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# Autonomic dysfunction: a link between depression and cardiovascular mortality? The FINE Study

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***Background*** **Depression is associated with an increased risk of cardiovascular diseases (CVD) in vascular patients as well as in the general population. We investigated whether autonomic dysfunction could explain this relationship.**

***Design*** **The Finland, Italy and The Netherlands Elderly (FINE) Study is a prospective cohort study.**

***Methods*** **Depressive symptoms were measured with the Zung Self-rating Depression Scale in 870 men, aged 70–90 years, free of CVD and diabetes in 1990. Resting heart rate was determined from a 15–30-s resting electrocardiogram in The Netherlands and Italy and as pulse rate in Finland. In addition, in The Netherlands, heart-rate variability (HRV) and QTc interval were determined.**

***Results*** **At baseline, depressive symptoms were associated with an increase in resting heart rate, and nonsignificantly with low HRV and prolonged QTc interval. After 10 years of follow-up, 233 (27%) men died from CVD. Prospectively, an increase in resting heart rate with 1 SD was associated with an increased risk of cardiovascular mortality [hazard ratio (HR), 1.22; 95% confidence interval (CI), 1.08–1.38]. In addition, low HRV (HR, 0.78; 95% CI, 0.61–1.01) and prolonged QTc interval (HR, 1.28; 95% CI, 1.06–1.53) per SD were associated with cardiovascular mortality. The increased risk of depressive symptoms for cardiovascular mortality (HR, 1.38; 95% CI, 1.21–1.58) did not change after adjustments for several indicators of autonomic dysfunction.**

***Conclusion*** **This study suggests that mild depressive symptoms are associated with autonomic dysfunction in elderly men. The increased risk of cardiovascular mortality with increasing magnitude of depressive symptoms could, however, not be explained by autonomic dysfunction.** ***Eur J Cardiovasc Prev Rehabil*** **14:796–802 © 2007 The European Society of Cardiology**

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## Introduction

Depression is associated with an increased risk of cardiovascular mortality in patients with cardiovascular diseases (CVD) as well as middle-aged and elderly persons without CVD [1,2]. Several mechanisms to explain this association have been proposed, such as higher prevalence of cardiovascular risk factors in depressed persons, antidepressant cardiotoxicity, induction of the hypothalamic–pituitary–adrenocortical (HPA) axis, inflammation and increased platelet reactivity [3]. Ongoing studies are performed to gain more insight in these mechanisms.

Another explanation for the relationship between depression and increased cardiovascular mortality is through

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autonomic dysfunction [4]. This reflects reduced parasympathetic and increased sympathetic nervous system activity, which are involved in the pathophysiology of myocardial ischemia, heart failure, diabetes, ventricular tachycardia, ventricular fibrillation and sudden cardiac death [5]. Indicators of autonomic dysfunction are elevated resting heart rate, low heart-rate variability (HRV) and prolonged QTc intervals. These indicators are associated with increased cardiovascular and all-cause mortality in patients with and without myocardial infarction [6–10].

In depressed patients, autonomic dysfunction was first demonstrated by elevated levels of plasma and urinary cathecholamines, primarily norepinephrine, which are markers of increased sympathetic nervous system activation [11,12]. More recently, elevated resting heart rates and low HRV have been associated with depressive symptoms in cardiac patients as well as in older primary care patients and older women without CVD [5,13–18].

To investigate whether autonomic dysfunction may explain the relationship between depression and cardiovascular mortality, the contribution of autonomic dysfunction on the relationship between depression and cardiovascular mortality should be investigated. Reduced HRV may partly explain the relationship between depression and mortality in cardiac patients [19]. Whether autonomic dysfunction explains the increased risk of depressive symptoms for cardiovascular mortality in men without cardiac disease, has not been investigated so far.

In this study, we investigated whether depressive symptoms were associated with autonomic dysfunction, indicated by resting heart rate, HRV and QTc intervals in elderly men without prevalent CVD or diabetes. Furthermore, we studied whether the increased risk of depressive symptoms on 10-year cardiovascular mortality [2] could be explained by autonomic dysfunction.

