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Research Paper

Depressive symptoms and dispositional optimism in relation to mortality in older post-myocardial infarction patients

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ABSTRACT

Background: Mental well-being, characterized by low depressive symptoms and high dispositional optimism, is a protective factor against (cardiovascular) mortality in the general population. We aimed to assess whether such a relationship is also present in patients who have a history of MI, and whether it is independent of classic CVD risk factors.

Methods: A secondary analysis of the Alpha Omega Trial cohort study was carried out, including 3566 patients with MI in their medical history and a mean follow-up period of 9.0 (SD 2.6) years. The 4Q and GDS were analysed in relation to (cause-specific) mortality using Cox proportionalhazards models adjusted for demographic and classic CVD risk factors.

Results: Patients were on average 71.2 years old (SD 5.4), and 20.5% were women. During the follow-up period, there were 1,219 deaths of which 448 (46.7%) as a result of CVD. For the allcause and CVD mortality, the multivariate-adjusted HR for depressive symptoms was 1.85 and 1.90 for the upper tertile versus the lower tertile (95% CI: 1.47–2.33; P for trend <0.001; and 95%CI: 1.31–2.76; P for trend <0.001). For non-cardiovascular/non-cancer mortality the relationship was even stronger (HR 2.16; 95% CI: 1.51–3.09; P for trend <0.001). Although similar protective trend relationships were observed for dispositional optimism, these were not independent of depressive symptoms.

Conclusions: Depressive symptoms, rather than dispositional optimism, were independently predictive of all-cause, cardiovascular, and non-cardiovascular/non-cancer mortality in older post-MI patients.

1. Background

Cardiovascular disease (CVD) and depression are both highly prevalent disorders. CVD is the leading global cause of death, with increasing numbers from around 3.9 million deaths in Europe to 17.8 million deaths globally in 2017. In Europe CVD accounts for 45% of all deaths, being coronary heart disease (CHD) the leading cause of CVD deaths (2019; Benjamin et al., 2019; European Heart Network, 2017; Feng et al., 2019; McAloon et al., 2016). Depression is also a highly prevalent disorder with an estimated 4.4% of the global population suffering of depression, which accounts for 322 million people (World Health Organization, 2017). The bidirectional relationship between CVD and depression has been supported by numerous studies (Dong et al., 2012; Feng et al., 2019; Mitchell et al., 2017). The meta-analysis of Wei et al. (2019) with 198,589 elderly reported that depression increased the risk of all-cause and CVD mortality with about 30%, but with large heterogeneity across studies (Wei et al., 2019). Another systematic review on depression in patients with myocardial infarction (MI) found conflicting results, with 15 studies showing a positive association between depression and mortality, but 14 studies showing no significant associations. Pooling of effect sizes was not possible due to study heterogeneity and low overall methodological quality (Sorensenf et al., 2005).

Another construct that has been related to CVD morbidity and mortality is dispositional optimism. Dispositional optimism is a cognitive construct referring to the relatively stable, generalized expectation that positive outcomes will occur across important life domains in the future

Abbreviations: MI, myocardial infarction; CVD, cardiovascular disease; SD, standard deviation; HR, hazard ratio; CI, confidence interval.

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(Carver and Scheier, 2014; Scheier and Carver, 2018). Independent protective relationships have been found between dispositional optimism and subsequent CVD morbidity and mortality in several prospective cohort studies, both in women (Kim et al., 2017; Tindle et al., 2009), men (Giltay et al., 2006; Kubzansky et al., 2001), and mixed cohorts (Anthony et al., 2016; Giltay et al., 2004). In a meta-analysis (2019) of 15 studies comprising 229,391 patients, high dispositional optimism was associated with a 35% lower risk of cardiovascular events, but again with large heterogeneity across studies (Rozanski et al., 2019). As previous studies excluded patients with prevalent CVD (Giltay et al., 2006; Kim et al., 2017, 2011, 2014; Pankalainen et al., 2016; Tindle et al., 2009), or adjusted for it at baseline CVD (Anthony et al., 2016; Giltay et al., 2004), the effects of dispositional optimism in a cohort of patients with prevalent CVD is largely unknown.

Although there is robust evidence for an adverse association between depression and CVD mortality as well as a beneficial association between dispositional optimism and CVD mortality in the general population, it is still unclear whether these associations hold in samples of older patients with prevalent CVD. Few studies comprised CVD patients, ranging from hypertension (Axon et al., 2010; Chowdhury et al., 2019; Hamer et al., 2010) to post coronary artery bypass graft surgery (Tindle et al., 2012). These studies differed greatly regarding the study population ranging from 430 to 31 495 patients, with a mean age from 53 to 72 years and a follow-up of 8 months to 11 years. These studies did not take both depressive symptoms and dispositional optimism into account in their statistical models (Axon et al., 2010; Chowdhury et al., 2019; Hamer et al., 2010). Therefore, we aimed to assess whether both mental well-being scales independently predicted for CVD, cancer, non-cardiovascular/non-cancer and all-cause mortality in older post-MI patients.

