1):S29–33. [PubMed: 15953797]

15. Veith RC, Lewis N, Linares OA, et al. Sympathetic nervous system activity in major depression. Basal and desipramine-induced alterations in plasma norepinephrine kinetics. Arch Gen Psychiatry. 1994 May; 51(5):411–422. [PubMed: 8179465]

16. Carney RM, Freedland KE, Veith RC, et al. Major depression, heart rate, and plasma norepinephrine in patients with coronary heart disease. Biol Psychiatry. 1999 Feb 15; 45(4):458–463. [PubMed: 10071718]

17. Carney RM, Freedland KE, Stein PK, Skala JA, Hoffman P, Jaffe AS. Change in heart rate and heart rate variability during treatment for depression in patients with coronary heart disease. Psychosom Med. 2000 Sep-Oct; 62(5):639–647. [PubMed: 11020093]

18. Lahmeyer HW, Bellur SN. Cardiac regulation and depression. J Psychiatr Res. 1987; 21(1):1–6. [PubMed: 3560004]

19. Dawson ME, Schell AM, Catania JJ. Autonomic correlates of depression and clinical improvement following electroconvulsive shock therapy. Psychophysiology. 1977 Nov; 14(6):569–578. [PubMed: 928608]

20. Wyatt RJ, Portnoy B, Kupfer DJ, Snyder F, Engelman K. Resting plasma catecholamine concentrations in patients with depression and anxiety. Arch Gen Psychiatry. 1971 Jan; 24(1):65–70. [PubMed: 5538854]

21. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Applied Psychological Measurement. 1977; 1(3):385.

22. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation): developed in Collaboration With the North American Society of Pacing and Electrophysiology. J Am Coll Cardiol. 2001 Oct; 38(4):1231–1266. [PubMed: 11583910]

23. Rose, GA. Cardiovascular survey methods. 2. Geneva: World Health Organization; Albany, N.Y.: WHO Publications Centre USA [distributor]; 1982.

24. Gutzwiller F. Monitoring of cardiovascular disease and risk factor trends: experiences from the WHO/MONICA project. Annals of medicine. 1994 Feb; 26(1):61–65. [PubMed: 8166990]

25. Rothman, KJ. Epidemiology: an introduction. Oxford University Press; New York: 2002.

26. Ferreri M, Bonelli L, Capasso A, et al. Planning of a screening programme for cervical cancer in Liguria and evaluation of the attitude of the female population towards cancer detection. Eur J Epidemiol. 1993 Jan; 9(1):10–16. [PubMed: 8472796]

27. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol. 2005; 20(7):575–579. [PubMed: 16119429]

28. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. Epidemiology. 1992 Sep; 3(5):452–456. [PubMed: 1391139]

29. Alexopoulos GS. Depression in the elderly. Lancet. 2005 Jun 4–10; 365(9475):1961–1970. [PubMed: 15936426]

30. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. Eur Heart J. 2006 Dec; 27(23):2763–2774. [PubMed: 17082208]

31. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. Jama. 1993 Oct 20; 270(15):1819–1825. [PubMed: 8411525]

32. Goodnick PJ, Henry JH, Buki VM. Treatment of depression in patients with diabetes mellitus. J Clin Psychiatry. 1995 Apr; 56(4):128–136. [PubMed: 7713850]

33. Penninx BW, Guralnik JM, Ferrucci L, Simonsick EM, Deeg DJ, Wallace RB. Depressive symptoms and physical decline in community-dwelling older persons. Jama. 1998 Jun 3; 279(21):1720–1726. [PubMed: 9624025]

34. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002 Mar 14; 346(11):793–801. [PubMed: 11893790]

35. Schwartz PJ. The autonomic nervous system and sudden death. Eur Heart J. 1998 Jun; 19(Suppl F):F72–80. [PubMed: 9651739]

36. Black A, Murray L, Cardwell C, Smith GD, McCarron P. Secular trends in heart rate in young adults, 1949 to 2004: analyses of cross sectional studies. Heart. 2006 Apr; 92(4):468–473. [PubMed: 16159976]