## Methods

### The Finland, Italy and The Netherlands Elderly (FINE) Study

The Finland, Italy and The Netherlands Elderly (FINE) Study is a prospective population-based cohort study on the risk factors and health in elderly men. The study design and measurements have been described in detail elsewhere [20]. In brief, the FINE Study started in 1984 as a continuation of the Seven Countries Study (SCS), which was originally initiated in 1958 by Keys *et al.* [21] as a cardiovascular risk factor survey among 12 763 middle-aged men. In total, 2285 men from Finland ($n = 716$), Italy ($n = 682$) and The Netherlands ($n = 887$) participated in the baseline examination of the study in 1985. Informed consent was obtained from all study participants. Data collection followed the international protocol used in previous surveys of the SCS [21], extended with gerontologic variables. During 1989–1991 the second round of the FINE Study took place. In this round, measures on depression were added. Mortality data were collected until the year 2000.

### Depressive symptoms

Depressive symptoms were measured using the Self-rating Depression Scale (SDS), developed by Zung [22]. This scale was developed to assess depression among patients admitted to a psychiatric hospital, and also for noninstitutionalized elderly patients [23], and was found to be highly comparable among different countries [24]. The reliability of the SDS is good in elderly men (Cronbach $\alpha = 0.75$) [25] and has been validated repeatedly with other questionnaires on depressive symptoms, such as the Center for Epidemiological Studies-Depression (CES-D) ($r = 0.69$) [26], the geriatric depression scale ($r = 0.59$) [27] and the Hamilton Depression scale ($r = 0.80$) [28]. The questionnaire contains 20 either positively or negatively formulated items, based on clinical diagnostic criteria commonly used to diagnose depressive disorders. The answers on those items are coded on a four-point Likert-type scale varying from 'none or sometimes' to 'most or always'. Positive items on the absence of depressive symptoms were recoded, so that a higher score indicated more depressive symptoms. An index for the SDS was derived by dividing the sum of the answers by 80 and multiplying by 100 (range 25–100), with a higher score indicating more depressive symptoms [23]. The original clinical cut-off values are no depression (less than 50), mild depression (50–59) and moderate–severe depression ($\geq 60$) [23]. To increase power for the analyses a continuous measure was used per standard deviation (SD) (Finland SD = 10.8, Italy SD = 11.3 and The Netherlands SD = 9.5) and the SDS was categorized into country-specific tertiles. The cut-off values for the middle and high tertile were 42 and 51 for Finland, 45 and 54 for Italy, and 39 and 46 for The Netherlands.

### Autonomic dysfunction

Data on autonomic function were gathered during the same period of time as the data on depressive symptoms. Standard resting 12-lead electrocardiographic (ECG) recordings were performed according to the protocol of the SCS [21]. The duration of recording ranged from 15 to 30 s. Readings were made according to the 1968 edition of the Minnesota Code [29]. In The Netherlands and Italy, resting heart rate was derived from the ECG. In Finland, resting heart rate was measured from the radial artery with the men in supine position and counted for 30 s. Resting heart rate was expressed as beats/min and used in the analyses as a continuous measure (per SD; Finland SD = 11.7, Italy SD = 12.4, The Netherlands SD = 13.5).

In addition, for the Dutch cohort HRV and QTc intervals were determined. Intervals between all sinus beats were measured, using a digitizing table (Calcomp) and a personal computer. The resolution of the tables is 100 lines/mm and the reproducibility is 0.25 mm (corresponding to 10 ms). HRV (ms) was defined as the SD of the duration of all normal RR-intervals [7]. QT intervals were read from three leads: V2, V6 and lead I, II, or III of which the lead with the longest QT was chosen [8]. QT intervals were adjusted for heart rate according to Bazett's formula resulting in QTc intervals [30].

### Cardiovascular end points

Mortality data were collected during 10 years of follow-up. In Finland, information on causes of death was obtained from the Finnish death register; in Italy and in The Netherlands information was obtained from hospital registries and/or general practitioners. One person from Finland, one from Italy and one from The Netherlands were lost to follow-up. They were included in the analyses, but censored at the date of the last examination, before they were lost to follow-up. Coding of causes of death was carried out by one clinical epidemiologist who was blinded for the risk factor status of the patient. Mortality from CVD was coded according to the *International Classification of Diseases*, ninth revision (ICD-9: 390–459). In the analyses, primary ($n = 199$) and secondary ($n = 107$) causes of cardiovascular death were combined and 233 men died of CVD. Men who died of causes other than CVD ($n = 209$) were censored at date of death. Men who were still alive at the end of the study were censored at the last examination date.