2. Methods

2.1. Study design and patients

This is a secondary analysis carried out using the data of the AOT cohort (ClinicalTrials.gov number, NCT00127452). The design of this study has been described in detail elsewhere (Kromhout et al., 2010). In brief, the AOT was a multicentre randomised double-blind, placebo-controlled study designed to investigate the effect of the n-3 polyunsaturated fatty acids α-linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on cardiovascular events in Dutch patients between 60 and 80 years of age with a clinically diagnosed MI up to 10 years before randomization. The end The endpoints were all-cause mortality and specific causes of death. Between 2002 and 2006, 5665 post-MI patients were recruited by cardiologists from 32 hospitals, of whom 4837 were included. All patients provided a written informed consent. After 41 months of follow-up, the endpoint assessment took place in 4116 (85.1%) patients. This assessment included questionnaires about depressive symptoms and optimism, and therefore was considered the baseline of the present study (Supplementary figure 1). Person-years were calculated from study enrolment to date of death or end of the follow-up (i.e.. 31 December 2018), which came first. One patient was lost to follow-up and censored after 2.9 years (Supplement 1).

2.2. Assessment

2.2.1. Mental well-being

Depressive symptoms were measured with the 15-item Geriatric Depression Scale (GDS-15) containing yes/no questions. De scores range from 0 to 15 points, being a higher score indicative for depressive symptoms in the preceding week. The GDS-15 has a 0.76 specificity and 0.88 sensitivity for depressive symptoms in older patients, and a Cronbach's alpha of 0.76 in our sample. A cut-off score of ≥ 4 indicates mild to severe depressive symptoms (de Craen et al., 2003). A maximum of 2 missing items was allowed and were subsequently imputed with the mean of the remaining GDS-items. In addition, previous treatment for depression or depressive symptoms and a history of depression in any first-degree biological relative was asked.

Dispositional optimism was measured with the 4Q, a four-item questionnaire with a 0–2 Likert scale. Patients were asked in which extent they agreed with the following four statements; 'I still expect much from life', 'I do not look forward to what lies ahead for me in the years to come', 'My days seem to be passing by slowly', and 'I am still full of plans'. The answer 'I don't know' was coded as 1, a midpoint. The two negatively formulated sentences were reversed coded. The scores range from 0 to 8 points, with higher scores being indicative of higher optimism levels. A cut-off score <6 was used to indicate low dispositional optimism (Giltay et al., 2008). The Cronbach's alpha was 0.61 in our sample.

2.2.2. Mortality

In 2006–2009 the GDS and 4Q were introduced, that were completed by 3566 patients. The cause-specific mortality was obtained from the national mortality registry (Statistics Netherlands, [CBS]), treating physicians and family members. We collected mortality data only from Statistics Netherlands in 668 (54.8%) cases and both from Statistics Netherlands and physician in 551 (45.2%) of the total of 1219 cases. The causes of death were coded according to the International Classification of Diseases, tenth revision (ICD-10) and were divided in the categories CVD, cancer related, non-cardiovascular/non-cancer and all-cause mortality (World Health Organization, 1992). CVD mortality comprised I20-I25, I46, R96, I50 (heart failure) and I60-I69 (stroke). Cancer related mortality comprised C00-C97 (malignant neoplasm) and D00-D48 (neoplasm of uncertain or unknown behaviour). Non-cardiovascular/non-cancer mortality comprised the other ICD-codes (e.g., respiratory diseases, pneumonia, influenza, kidney diseases). Coding was executed by a physician (RB). In doubt, the case was presented to an independent physician (NR) (n = 12). When the two outcomes were contradictory, a third physician was asked for a decisive answer (n = 0). There were no indeterminate cases. Statistics Netherlands and the general practitioner reported contradicting in 45 cases, consisting of CVD and cancer as causes of death. These causes of death were coded as CVD. CVD as a cause of death was more often reported by GPs than by Statistics Netherlands.

2.2.3. Covariates

As blood sampling and physical examination were no longer performed after 1 January 2009 due to budgetary constraints, these data were available for 2196 patients (61.6%). If data on body mass index (BMI), systolic blood pressure (SBP), low density lipoprotein (LDL) cholesterol or alcohol use were missing, data from the earlier baseline assessments were imputed (BMI $n = 1408$; 39.5%, SPB $n = 1405$; 39.4%, LDL $n = 1412$; 39.6%, alcohol use $n = 16$; 0.4%)(Geleijnse et al., 2010). Questionnaires on demographic factors, lifestyle, medical history, mental wellbeing and antidepressants were completed by trained research nurses or self-completed by the patients at their homes. The highest attained level of education was dichotomized into low and higher education, with higher education defined as having completed at least secondary education. Marital status was dichotomized into the categories being married (or cohabiting) or not (e.g., widowed). The covariates smoking was dichotomized into current use or not. Alcohol use was dichotomized into current use or not for the baseline characteristics, but was for further statistics divided in tertiles (i.e., no current use, less than 10 g per day, and more than 10 g per day). Physical activity was assessed by the self-report questionnaire Physical Activity Scale for the Elderly (PASE), in which occupational, household and leisure activities items over one week period were included (Schuit et al., 1997). The covariate was dichotomized into at least 5 days per week physical active or less which varied from no activity, light activity (<3 metabolic equivalents of task (MET)) to 0–4 days per week physical activity (>3

MET). Self-reported medication of the patients was coded according to the Anatomical Therapeutic Chemical Classification System (ATC).

2.3. Statistical analysis

For baseline characteristics, patients were classified according to the cut-off scores of the GDS (≥ 4) or 4Q (<6). Because causal inference is limited by potential reverse causation, we excluded the first 2 years of observation of deaths from all survival analyses (i.e., lag-time analyses). The Kaplan-Meier (KM) method was used to present crude mortality rates. Cox proportional hazards models were used to estimate HRs with 95% confidence intervals (CI) for which the patients were classified in tertiles both for GDS and for the 4Q. The GDS categories ranged from low (0–3), middle (4–6), to high (7–15), and the 4Q categories ranged from low (0–5), middle (6–7), to high (8). The proportional hazard assumption was tested using the log-minus-log graphical method.

