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Individual depressive symptoms and all-cause mortality in 6673 patients with myocardial infarction: heterogeneity across age and sex subgroups

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Title	Individual Depressive Symptoms and All-Cause Mortality In 6,673 Patients With Myocardial Infarction: Heterogeneity Across Age and Sex Subgroups.
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Abstract

Background: Depression predicts poor prognosis in patients with myocardial infarction (MI). However, individual depressive symptoms may have different prognostic value, and age and sex could be important effect modifiers. This study compared the prognostic value of individual depressive symptoms across age and sex subgroups in post-MI patients. Methods: Individual patient-data were compiled for 6,673 post-MI patients from seven studies. Depressive symptoms were measured with 10 items of the Beck Depression Inventory (BDI10). The endpoint was all-cause mortality (mean=3.8 years). Multilevel multivariable Cox regression analysis was used to estimate the mortality risk across age groups (≤55, 56-69 and ≥70 years) and sex for symptoms that potentially interacted with age and sex. Results: At follow-up, 995 (15%) post-MI patients had died. BDI10 depression scores were associated with an increased mortality risk (HR:1.20;95%CI:1.11-1.28,p<.001). Negative self-image (HR:1.53;1.06-2.21;p=.022) and indecisiveness (HR:1.53;1.15-2.04;p=.003) were associated with increased mortality in men <55. Dissatisfaction was associated with increased mortality in men aged 56-69 (HR:1.35;1.07-1.71;p=. 011), and dissatisfaction (HR:1.34;1.10-1.63;p=.003) and fatigue (HR:1.45;1.20-1.74;p<.001) in men >70. Fatigue was associated with mortality in women aged 56-69 (HR:1.54;1.09-2.15;p=.012), and suicidal ideation in women aged >70 (HR:1.58;1.03-2.43;p=.037). Left-ventricular ejection fraction (LVEF) accounted for much of the associations in men ≤55 years and women ≥70 years. Limitations: Findings are sample-specific and need replication in future research; BDI10 items were derived from the original BDI assessment. Conclusions: There is large heterogeneity in the prognostic value of individual depressive symptoms in post-MI patients across sex and age subgroups. LVEF partially explained the depression-prognosis association in specific subgroups.

Keywords	Myocardial infarction, depression, epidemiology.

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Highlights

- The prognostic value of individual depressive symptoms is heterogeneous
- Negative self-image and indecisiveness predicted mortality in men ≤55 years
- Dissatisfaction and fatigue predicted mortality in men ≥70 years
- None of the symptoms predicted mortality in women ≤55 years

Abstract

Background: Depression predicts poor prognosis in patients with myocardial infarction (MI). However, individual depressive symptoms may have different prognostic value, and age and sex could be important effect modifiers. This study compared the prognostic value of individual depressive symptoms across age and sex subgroups in post-MI patients.

Methods: Individual patient-data were compiled for 6,673 post-MI patients from seven studies. Depressive symptoms were measured with 10 items of the Beck Depression Inventory (BDI10). The endpoint was all-cause mortality (mean=3.8 years). Multilevel multivariable Cox regression analysis was used to estimate the mortality risk across age groups (≤55, 56-69 and ≥70 years) and sex for symptoms that potentially interacted with age and sex.

Results: At follow-up, 995 (15%) post-MI patients had died. BDI10 depression scores were associated with an increased mortality risk (HR:1.20;95%CI:1.11-1.28,p<.001). *Negative self-image* (HR:1.53;1.06-2.21;p=.022) and *indecisiveness* (HR:1.53;1.15-2.04;p=.003) were associated with increased mortality in men ≤55. *Dissatisfaction* was associated with increased mortality in men aged 56-69 (HR:1.35;1.07-1.71;p=. 011), and *dissatisfaction* (HR:1.34;1.10-1.63;p=.003) and *fatigue* (HR:1.45;1.20-1.74;p<.001) in men ≥70. *Fatigue* was associated with mortality in women aged 56-69 (HR:1.54;1.09-2.15;p=.012)**,** and *suicidal ideation* in women aged ≥70 (HR:1.58;1.03-2.43;p=.037). Left-ventricular ejection fraction (LVEF) accounted for much of the associations in men ≤55 years and women ≥70 years.

Limitations:, Findings are sample-specific and need replication in future research; BDI10 items were derived from the original BDI assessment.

Conclusions: There is large heterogeneity in the prognostic value of individual depressive symptoms in post-MI patients across sex and age subgroups. LVEF partially explained the depression-prognosis association in specific subgroups.

Introduction

Depression has been associated with poor prognosis in patients with myocardial infarction (MI) (Meijer et al. 2013). However, depression is a heterogeneous syndrome, and major depressive disorder is a polythetic diagnostic category (Østergaard, Jensen & Bech 2011). An analysis of a sample of patients who met the DSM-V criteria for major depression identified 1030 different symptom profiles (Fried, Nesse 2015).