### Other variables

The self-administered questionnaire contained questions on demographic characteristics, educational level and lifestyle habits. Marital status was classified as living alone (unmarried, separated or widow) or with other person(s). In The Netherlands, usual alcohol consumption was assessed in the dietary survey and in Finland and Italy with a self-administered questionnaire, and classified as alcohol consumption and nonconsumption. Participants were classified as current and nonsmokers. Body mass index (BMI) was calculated from weight and height (kg/m$^2$), which were measured while the participant was standing in light clothing without shoes. Physical activity was assessed with a self-administered validated questionnaire designed for retired men [31]. All types of activity with an intensity of more than 2 kcal energy expended per kilogram of body weight during 1 h, were summed and expressed as minutes of total physical activity per week (min/week).

Arterial blood pressure was measured twice on the right arm after 5 min rest, in a supine position. In Finland and Italy, standard sphygmomanometers were used, whereas in The Netherlands, a random zero sphygmomanometer was used. The average of two readings of both systolic blood pressure (SBP) and diastolic blood pressure (fifth Korotkoff phase) was calculated. Nonfasting venous blood samples were taken and total and high-density lipoprotein (HDL) cholesterol (mmol/l) were determined using standardized procedures according to the criteria of the World Health Organization's Lipid Reference Laboratories in Prague, Czech Republic, or Atlanta, Georgia, USA [32]. History of myocardial infarction was obtained using the London School of Hygiene and Tropical Medicine questionnaire [29], verified by information from general practitioners or hospital registries. Information was obtained on the use of antihypertensive drugs. A clinical history of stroke, heart failure, diabetes and chronic obstructive pulmonary disease (COPD) was based on a doctor's conclusion using questionnaire information and the results of the physical examination.

### Study samples

Depressive symptoms were measured for the first time during the second round of the FINE study, between October 1989 and November 1991, when in total 1416 men (82%) participated of the 1734 men still alive. Of these, 909 (64%) were free of CVD and diabetes. From these, 39 with artrial fibrillation based on the Minnesota code were excluded. Thus, a study sample of 870 men remained for analysis, 253 men from Finland, 362 men from The Netherlands and 255 men from Italy. For the analyses of HRV and QTc interval, data for 362 men of the Dutch cohort were available.

### Data analysis

To retain power and to prevent bias from missing values in a selective group of respondents a single imputation procedure in SPSS version 12.0.1 (SPSS Inc., Chicago, Illinois, USA) was used. We imputed missing values on the items of the SDS (on average 7%), HRV (2%), and the other covariates (on average 2%). All information of the baseline examination in 1990 and follow-up examinations was used to fill in missing values.

Frequency distributions are given for categorical variables for each country. Means and SD were computed for continuous baseline variables, and medians and 10–90 percentiles for continuous variables with a skewed distribution. Differences between countries were tested with analysis of variance, Kruskal–Wallis (in case of skewed distribution) or $\chi^2$-test.

Multiple linear regression analysis was used to calculate differences in resting heart rate across country-specific tertiles of depressive symptoms, and HRV and QTc intervals, respectively, in the Dutch cohort. The HRV distribution was skewed and therefore log-transformed. The transformed values were then used to compute

geometric means. In the first model, we adjusted for age (years). In the second model, we also adjusted for the following potential confounders or intermediate factors: country (Finland vs. The Netherlands and Italy vs. the Netherlands), years of education, living alone (yes vs. no), current smoking (no vs. yes), alcohol consumption (yes vs. no), physical activity (min/week), SBP (mmHg), BMI (kg/m$^2$), total and HDL-cholesterol levels (mmol/l), COPD (no vs. yes) and the use of antihypertensive drugs (no vs. yes).

The prospective associations of resting heart rates/SD (in the FINE cohort), and HRV and QTc interval (in the Dutch cohort) with cardiovascular mortality were estimated using Cox proportional hazard models. In the first model, we adjusted for age (as the time scale), and in the second model we also adjusted for cardiovascular risk factors. With a log minus log plot the assumptions of proportional hazards were checked. The assumptions of proportionality were not violated.

Finally, we investigated whether the relationship between depressive symptoms and cardiovascular mortality could be explained by autonomic dysfunction, by adding resting heart rate, HRV or QTc interval to the adjusted model.

All analyses were repeated after stratification by country and performed with the SAS statistical software package, version 9.1.2 [33] Point estimates are given with corresponding 95% confidence intervals (CI).