Three Cox regression models were tested for each of the two predictor variables and four mortality outcomes (i.e., all-cause, CVD, cancer-related and non-cardiovascular/non-cancer mortality). Model 1 was a crude unadjusted model; model 2 adjusted for classical CVD factors: sex, age, smoking, physical activity, LDL cholesterol levels, SBP, diabetes mellitus, and use of antihypertensive drugs; and model 3 additionally adjusted for socioeconomic and health risk factors: education, marriage or cohabiting, alcohol use, treatment for depression, a positive family history for depression, use of antidiabetics, use of lipid-lowering medication, and use of antidepressants. We tested for linear trends across the tertiles of the 4Q and GDS scores.

Next, to assess whether either depressive symptoms or dispositional optimism drove the relationships with mortality, Cox regression analyses were repeated with standardized scores of the $\log_e$-transformed GDS and 4Q scores. The survival analyses were adjusted for all covariates mentioned above. Finally, we tested which of the standardized individual item scores of the GDS and 4Q scales showed the strongest predictive value in Cox regression models, again adjusted for all covariates mentioned above. These HRs (with 95% CI) are shown in forest plots.

A two tailed $p<0.05$ was considered statistically significant. For the analysis, we used IBM SPSS Statistics for Windows version 24 (IBM Corp. Armonk, N.Y., USA) and RStudio (R version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: https://www.R-project.org/), with main packages 'survival' (version 2.44), 'survminer' (version 0.4.4), and 'forestplot' (version 1.9).

3. Results

3.1. Baseline characteristics

The 3566 patients were on average 71.2 years old (SD 5.4), and 20.5% were female. Compared to the group with a lower GDS score, the patients with a higher score were more likely to be man, older, unmarried (or not cohabiting), less educated, and being and feeling more unhealthy (i.e., less daily physical activity, more smoking, and had more frequently a history of depression) (Table 1). Similar differences were observed when the patients were classified based on the dispositional optimism score.

3.2. Outcomes

3.2.1. Depressive symptoms

During the follow-up period of mean 9.0 years and median 9.5 years, 1219 (34.2%) of 3566 MI-patients died, of whom 531 (43.6%) of CVD causes, 326 (26.7%) from cancer, and 362 (29.7%) from non-cardiovascular/non-cancer causes. There were 45 patients with a combined CVD and cancer-related cause of death, in which CVD was preferred. KM analysis of survival according to the categories of GDS scores showed that those with higher levels of depressive symptoms had higher rates of CVD, non-cardiovascular/non-cancer and all-cause mortality (Fig. 1, Table 2).

Compared with the lowest category of GDS, those in the top category had an 86% higher multivariate-adjusted HR of all-cause mortality (Table 2). Comparing the lowest with the top category of GDS resulted in a 66% higher risk of CVD mortality, a 52% higher risk of cancer-related mortality, and a 137% higher risk of non-cardiovascular/non-cancer mortality. These relationships were statistically significant after adjustment for socioeconomic and classic CVD risk factors. Similar results were found when using standardized GDS-scores as predictor of mortality, except for the relationship with cancer related mortality that did not reach statistical significance after full adjustment (Table 4). The forest plots show the fully adjusted HRs for the different outcomes according to each of the items and sum scores for depressive symptoms and dispositional optimism. The items 'dropped activities and interests', 'feel helpless' and 'feel hopeless' showed the strongest association with the four fatalities (Fig. 2 and Supplementary figures 2–4).

3.2.2. Dispositional optimism

Table 3 shows the results of the analyses between dispositional optimism and mortality, with higher levels of dispositional optimism being associated with lower all-cause, CVD and non-cardiovascular/non-cancer mortality. The significant associations persisted after adjustment for classic CVD and socioeconomic risk factors (Table 3), except for CVD mortality. The adjusted HRs of the 4Q items in the forest plot for all-cause mortality were relatively small but were all statistically significant (Fig. 2). The forest plot of non-cardiovascular/non-cancer mortality showed the strongest associations with dispositional optimism items except for the GDS items 'full of energy' and 'dropped activities and interests' (Supplementary figure 3). For cancer-related mortality, only the GDS items 'full of energy' and 'feel helpless' showed a significant association (Supplementary figure 4).

Full-adjusted models tested whether the risk of mortality was statistically driven by depressive symptoms, dispositional optimism, or both. The CVD, non-cardiovascular/non-cancer and all-cause mortality were significantly associated with depressive symptoms, but no longer with dispositional optimism (Table 4).

4. Discussion

We found that depressive symptoms were independently predictive of a higher all-cause, cardiovascular, cancer related and non-cardiovascular/non-cancer related mortality in older persons with a medical history of MI, even when adjusting for classic CVD and socioeconomic risk factors. Although similar results were found for low dispositional optimism, these did not persist after adjustment for depressive symptoms, suggesting that the relationship with depressive symptoms drove the associations. Remarkable were the strong associations with non-cardiovascular/non-cancer mortality in all analyses. Furthermore, our item-level analyses showed that the apathy and vitality items of the GDS and 4Q were most influential in relation to outcome variables.