The analysis of individual depression symptoms may offer a way forward to better understand the complex nature of depression and its consequences (Fried 2017, Fried, Nesse 2015), including the adverse effect of specific depression symptoms on cardiac prognosis. An unresolved issue is the degree to which individual symptoms of depression may be differentially related to cardiovascular disease outcomes. Therefore, a solution authors found for addressing this heterogeneity was to use symptom dimensions such as a cognitive/affective dimension (e.g. guilt, sense of failure, self-punishment) and a somatic/affective dimension (e.g. work difficulties, insomnia, fatigue) to predict cardiovascular outcomes (de Miranda Azevedo et al. 2014). Another, more in-depth, approach to address the heterogeneity of depressive symptoms is individual item-level analysis, in which the prognostic value of each depressive symptom is evaluated (Denollet et al. 2013). Moreover, specific depressive symptoms may refer to distinct phenomena that differ from each other in important dimensions, including biology, risk factors, and impact on impairment and prognosis (Fried, Nesse 2015).

Another unresolved issue is whether age modifies the prognostic value of depressive symptoms in patients with MI(Denollet et al. 2013). Age is an important determinant of medical prognosis in patients with MI(Kral et al. 2011) and therefore statistical adjustment for age is commonly seen in prognostic studies. A previous study suggested that cognitive/affective symptoms are especially deleterious in younger patients with MI(Denollet et al. 2013). However, few of the previous analyses have been stratified by age, leaving no possibility to investigate whether the prognostic effect of depression is age-dependent (Gupta et al. 2014). In terms of clinical profile, older patients are more likely to have greater comorbidity, increased cardiac dysfunction, history of previous MI, left-ventricular ejection fraction (LVEF) ≤ 40%, and Killip class >1 as compared with younger patients(Shih et al. 2010). Regarding lifestyle factors, younger patients may display a worse risk profile as compared with older patients(Egred, Viswanathan & Davis 2005).

Sex also appears to modify the association between depression and medical prognosis of patients with MI. On average, women have their first MI at an older age, have more comorbidities and stay longer hospitalized than men(Gupta et al. 2014). Also, the incidence of post-MI mortality is higher among women than men(Pancholy et al. 2014, Hanratty et al. 2000). Meta-analysis of individual-participant data (IPD) from 16 studies suggests that depression

is associated with adverse prognosis in men but not in women (Doyle et al. 2015), but other studies have found the opposite or no difference(Shah et al. 2014). Moreover, the prevalence of symptoms of depression is higher in women than in men(Martin LA, Neighbors HW,Griffith DM 2013). Hence, more research is needed to investigate whether any potential sex differences in the predictive power of depression may depend on the symptoms reported.

The objective of this study is to investigate possible interactions among age, sex, and individual depressive symptoms in relation to all-cause mortality following acute MI.

Methods

Patients

A systematic search of the Medline, EMBASE and PsycINFO databases was conducted to identify intervention and prognostic studies published prior to January 5, 2011. Studies were included if they had analyzed the association between depression and cardiovascular prognosis in post-MI patients. More information on this systematic search is available elsewhere (Meijer et al. 2013). Information on individual studies characteristics is presented in **Table 1.**

Endpoint

The primary endpoint of the present study was all-cause mortality. On average, a follow up time of 3.8 ± 2.5 years (median = 2.28; interquartile range = 3.67) for all-cause mortality was recorded.

Symptoms of depression

We selected studies in post-MI patients that included depressive symptoms as measured by the Beck Depression Inventory (BDI) and that included time-to-event data.

The BDI (Beck, Steer 1987) is a 21-item questionnaire that is often used in studies of patients with MI, but several shorter versions exist (Furlanetto, Mendlowicz & Romildo Bueno 2005, Denollet et al. 2010). In the present study, we used 10 items of the BDI that compose a shorter version of the BDI: the BDI10. The BDI10 is designed to assess 10 symptoms in cardiac patients across three dimensions of: *core symptoms* (sadness and hopelessness); *negative self-view* (sense of failure, self- dislike, suicidal ideation and negative self-image), and *lack of satisfaction/energy* (dissatisfaction, indecisiveness, work inhibition and fatigue). Denollet and colleagues suggested that the 4^{th} response category (the most severe form of each symptom) is seldom checked by patients with MI. Therefore only three response categories were used, by merging the 3^{rd} and 4^{th} response categories.