## Results

Table 1 presents the baseline characteristics of the study sample per country. The average depression score was highest in Italy (49.4 ± 11) and lowest in The Netherlands (43.2 ± 10). The average depression scores were low in comparison with the clinical cut-off value for mild depression (≥ 50). Average resting heart rate was higher in The Netherlands (75.2 ± 14) compared with Finland (68.2 ± 12) and Italy (69.3 ± 12). In addition, men in Italy were older, more physically active, and had higher HDL-cholesterol levels than men in Finland and The Netherlands, whereas men in The Netherlands had higher levels of education, were more likely to smoke, had a lower SBP and diastolic blood pressure, and higher total cholesterol levels compared with those in Finland and Italy ($P < 0.05$).

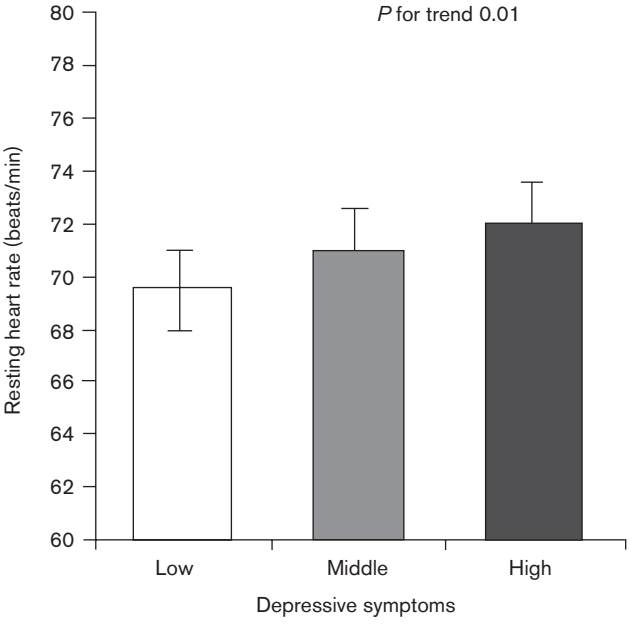
Multiple linear regression analyses showed a dose–response relationship between depressive symptoms and resting heart rate ($P$ for trend 0.01) (Fig. 1). Men in the high tertile of depressive symptoms had an increased mean resting heart rate adjusted for age (73.1 beats/min; 95% CI, 71.6–74.6) compared with men in the low tertile of depressive symptoms (69.6 beats/min; 95% CI, 68.1–71.1). In the second model, after additionally adjusting for country, education, SBP, use of antihypertensive drugs, COPD and physical activity these estimates became 72.0 (95% CI 70.5–73.5) and 69.4 (95% CI,

**Table 1 Baseline characteristics for each country ($n = 870$)**

| Characteristic | Finland $n = 253$ | Italy $n = 255$ | The Netherlands $n = 362$ |
|---|---|---|---|
| Age, mean (SD) (years) | 76.5 (4.9) | 77.5 (3.9) | 75.5 (4.5) |
| Depressive symptoms, mean (SD) | 46.6 (10.8) | 49.4 (11.3) | 43.2 (9.5) |
| Education, mean (SD) (years) | 4.2 (3.1) | 4.7 (2.6) | 10.4 (4.2) |
| Living alone (%) | 31 | 25 | 21 |
| Physical activity, Median (P10–90) (min/week) | 520 (60–1965) | 580 (15–2100) | 483 (75–1160) |
| Alcohol consumption (%) | 80 | 82 | 75 |
| Current smoking (%) | 13 | 17 | 24 |
| BMI, mean (SD) (kg/m$^2$) | 26.0 (3.8) | 26.1 (3.8) | 25.5 (3.1) |
| SBP, mean (SD) (mmHg) | 156 (22) | 162 (20) | 151 (21) |
| DBP, mean (SD) (mmHg) | 84 (11) | 86 (9) | 82 (12) |
| Use of antihypertensive drugs (%) | 25 | 46 | 12 |
| Total cholesterol, mean (SD) (mmol/l) | 5.6 (1.1) | 5.5 (1.1) | 6.1 (1.1) |
| HDL cholesterol, mean (SD) (mmol/l) | 1.2 (0.3) | 1.3 (0.3) | 1.2 (0.3) |
| COPD (%) | 22 | 78 | 28 |
| Heart rate, mean (SD) (beats/min) | 68.2 (11.7) | 69.3 (12.4) | 75.2 (13.5) |
| Heart rate variability, median (P10–90) (ms) | | | 18.1 (8.2–49.0) |
| QTc-interval, mean (SD) (ms) | | | 412 (29) |

BMI, body mass index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.