Our findings of an association between depressive symptoms linked to higher mortality are consistent with those from earlier cohort studies. We confirmed this relationship in a cohort of older patients with prevalent CVD, whereas most previous studies did not include (solely) this group of patients (Abas et al., 2002; Carney et al., 2008; Gump et al., 2005; Kozela et al., 2016; Penninx et al., 1999; Schulz et al., 2000; Zheng et al., 1997). The few cohort studies with patients with CVD included somewhat younger patients (< 65 year), and used different assessment tools for depressive symptom severity (e.g., General Health Questionnaire-12). Only some of the previous studies adjusted for antidepressants use and a history of depression, and dispositional optimism was often not included in their statistical models (Axon et al., 2010; Barefoot et al., 1996; Chowdhury et al., 2019; Connerney et al., 2010; de Mello et al., 2016; Hamer et al., 2010; Naess et al., 2010).

Table 1
Baseline characteristics of 3566 post-myocardial infarction patients according to the mental well-being.

	Dispositional Optimism (4Q)		Geriatric depression scale (GDS)	
	Middle to high (n = 2739)	Low (n = 827)	Low (n = 2967)	High (n = 599)
Age, mean in years (SD)	70.6 (5.2)	73.2 (5.6)	71.0 (5.4)	72.3 (5.6)
Male sex (%)	2243 (81.9)	603 (72.9)	2424 (81.7)	422 (70.5)
Higher education (%) no./ total no. (%)	1308 (48.1)	307 (37.3)	1389 (47.1)	226 (38.1)
Married of cohabiting (%)	2312 (84.4)	599 (72.4)	2464 (83.0)	447 (74.6)
Body mass index, mean (SD)	27.8 (3.6)	27.6 (4.0)	27.7 (3.6)	27.8 (4.2)
Physically active (%)	658 (24.0)	122 (14.8)	708 (23.9)	72 (12.0)
Alcohol ≥ 10 g/w (%)	2244 (81.9)	603 (72.9)	2439 (82.2)	408 (68.1)
Current smoker (%)	364 (13.3)	142 (17.2)	400 (13.5)	106 (17.7)
Serum LDL in mmol/l (SD)	2.33 (0.71)	2.38 (0.76)	2.33 (0.71)	2.40 (0.77)
Systolic blood pressure in mmHg (SD)	143.5 (20.9)	141.1 (21.8)	143.7 (20.9)	138.9 (21.9)
History of depression (%)	307 (11.2)	153 (18.8)	309 (10.5)	151 (25.5)
Family history of depression (%)	519 (19.0)	164 (19.9)	563 (19.0)	120 (20.1)
Medication use:				
- anti-hypertension drugs (%)	2472 (90.3%)	756 (91.4%)	2671 (90.0%)	557 (93.0%)
- anti-diabetes drugs (%)	459 (16.8%)	176 (21.3%)	499 (16.8%)	136 (22.7%)
- lipid-lowering drugs (%)	2483 (90.7%)	712 (86.1%)	2681 (90.4%)	514 (85.8%)
- antidepressants (%)	99 (3.6%)	52 (6.3%)	90 (3.0%)	61 (10.2%)

Higher education was defined as having at least completed secondary education and was available for 3544 of 3566 patients.
Body mass index was calculated as weight in kilograms divided by height in meters squared and was available for 3563 patients; LDL cholesterol was available for 3449 patients, systolic blood pressure was available for 3565 patients, history of depression for which treatment was available for 3546 patients, and family history of depression was available for 3557 patients. Physically active was defined as ≥5 days/week of moderate or vigorous activity (>METs).

Table 2
Mortality according to depressive symptoms in 3566 post myocardial infarction patients during up to 13 years of follow-up*.

	Categories of Geriatric Depression Scale (GDS) score			
Variable	Low (score 0–3)	Middle(score 4–6)	High (score 7–15)	*P*-value for trend
Patients, No.	2939	453	174	NA
Cardiovascular mortality†				
Casus, No. (%)	328 (11.2%)	76 (16.8%)	44 (25.3%)	< 0.001
Crude	1.0 (ref.)	1.70 (1.33–2.19)	3.21 (2.34–4.39)	< 0.001
Adjusted‡	1.0 (ref.)	1.46 (1.13–1.89)	2.08 (1.47–2.94)	< 0.001
Fully adjusted§	1.0 (ref.)	1.36 (1.03–1.78)	1.90 (1.31–2.76)	< 0.001
Cancer related mortality†				
Casus, No. (%)	265 (9.0%)	52 (11.5%)	17 (9.8%)	0.242
Crude	1.0 (ref.)	1.42 (1.05–1.91)	1.46 (0.89–2.39)	0.012
Adjusted‡	1.0 (ref.)	1.37 (1.01–1.85)	1.37 (0.83–2.25)	0.036
Fully adjusted§	1.0 (ref.)	1.38 (1.01–1.89)	1.29 (0.76–2.18)	0.064
Non-cardiovascular/ non-cancer mortality†				
Casus, No. (%)	314 (10.7%)	76 (16.8%)	47 (27.0%)	< 0.001
Crude	1.0 (ref.)	1.79 (1.39–2.30)	3.62 (2.67–4.93)	< 0.001
Adjusted‡	1.0 (ref.)	1.49 (1.15–1.94)	2.55 (1.83–3.54)	< 0.001
Fully adjusted§	1.0 (ref.)	1.34 (1.02–1.77)	2.16 (1.51–3.09)	< 0.001
All-cause mortality†				
Casus, No. (%)	907 (30.9%)	204 (45.0%)	108 (62.1%)	< 0.001
Crude	1.0 (ref.)	1.65 (1.42–1.92)	2.82 (2.31–3.45)	< 0.001
Adjusted‡	1.0 (ref.)	1.45 (1.24–1.69)	2.06 (1.66–2.55)	< 0.001
Fully adjusted§	1.0 (ref.)	1.36 (1.15–1.60)	1.85 (1.47–2.33)	< 0.001