37. Hollenberg M, Haight T, Tager IB. Depression decreases cardiorespiratory fitness in older women. J Clin Epidemiol. 2003 Nov; 56(11):1111–1117. [PubMed: 14615002]

38. Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. Neuroscience and biobehavioral reviews. 2002 Dec; 26(8):941–962. [PubMed: 12667498]

39. Reed MJ, Robertson CE, Addison PS. Heart rate variability measurements and the prediction of ventricular arrhythmias. Qjm. 2005 Feb; 98(2):87–95. [PubMed: 15671474]

40. Moser M, Lehofer M, Hoehn-Saric R, et al. Increased heart rate in depressed subjects in spite of unchanged autonomic balance? J Affect Disord. 1998 Mar; 48(2–3):115–124. [PubMed: 9543200]

41. Carney RM, Saunders RD, Freedland KE, Stein P, Rich MW, Jaffe AS. Association of depression with reduced heart rate variability in coronary artery disease. Am J Cardiol. 1995 Sep 15; 76(8): 562–564. [PubMed: 7677077]

42. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. J Psychosom Res. 2002 Oct; 53(4):897–902. [PubMed: 12377300]

43. Tsuji H, Venditti FJ Jr, Manders ES, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation. 1994 Aug; 90(2):878–883. [PubMed: 8044959]

44. Tsuji H, Larson MG, Venditti FJ Jr, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation. 1996 Dec 1; 94(11):2850–2855. [PubMed: 8941112]

45. Kristal-Boneh E, Silber H, Harari G, Froom P. The association of resting heart rate with cardiovascular, cancer and all-cause mortality. Eight year follow-up of 3527 male Israeli employees (the CORDIS Study). Eur Heart J. 2000 Jan; 21(2):116–124. [PubMed: 10637085]

Table 1

Sample characteristics as a function of Depression and Resting Heart Rate at phase 7

Variables	N total	Depressive symptoms (CES-D score ≥16) N (%)	p value	Resting Heart Rate categories			p value
				<60 bpm N (%)	60–80 bpm N (%)	>80 bpm N (%)	
Sex			< 0.001				< 0.001
Male	4268	559 (13.1)		1124 (79.2)	2498 (68.8)	646 (73.0)	
Female	1668	326 (19.5)		296 (20.8)	1133 (31.2)	239 (27.0)	
Age in years			< 0.001				0.703
<54	1110	212 (19.1)		250 (17.6)	721 (19.9)	139 (15.7)	
54–59	1822	272 (14.9)		421 (29.6)	1139 (31.4)	262 (29.6)	
60–64	1259	163 (12.9)		321 (22.6)	746 (20.5)	192 (21.7)	
65–69	1196	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)	
SEP			< 0.001				< 0.001
High	2040	201 (9.9)		546 (38.5)	1221 (33.6)	273 (30.8)	
Middle	3032	469 (15.5)		717 (50.5)	1831 (50.4)	484 (54.7)	
Low	864	215 (24.9)		157 (11.1)	579 (15.9)	128 (14.5)	
Ethnicity			< 0.001				0.543
White	5485	743 (13.5)		1320 (93.0)	3347 (92.2)	818 (92.4)	
Other	451	142 (31.5)		100 (7.0)	284 (7.8)	67 (7.6)	
Smoking status			< 0.001				0.479
Never smoker	2678	377 (14.1)		639 (45.0)	1637 (45.1)	402 (45.4)	
Ex smoker	2282	297 (13.0)		556 (39.2)	1364 (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			0.514				0.755
Abstainers	973	220 (22.9)		206 (14.5)	604 (16.6)	163 (18.4)	
Moderate	3725	484 (13.0)		939 (66.1)	2286 (63.0)	500 (56.5)	
High	1158	153 (13.2)		254 (17.9)	691 (19)	213 (24.1)	
Missing	80	28 (35.0)		21 (1.5)	50 (1.5)	9 (1.0)	
Exercise			< 0.001				< 0.001