**Fig. 1**




Autonomic function expressed as resting heart rate by tertiles of depressive symptoms for elderly men from Finland, Italy and The Netherlands, adjusted for age (years), country [Finland, Italy, The Netherlands (reference)], years of education, systolic blood pressure (mmHg), antihypertensive drugs (no vs. yes), COPD (no vs. yes) and physical activity (min/week).

68.0–70.9), respectively, for men in the high and low tertile of depressive symptoms. After additional adjustments for living alone, current smoking, alcohol consumption, BMI, total and HDL-cholesterol levels these estimates did not change.

In The Netherlands, data on HRV and QTc interval were also assessed. Men with high depressive symptoms had a nonsignificantly lower HRV (17.8 ms; 95% CI, 15.6–20.2) compared with men with low depressive symptoms (19.7 ms; 95% CI, 17.2–22.4), adjusted for age, country, education, SBP, use of antihypertensive drugs, COPD and physical activity. In addition, men with high depressive symptoms had a nonsignificantly longer QTc interval (415 ms; 95% CI, 410–420), compared with men with low depressive symptoms (411 ms; 95% CI, 406–415).

After 10 years of follow-up, 442 of the 870 men (51%) had died. Two-hundred and thirty-three men (27%) had died of CVD. The total number of person years was 6321 and the mean follow-up duration was 7.3 years (SD = 3.1). Prospectively, an increase in resting heart rate/SD, adjusted for age was associated with a 26% (95% CI, 1.12–1.42) increased risk of cardiovascular mortality. After additional adjustment, this risk became 22% (95% CI, 1.08–1.38). In addition, in the Dutch sample a longer QTc-interval [hazard ratio (HR) 1.28; 95% CI, 1.06–1.53] was associated with an increased risk of cardiovascular mortality, whereas increased HRV (HR 0.78; 95% CI, 0.61–1.01) was nonsignificantly associated with a lower risk of cardiovascular mortality (Table 2). These indicators of autonomic dysfunction were also associated with total mortality, but less strongly (results not shown).

Finally, an increase in depressive symptoms per SD on the SDS, adjusted for age, country, living alone and physical activity, was associated with a 38% (95% CI, 1.21–1.58) increased risk of cardiovascular mortality. Adjustment for current smoking, alcohol consumption, BMI, SBP, total and HDL cholesterol, COPD and use of antihypertensive drugs did not change this risk. After additional adjustment for separate measures of autonomic dysfunction (Table 3) this risk did not materially change. No differences were seen between countries (results not shown).

**Table 2 Adjusted hazard ratios (HR) of 10-year cardiovascular mortality for tertiles of autonomic dysfunction ($n=870$)**

| | Model 1[a] | Model 2[b] |
|---|---|---|
| | HR (95% CI) | HR (95% CI) |
| Resting heart rate | | |
| Per SD beats/min increase | 1.26 (1.12–1.42) | 1.22 (1.08–1.38) |
| **Dutch cohort (n=362)** | | |
| Heart rate variability | | |
| Per SD ms increase | 0.80 (0.61–1.04) | 0.78 (0.61–1.01) |
| QTc-interval | | |
| Per SD ms increase | 1.32 (1.11–1.57) | 1.28 (1.06–1.53) |

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein. [a]Model 1: adjusted for age. [b]Model 2: additionally adjusted for country [Finland, Italy, The Netherlands (reference)], living alone (yes vs. no), systolic blood pressure (mmHg), physical activity (min/week), total and HDL cholesterol levels (mmol/l), COPD (no vs. yes) and use of antihypertensive drugs (no vs. yes).

**Table 3 Hazard ratios of 10-year cardiovascular mortality for depressive symptoms ($n=870$)**

| | HR (95% CI) |
|---|---|
| Depressive symptoms (per SD) | |
| Model 1[a] | 1.38 (1.21–1.58) |
| Additional adjustment: | |
| Resting heart rate | 1.39 (1.22–1.59) |
| Dutch cohort ($n=362$) | |
| Model 1[a] | 1.37 (1.14–1.65) |
| Additional adjustment: | |
| Heart-rate variability | 1.39 (1.13–1.70) |
| QTc-interval | 1.35 (1.10–1.65) |

CI, confidence interval; HR, hazard ratios; SD, standard deviation. [a]Model 1: adjusted for age (as time scale), country [Finland, Italy, The Netherlands (reference)], years of education, living alone (yes vs. no) and physical activity (min/week).