Abbreviation: NA, data not applicable.
* Data are presented as hazard ratio (with 95% confidence interval) unless otherwise indicated. P values were determined by Cox proportional hazards analysis.
† Mortality data were analysed with a lag of the first 2 years of follow-up.
‡ Adjusted for sex, age, body mass index, smoking status, physical activity, low-density lipoprotein cholesterol levels, mean arterial pressure, diabetes mellitus, and use of anti-hypertension drugs.
§ Adjusted for all the variables mentioned previously, as well as education, marital status, alcohol use, history of depression, family history of depression, use of anti-diabetes drugs, use of lipid-lowering drugs, and use of antidepressants.

The model may have been overadjusted by correcting for antidepressant use, but antidepressants are prescribed for indications other than depression, among which anxiety disorders or obsessive-compulsive disorder. As a history of depression, antidepressants and/or psychotherapy could present a subgroup of patients with complex psychiatric problems and therefore higher GDS-scores in general, adjustment provides the opportunity to look solely at the association of the GDS score with mortality. Moreover, when we removed antidepressant use as a confounder from the multivariate model, the risk estimate did not change. Our findings of an association of apathy and vitality items of the GDS with all-cause, cardiovascular and non-cardiovascular/non-cancer mortality corresponds with earlier findings, which might be explained by patients who may tend be more disinclined to engage actively in physical activity and other health-promoting behaviours, resulting in diminish activities, poor medication adherence, and withdrawal from medical care (Eurelings et al., 2014, 2018). Apathy and vitality could also be a prodrome of vascular dementia, which is associated with a higher mortality (Knopman et al., 2003).