Variables	N total	Depressive symptoms (CES-D score ≥16)		Resting Heart Rate categories			
		N (%)	p value	<60 bpm N (%)	60–80 bpm N (%)	>80 bpm N (%)	p value
≥ 1.5 h/week	5152	699 (13.6)		1277 (89.9)	3134 (86.3)	741 (83.7)	
< 1.5 h/week	784	186 (23.7)		143 (10.1)	497 (13.7)	144 (16.3)	
Hypertension			0.315				0.032
No	3585	521 (14.5)		811 (57.1)	2336 (64.3)	438 (49.5)	
Yes	2351	364 (15.5)		609 (42.9)	1295 (35.7)	447 (50.5)	
BMI (kg/m²)			0.002				< 0.001
< 20	179	38 (21.2)		53 (3.7)	108 (3.0)	18 (2.0)	
20–24.9	2028	263 (13.0)		570 (40.1)	1242 (34.2)	216 (24.4)	
25–29.9	2606	365 (14.0)		588 (41.4)	1627 (44.8)	391 (44.2)	
≥ 30	1099	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			< 0.001				< 0.001
No	5656	816 (14.4)		1371 (96.5)	3470 (95.5)	815 (92.1)	
Yes	281	69 (24.6)		49 (3.5)	162 (4.5)	70 (7.9)	
High blood cholesterol			0.266				< 0.174
No	3940	599 (15.2)		991 (69.2)	2401 (66.1)	548 (61.9)	
Yes	1886	263 (13.9)		396 (27.9)	1174 (32.2)	316 (35.7)	
Missing	110	23 (20.9)		33 (2.3)	56 (1.5)	21 (2.4)	
Antidepressant drugs			< 0.001				0.842
No	5728	786 (13.7)		1366 (96.2)	3514 (96.8)	848 (95.8)	
Yes	208	99 (47.9)		54 (3.8)	117 (3.2)	37 (4.2)	
CVD medications (Yes)							
Diuretics	494	76 (15.4)	0.757	135 (9.5)	277 (7.6)	82 (9.3)	0.518
Beta Blockers	584	91 (15.6)	0.631	345 (24.3)	223 (6.1)	16 (1.8)	< 0.001
ACE Inhibitors	649	110 (16.9)	0.122	164 (11.5)	356 (9.8)	129 (14.6)	0.113
Calcium Channel Blockers	420	67 (16.0)	0.533	118 (8.3)	228 (6.3)	74 (8.4)	0.614
Nitrates	62	18 (29.0)	0.002	27 (1.9)	33 (0.9)	2 (0.2)	< 0.001
Antiplatelets	584	104 (17.8)	0.038	199 (14.0)	310 (8.5)	75 (8.5)	< 0.001
Lipid lowering medications			0.242				0.001

Variables	N total	Depressive symptoms (CES-D score ≥16)		Resting Heart Rate categories			
		N (%)	p value	<60 bpm N (%)	60–80 bpm N (%)	>80 bpm N (%)	p value
No	5247	772 (14.7)		1207 (85.0)	3253 (89.6)	787 (88.9)	
Yes	689	113 (16.4)		213 (15.0)	378 (10.4)	98 (11.1)	
History of CHD			0.001				< 0.001
No	5385	777 (14.4)		1229 (86.5)	3348 (92.2)	808 (91.3)	
Yes	551	108 (19.7)		191 (13.5)	283 (7.8)	77 (8.7)	
Depressive symptoms (CES-D ≥ 16)							0.007
No	5051			1239 (87.3)	3074 (84.7)	738 (83.4)	
Yes	885			181 (12.7)	557 (15.3)	147 (16.6)	