## Discussion

This study examined whether depressive symptoms in old men were associated with autonomic dysfunction, and whether autonomic dysfunction could explain an increased risk of depressive symptoms on cardiovascular mortality. We observed that depressive symptoms were associated with increased resting heart rate, but not significantly with lower HRV or prolonged QTc intervals. Increased resting heart rate, however, did not explain the increased risk of cardiovascular mortality associated with depressive symptoms observed in this study.

Strengths of this study are its prospective design with a long follow-up period, in a study sample of elderly men free of CVD and diabetes at baseline. This made it possible to examine the causal direction between depressive symptoms, autonomic dysfunction and cardiovascular mortality. Second, the mortality follow-up was virtually complete, and the findings will thus not be influenced by selective loss to follow-up. Third, we were able to adjust for a large number of potential confounding factors.

Some methodological limitations of this study also need to be considered. First, selective participation of healthier respondents [34] may have diluted the associations. Moreover, this study population consisted of older men and the results may not be generalizable to younger men and females. Second, although we adjusted for a range of known classical cardiovascular risk factors, the possibility of residual confounding cannot be excluded. Third, HRV was based on one short-term ECG recording during daytime. It is known that HRV changes during the day and the reliability of short-term measurements seems to be lower in sick people [35]. Short-term HRV measure-

ments during daytime, however, are correlated with 24-h HRV measures and [9] for this study population, we excluded men with CVD or atrial fibrillation to lower the risk of measurement errors. If misclassification might have occurred, however, it was likely to be random, which may have diluted the observed associations. Fourth, unfortunately, we did not have information on depression treatment. It should be noted though that the average SDS score was below the clinical cutpoint for mild depression (more than 50). Therefore, we expect that the majority of the men were not treated for depression.

Our finding of an increased resting heart rate with increase in depressive symptoms is concordant with several other studies, although not all, showing an association between depression and several indicators of autonomic dysfunction in patients with myocardial infarction [5,14,18,36–40]. In patients without myocardial infarction, associations between depression and indicators of autonomic dysfunction have also been observed [15–17]. We did not find a significant association of low HRV and QTc-prolongation with depressive symptoms. The mean depression score in this study population was low compared with the clinical cut-off values of depression; this may have decreased the power to detect an association. It is notable therefore that these mild depressive symptoms were associated with resting heart rate and cardiovascular mortality. Autonomic dysfunction was associated with cardiovascular mortality, which is in concordance with results from the literature [6,8–10,41–43].

The exact mechanisms how depression may affect the autonomic nervous system are not well understood, but are thought to involve deactivation of the right hemisphere, promoting predominance of the left hemisphere associated with cardiac arrhythmia [44]. Alternatively, autonomic dysfunction may also predispose to depression, because recent studies indicated that vagal nerve stimulation in patients with major depression might improve remission [45].

To our knowledge, this is the first study that investigated whether indicators of autonomic dysfunction could explain the increased risk of depressive symptoms for cardiovascular mortality in patients without CVD. One previous study showed that decreased HRV partly explained the relationship between depression and mortality in patients after acute myocardial infarction [19]. In our study, autonomic dysfunction could not explain the increased risk between depression and cardiovascular mortality. An explanation for these seemingly discordant findings may be that autonomic dysfunction is stronger associated with mortality in patients after acute myocardial infarction [19], than in patients without CVD. A recent study in a small sample of patients with acute myocardial infarction, however, also showed that autonomic dysfunction could not explain the association between depression and mortality, supporting our findings [46].

If autonomic dysfunction cannot explain the increased risk of depression on cardiovascular mortality in older men without prevalent CVD, what other mechanism may explain this relationship? Alternative hypotheses may include, dysregulation of the HPA axis, with its elevated cortisol levels and often present in depression, promotes atherosclerosis through injury of vascular cells, hypertension, hypercholesterolemia and inflammation [3]. Second, inflammation and platelet reactivity may explain the relationship between depression and CVD [3] and genetic vulnerability may play a role in these mechanisms [47]. In addition, in the elderly atherosclerosis and cerebral white-matter lesions may increase the risk of depression and cerebrovascular disease [48].

In conclusion, this population-based study in older men shows that mild depressive symptoms are associated with a higher resting heart rate. This indicator of autonomic dysfunction did not, however, explain the increased risk of 10-year cardiovascular mortality associated with depressive symptoms that we observed in our study. Further studies are needed to examine what other mechanisms may explain the frequently observed relation between depression and cardiovascular disease.

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Conflict of interest – none declared.

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