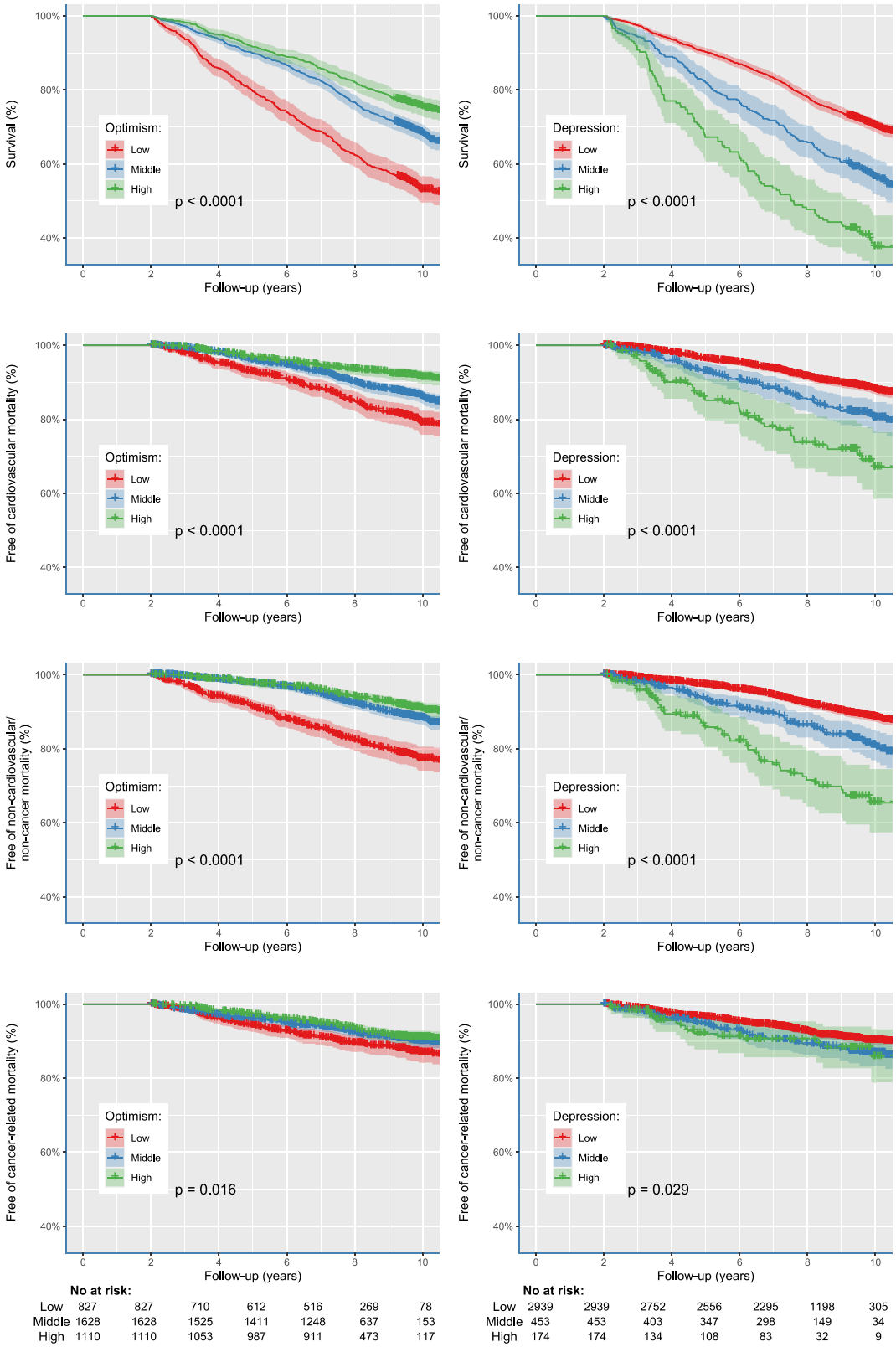

Fig. 1. Kaplan-Meier curves of all-cause, cardiovascular mortality, cancer related mortality and non-cardiovascular/non-cancer mortality, according to categories of optimism and depression. *P* value by log-rank (Mantel-Cox) test. Low optimism (4Q score 0-5), middle optimism (4Q score 5-6), High optimism (4Q score 8), Low depressive symptoms (GDS score 0-3), Middle depressive symptoms (GDS score 4-6), High depressive symptoms (GDS score 7-15).

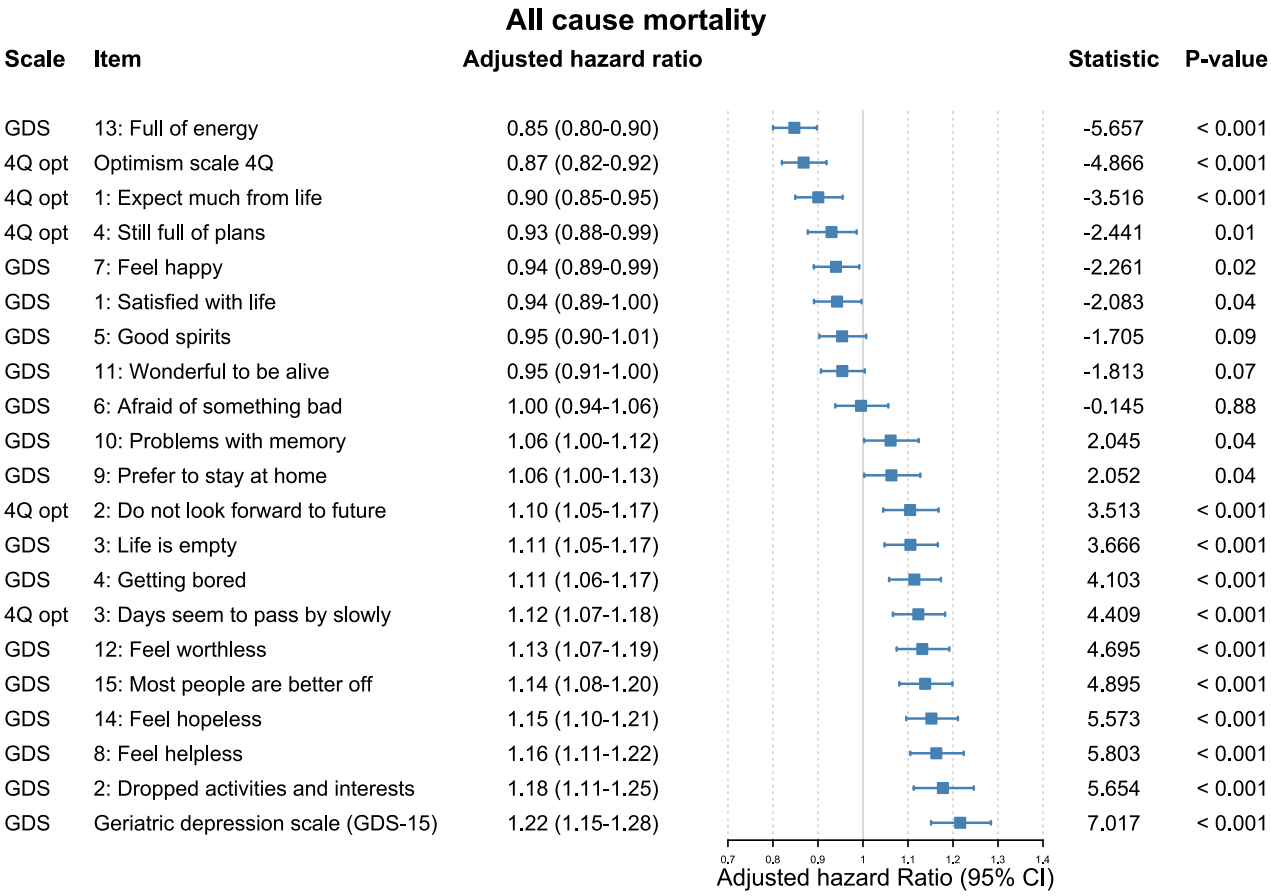

Fig. 2. Forest plot showing the fully adjusted hazard ratios for all-cause mortality according to each of the items and sum scores for dispositional optimism and depression. The item and sum scores were standardized. Square: Adjusted hazard ratio all-cause mortality, —> Higher risk of death, <— Lower risk of death.

Table 3
Mortality according to dispositional optimism in 3566 post myocardial infarction patients during up to 13 Years of Follow-up*.