Clinical covariates

We included in the combined dataset clinical and lifestyle covariates that are related to medical prognosis in patients with MI. History of prior MI was used as a marker of heart disease severity. Data on aspirin and beta-blocker use were available in all individual studies, and were included to control for medication use in the present study. Diabetes was included as a covariate to represent comorbidity and smoking as an unhealthy lifestyle factor. These covariates were selected because they were generally available in all included studies, and a number of individual studies had no data on left-ventricular ejection fraction (LVEF), statins, or platelet inhibitors. Because LVEF is associated with poor prognosis in patients with MI (Doyle et al. 2015), we also used this covariate in sensitivity analyses in the subset of studies that included LVEF.

Statistical analysis

Risks for all-cause mortality were estimated with multivariable mixed-effects Cox proportional hazards models. Since data were multi-level, between-study heterogeneity was accounted by modeling the study level as a random intercept. Since there was low between-study variation, a random slope was not included. Since between-study heterogeneity between individual studies was low (Q-value = 8.297 (6); p = 0.217; I^2= 28%) a random slope was not included. The assumption of proportionality of hazards for the Cox proportional hazards models was checked, by including time-dependent covariates in the models. A statistically significant time-dependent covariate ($p < .05$) is indicative of violation of the assumption.

To assess how age and sex modifies the association of depressive symptoms in predicting all-cause mortality, the following steps were taken. First (step 1a), we built multivariable models including three-way interaction terms (i.e. Age X Sex X BDI10 individual item) and clinical covariates (history of MI, aspirin use, beta blocker use, smoking and diabetes). A model assessing the three-way interaction between the BDI10 sum score was also built. Step 1b consisted of stratifying the sample according to sex and age groups, and to conduct multivariable subgroup analyses for symptoms that potentially interacted with age and sex simultaneously. In step 2a the same procedure was repeated for the symptoms that did not indicate a three-way interaction. Instead, two-way interaction terms were used in separate models (Age X BDI10; Sex X BDI10). Afterwards, in step 2b, subgroup analyses were conducted for symptoms that potentially interacted either with age or sex. The same procedure was conducted for the BDI10 sum score. To evaluate the internal consistency of the BDI10, Crohnbach's α was computed.

Because the association between depression and cardiovascular-related variables is often curvilinear, we also explored the possibility of curvilinear relationships by adding quadratic terms for age to the models. When the quadratic

term did not reach statistical significance, a linear term was investigated. Three age subgroups were evaluated: 55 years or younger, from 56 to 69 years and 70 years or older. These age categories were defined according to a previously published prognostic study (Gupta et al. 2014). Sex stratification was performed within the age groups for three-way interaction and separately for two-way interaction assessment.

Since between-study heterogeneity between individual studies was low (Q-value = 8.297 (6); p = 0.217; I^2= 28%) a random slope was not included. Following previous recommendations, a confidence level of α=.20 was used when screening for interactions (Selvin 1996) in steps 1a and 2a. For main effects in subgroup analyses, a confidence level of α=.05 was used. All the analyses were conducted using Stata 13.0.

Sensitivity analyses

Due to the considerable shared variance among depressive symptoms, additional sensitivity analyses were conducted by including statistical adjustment for the remaining depressive symptoms (additionally to the other covariates already included in the main models).

Assessment for LVEF was not included in two of the studies composing the total sample(Lauzon et al. 2003, Lane et al. 2001). Therefore, we also conducted sensitivity analyses adjusting for LVEF (additionally to the other covariates already included in the main models) for symptoms that potentially interacted with age and sex in three-way and two-way interaction models in the subsample that included assessment for LVEF.

Missing data

As third parties provided the datasets used in the present study, missing data could not always be retrieved. A substantial part of the sample had imputed missing data on individual BDI items using the average of the available participants' symptoms (27%). Therefore, we did use the same technique for imputing missing data on the rest of the sample. Participants with more than six missing items on the BDI were excluded from the analyses. For other variables, data was missing in very few cases such as history of MI (1.24%); aspirin use (3.10%); beta-blocker use (2.79%) and smoking (2.08%).

Results

Age, sex and clinical characteristics

A total of 2,276 (36%) participants were aged ≤55 years, 2,448 (38%) were aged between 56-69 years and 1,639 (26%) were aged 70 years or more. The analogous figures for men in these age groups were: 1,738 (76%), 1,819 (71%) and 1,025 (57%), respectively. In the group aged ≥70 years, 1,025 were men (57%). More information on

individual studies and the combined sample characteristics is available in **Table 1.**

(TABLE 1 HERE)

Depressive symptoms as measured by the BDI10

The internal consistency of the depressive symptoms as calculated by the BDI10 was 0.83 in the present sample. The internal consistency did not improve by removing any of the items. Item-rest correlation coefficients were higher than 0.4 for all individual items except for the item "suicidal ideation", suggesting that all items correlated sufficiently with the total sum score. The median of the BDI10 score was 4, and the interquartile range was 6. The most reported item of the BDI10 was fatigue (74% of the participants), followed by work difficulties (63%). Suicidal ideation was the least reported item (7%). Individual BDI10 items response frequencies, reliability, and item-rest correlation coefficients are presented in **Table 2.**

(TABLE 2 HERE)

All-cause mortality

After a mean follow-up of 3.8 years (median = 2.28; interquartile range = 3.67), 995 (15%) post-MI patients had died. The assumption of proportionality of hazards was met for all variables. Higher levels of depressive symptoms as measured by the BDI10 sum score were associated with an increased risk of all-cause mortality (HR: 1.20; 1.11 – 1.28, $p < .001$) in the total sample.