Table 2

Associations between Depression, Resting Heart Rate and Mortality

Predictors	n events/n participants	Mortality risk	
		HR	95% CI
Model 1			
Depressive symptoms	170/5936		
Score ≤ 15	123/5051	1	reference
Score ≥ 16	47/885	2.46	(1.74–3.48)[‡]
Resting Heart Rate	170/5936		
< 60 bpm	33/1420	0.85	(0.57–1.26)
60 bpm ≥ HR ≤ 80 bpm	95/3631	1	reference
> 80 bpm	42/885	1.70	(1.18–2.44)[†]
Model 2			
Depressive symptoms			
Score ≤ 15		1	reference
Score ≥ 16		1.98	(1.39–2.82)[‡]
Resting Heart Rate			
< 60 bpm		0.85	(0.57–1.27)
60 bpm ≥ HR ≤ 80 bpm		1	reference
> 80 bpm		1.54	(1.06–2.23)[*]
Model 3			
Depressive symptoms			
Score ≤ 15		1	reference
Score ≥ 16		2.42	(1.70–3.45)[‡]
Resting Heart Rate			
< 60 bpm		0.69	(0.45–1.06)
60 bpm ≥ HR ≤ 80 bpm		1	reference
> 80 bpm		1.74	(1.21–2.52)[†]
Model 4			
Depressive symptoms			
Score ≤ 15		1	reference
Score ≥ 16		1.93	(1.35–2.76)[‡]
Resting Heart Rate			
< 60 bpm		0.75	(0.49–1.15)
60 bpm ≥ HR ≤ 80 bpm		1	reference
> 80 bpm		1.67	(1.14–2.45)[†]

[*]
p<0.05,

*†*p<0.01,

*‡*p<0.001

Model 1: adjusted for sex, age, ethnicity and SEP

Model 2: model 1 additionally adjusted for BMI, alcohol consumption, smoking status, exercise, hypertension, antihypertensive drugs, total blood cholesterol, and diabetes.

Model 3: model 1 additionally adjusted for: CVD medication (diuretics, beta blockers, ACE inhibitors, calcium channel blockers, nitrates, antiplatelets), antidepressant medication, lipid lowering medication and history of CHD

Model 4: 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.

** n events/n total is the same in all models.

Table 3

Hazard ratios for mortality as a function of combinations of depression and resting heart rate

		RHR < 60 bpm	60 ≥ RHR ≤ 80 bpm	RHR > 80 bpm
Model 1				
Depressive symptoms				
No	n events/n total	26/1239	66/3074	29/738
	HR (95% CI)	0.92(0.58–1.45)	1 (reference)	1.80 (1.17–2.76)[†]
Yes	n events/n total	7/181	29/557	11/147
	HR (95% CI)	1.88(0.86–4.13)	2.71 (1.73–4.23)[‡]	3.85(2.03–7.31)[‡]
Model 2				
Depressive symptoms				
No	HR (95% CI)	0.92 (0.58–1.46)	1 (reference)	1.66 (1.08–2.56)[*]
Yes	HR (95% CI)	1.55 (0.70–3.42)	2.21 (1.41–3.49)[‡]	2.81 (1.46–5.56)[†]
Model 3				
Depressive symptoms				
No	HR (95% CI)	0.75 (0.46–1.21)	1 (reference)	1.84 (1.20–2.83)[†]
Yes	HR (95% CI)	1.67 (0.76–3.70)	2.55 (1.62–4.04)[‡]	3.67 (1.92–7.02)[‡]
Model 4				
Depressive symptoms				
No	HR (95% CI)	0.79 (0.48–1.28)	1 (reference)	1.77 (1.14–2.75)[†]
Yes	HR (95% CI)	1.40 (0.63–3.13)	2.10 (1.32–3.32)[‡]	2.99(1.53–5.81)[‡]

[*] $p<0.05$,

[†] $p<0.01$,

[‡] $p<0.001$

Model 1: hazard ratios (HR) adjusted for sex, age, ethnicity and SEP

Model 2: model 1 additionally adjusted for BMI, alcohol consumption, smoking status, exercise, hypertension, antihypertensive drugs, total blood cholesterol, and diabetes.

Model 3: model 1 additionally adjusted for: CVD medication (diuretics, beta blockers, ACE inhibitors, calcium channel blockers, nitrates, antiplatelets), antidepressant medication, lipid lowering medication and history of CHD

Model 4: HRs adjusted for all aforementioned variables

[**] n events/n total is the same in all models.