Variable	Categories of Dispositional Optimism (4Q) score			
	Low (score 0–5)	Middle(score 6–7)	High(score 8)	*P*-value for trend
Participants, No.†	827	1628	1111	NA
Cardiovascular mortality†				
Casus, No. (%)	143 (17.3%)	212 (13.0%)	93 (8.4%)	< 0.001
Crude	1.0 (ref.)	0.66 (0.53–0.81)	0.41 (0.31–0.53)	< 0.001
Adjusted‡	1.0 (ref.)	0.85 (0.68–1.06)	0.67 (0.51–0.88)	0.004
Fully adjusted§	1.0 (ref.)	0.89 (0.71–1.13)	0.73 (0.55–0.97)	0.034
Cancer-related mortality†				
Casus, No. (%)	90 (10.9%)	149 (9.2%)	95 (8.6%)	0.204
Crude	1.0 (ref.)	0.74 (0.57–0.96)	0.67 (0.50–0.89)	0.008
Adjusted‡	1.0 (ref.)	0.83 (0.63–1.08)	0.85 (0.63–1.16)	0.331
Fully adjusted§	1.0 (ref.)	0.86 (0.65–1.14)	0.91 (0.67–1.25)	0.597
Non-cardiovascular / non-cancer mortality†				
Casus, No. (%)	164 (19.8%)	179 (11.0%)	94 (8.5%)	< 0.001
Crude	1.0 (ref.)	0.48 (0.39–0.60)	0.35 (0.28–0.46)	< 0.001
Adjusted‡	1.0 (ref.)	0.62 (0.49–0.77)	0.58 (0.44–0.75)	< 0.001
Fully adjusted§	1.0 (ref.)	0.68 (0.54–0.85)	0.62 (0.47–0.83)	< 0.001
All-cause mortality†				
Casus, No. (%)	397 (48.0%)	540 (33.2%)	282 (25.4%)	< 0.001
Crude	1.0 (ref.)	0.60 (0.53–0.69)	0.44 (0.38–0.52)	< 0.001
Adjusted‡	1.0 (ref.)	0.75 (0.65–0.85)	0.68 (0.58–0.80)	< 0.001
Fully adjusted§	1.0 (ref.)	0.80 (0.69–0.92)	0.74 (0.62–0.87)	< 0.001

Abbreviation: NA, data not applicable.

* Data are presented as hazard ratio (with 95% confidence interval) unless otherwise indicated. P values were determined by Cox proportional hazards analysis.

† Mortality data were analysed with a lag of the first 2 years of follow-up.

‡ Adjusted for sex, age, body mass index, smoking status, physical activity, low-density lipoprotein cholesterol levels, mean arterial pressure, diabetes mellitus, and use of anti-hypertension drugs.

§ Adjusted for all the variables mentioned previously, as well as education, marital status, alcohol use, history of depression, family history of depression, use of anti-diabetes drugs, use of lipid-lowering drugs, and use of antidepressants.

Table 4
Mortality according to standardized scores of depressive symptoms and dispositional optimism.

Variable	Geriatric Depression Scale (GDS)	*P*-value	Dispositional Optimism (4Q)	*P*-value
Cardiovascular mortality[†]				
Crude	1.27 (1.13–1.42)	< 0.001	0.79 (0.71–0.89)	< 0.001
Fully adjusted[§]	1.16 (1.03–1.32)	0.016	0.94 (0.83–1.06)	0.298
Cancer related mortality[†]				
Crude	1.10 (0.97–1.25)	0.152	0.91 (0.80–1.03)	0.146
Fully adjusted[§]	1.08 (0.93–1.24)	0.314	1.01 (0.88–1.16)	0.892
Non-cardiovascular/ non-cancer mortality[†]				
Crude	1.47 (1.31–1.65)	< 0.001	0.83 (0.74–0.93)	0.002
Fully adjusted[§]	1.33 (1.17–1.52)	< 0.001	0.95 (0.84–1.07)	0.387
All-cause mortality[†]				
Crude	1.29 (1.20–1.38)	< 0.001	0.83 (0.78–0.89)	< 0.001
Fully adjusted[§]	1.20 (1.11–1.29)	< 0.001	0.96 (0.89–1.03)	0.288

*Data are presented as hazard ratio (95% confidence interval) and P-values for the linear trend over the tertiles by Cox proportional hazards analysis.

† Mortality data were analysed with a lag of the first 2 years of follow-up.

§ Adjusted for all the variables mentioned previously, as well as education, marital status, alcohol use, history of depression, family history of depression, use of anti-diabetes drugs, use of lipid-lowering drugs, and use of antidepressants.

Our finding of an association that approached significance ($p = 0.07$) between low dispositional optimism linked to higher cardiovascular (Giltay et al., 2004, 2006; Kim et al., 2017, 2011, 2014; Tindle et al., 2009) and an association with all-cause mortality are in line with the results from previous studies (Anthony et al., 2016; Kim et al., 2017, 2014; Tindle et al., 2009). The few cohort studies which included patients with a history of CVD, showed similar results (Anthony et al., 2016; Giltay et al., 2004; Kim et al., 2011; Pankalainen et al., 2016; Weiss-Faratci et al., 2017). Almost all studies included older patients, adjusted for biological and psychosocial factors. Their follow-up periods varied strongly, with just one study having a very long follow-up period (Weiss-Faratci et al., 2017), and only three studies adjusted for a current depressive episode, but did not account for a history of depression or the current use of antidepressants (Giltay et al., 2006; Kim et al., 2017; Tindle et al., 2009). Therefore, our findings on dispositional optimism strengthen and extend these findings.

A remarkable finding was the association with non-cardiovascular/non-cancer mortality, which was stronger than with other causes of death and included causes of death such as respiratory disease, infections, renal disease, and gastrointestinal disease. Only few studies on this topic have reporting on non-cardiovascular/non-cancer mortality. This study showed that high dispositional optimism was associated with a 37% and 52% lower risk for respiratory (HR 0.63, 95% CI: 0.48–0.82) and infection-related mortality (HR 0.48, 95% CI: 0.29–0.80) (Kim et al., 2017). Large cohort studies are needed to research these relationships further.

We found a relationship with depressive symptoms and cancer mortality, which was based on a small number of cases (middle GDS $n = 50$; high GDS $n = 19$) and just partly supported by the figures (Fig. 1 and Supplementary figure 4). This corresponds with previous studies which reported inconsistent results. In an earlier mentioned large-scale American study of 97,253 women, dispositional optimism predicted for cancer mortality only in black women, but not in the much larger group white women (Tindle et al., 2009). Another study found a significant association between dispositional optimism and cancer mortality in 70,021 women. However, the effect size was much smaller than the associations with other causes of death (Kim et al., 2017). When they focused on specific types of cancer (i.e. lung, breast, colorectal or ovarian cancer), the associations did no longer reach statistical significance, probably due to the smaller number of fatalities. Although other studies found that depression was associated with cancer-related mortality (Penninx et al., 1999; Pinquart and Duberstein, 2010), the associations were generally rather weak and inconsistent (Penninx et al., 1999). In a meta-analysis, many of the studies assessed depressive symptoms after a cancer diagnosis had been made (Pinquart and Duberstein, 2010). In summary, previous and our results with cancer mortality seem to support the idea that potential relationships with either depressive symptoms and dispositional optimism are absent or small and of marginal clinical significance.

Our results are of clinical relevance in the management of older persons with CVD, as clinical awareness of depression and depressive symptoms signals an increased mortality risk. Future research will need to elucidate whether depression treatment may lower mortality, while it is likely to improve mental wellbeing and quality of life, extending quality-adjusted life-years. Sertraline or escitalopram did not show efficacy for depression or cardiovascular status in patients with heart failure (Diez-Quevedo et al., 2013). In small studies, however, gratitude journaling (Redwine et al., 2016), optimism promoting interventions (Mohammadi et al., 2020) and, positive psychology interventions (Nikrahan et al., 2016) revealed significant changes in biomarkers related to cardiac health. This supports the idea of targeted psychotherapy in CVD patients with low optimism and depressive symptoms to increase quality-adjusted life-years, targeting specific symptoms that showed the strongest independent relationships with mortality, such as apathy, feelings of helplessness, or worthlessness.

Major strengths of this study were the inclusion of a well-defined and large cohort of older patients with MI, assessment of all relevant risk factors and a long follow-up. The GDS-15 assesses subjective depressive symptoms, rather than somatic symptoms of depression, which could be attributed to the medical illness of MI. However, by omitting these symptoms, some of the somatic symptoms of depression have not been taken into account, which may have led to an underestimation of the strength of the effect of depressive symptoms on mortality. Furthermore, by also measuring dispositional optimism we could study the independent strengths of negative and positive affective states.

Some limitations of the present study also need to be addressed. First, the number of patients with a high sum score of depressive symptoms (i.e., GDS score of 7–15) was small. Second, the GDS assesses the presence of depressive symptoms during the preceding week and was only administered once, followed by a mean follow-up of 9.0 years. As previous or subsequent depressive symptoms are not measured by the GDS, this could lead to an underestimation of the predictive value in relation to mortality. Third, mental well-being was only introduced later on in the trial, and therefore not assessed at baseline during randomisation. Hence, the predictive value of changes in mental well-being could not be analysed. Fourth, besides death certificates, the GP reported the cause of death back in only 62% of cases. Fifth, multiple variables were categorized, which may have led to some loss of power and residual confounding. Sixth, reverse causation cannot be excluded as optimism is associated with better health in general, but this risk of bias was low-

ered by lag-time analyses (Giltay et al., 2004). The lag-time of two years was relatively long. We aimed to reduce the potential effects of reverse causation as depressive symptoms often have an episodic nature. Of the 216 deaths within the first 2 years of follow-up, there was an significant association with the 3 categories of GDS score, similar to the associations after a lag of 2 years (i.e., HR for the middle group = 2.07; 95%CI: 1.48- 2.89; HR for high group = 2.33; 95%CI: 1.50-3.64; P for trend <0.001). Finally, there is the possibility of residual confounding, even though we adjusted for many socioeconomic and classic CVD risk factors.

In conclusion, this study showed that depressive symptoms, rather than dispositional optimism, predicts CVD, non-cardiovascular/non-cancer, and all-cause mortality in post-MI older persons. These relationships were independent from classic CVD risk factors. Further research is needed to define the pathway of causality and to elucidate whether depression treatment may lower mortality and improve mental wellbeing in old, post-MI patients with depressive symptoms.

Declaration of Competing Interest

All authors declared no conflict of interest.

Contributions

Substantial contributions to conception and design were made by RB, JG, DK, and EG. Acquisition of data was done by RB, JG, NR and EG. Analysis and interpretation of data was performed by RB and EG. Drafting the manuscript or revising it critically for important intellectual content was done by RB, NR and EG. Final approval of the version to be published was given by all the authors. They agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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Availability of data and materials

All data supporting the study is presented in the manuscript or in the supplementary material.

Supplementary materials

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