All the covariates were significantly associated with all-cause mortality in univariable models (**Supplementary material 1)**. Unexpectedly, smoking was negatively associated with all-cause mortality, suggesting a protective effect. After running this same analysis while adjusting for age, the association between smoking and all-cause mortality became positive, suggesting that the association between smoking and all-cause mortality was confounded by age **(results not shown)**. In the present sample, most participants smoking were younger than 55 years. Therefore, the younger age of the smokers could have acted as a confounder in the relationship between smoking and mortality.

Multilevel multivariable proportional hazards models of mortality

Three-way interaction terms with mortality

The three-way interaction term between age, sex and BDI10 sum score in the multivariable model was not

significant (95% CI 0.99 – 1.02; p = .579. Results for the three-way interaction terms across individual items are presented in the **Supplementary material 2.** A potential significant quadratic term for age was found only for suicidal ideation. Potential interaction terms with p-values ≤ .20 were found for suicidal ideation (95% CI 0.99 – 1.00; (p = .065), negative self-image (95% CI 0.96 – 1.00; p = .127), dissatisfaction (95% CI 0.99 – 1.03; p = .170), indecisiveness (95% CI 0.97 – 1.00; p = .145) and fatigue (95% CI 1.00 – 1.04; p = .020).

Subgroup analyses of mortality according to both age and sex

When a potential interaction between an item of the BDI10, age and sex was identified (i.e. p ≤ .20), we performed subgroup analyses assessing the risk of all-cause mortality associated with these symptoms across age and sex groups (**Table 3)**. In women aged between 56 and 69 years, fatigue was associated with mortality (HR: 1.54; 95% CI 1.09-2.15). In women 70 years or older, suicidal ideation was associated with mortality (HR: 1.58; 95% CI 1.03-2.43). In men, dissatisfaction was associated with mortality in both the 56-69 year (HR: 1.35; 95% CI 1.07-1.71) and ≥70 year (HR: 1.34; 95% CI 1.10-1.63) age groups, but not in the younger age group. In men 55 years or younger, negative self-image (HR: 1.53; 95% CI 1.06-2.21) and indecisiveness (HR: 1.53; 95% CI 1.15-2.04) were associated with all-cause mortality, while fatigue was associated with all-cause mortality in men 70 years or older (HR: 1.45; 95% CI 1.20-1.74).

(TABLE 3 HERE)

Two-way interaction terms of mortality

When a potential three-way interaction between an item of the BDI10, age and sex could not be detected, we investigated for potential two-way interactions between these remaining BDI10 items and age or sex. We also investigated for a potential two-way interaction between BDI10 sum scores and age or sex. Potential two-way interactions between BDI10 sum scores and age (HR: 0.99; 0.99 – 1.00; p = .087) and between BDI10 sum scores and sex (HR: 1.15; 1.01–1.31; p =. 028) were found. There were also potential two-way interactions between age and the following depressive symptoms of the BDI10: hopelessness (HR: 0.99; 0.98 – 1.00, p = .051), sense of failure (HR: 0.98; 0.97 – 1.00, p = .020) and work difficulties (HR: 0.99; 0.98 – 1.00, p = .139). Potential two-way significant interactions between BDI10 and sex were found for sadness (HR: 1.25; 1.01 – 1.54, p = .035) and work difficulties (HR: 1.12; 0.94 – 1.33, p = .200).

Subgroup analyses of mortality according to either age or sex

Age subgroup analyses assessing the risk of all-cause mortality were conducted for the following variables: BDI10 sum score, hopelessness, sense of failure, and work difficulties **(Table 4)**. The BDI10 sum score and work difficulties were significantly associated with mortality across each of the three age subgroups. Hopelessness was also significantly associated with mortality in both the 56-69 year (HR: 1.26) and ≥70 age groups (HR: 1.24), but not those aged ≤55 years.

Sex subgroup analyses assessing the risk of all-cause mortality were conducted for the BDI10 sum score, sadness, and work difficulties (**Table 4**). The item "work difficulties" was associated with all-cause mortality in both women and men, but the effect was stronger in men (HR: 1.33) than in women (HR: 1.22). Sadness and the total BDI10 sum score were associated with all-cause mortality in men (HR: 1.24) but not in women (HR: 0.94).

(TABLE 4 HERE)

Sensitivity analyses with adjustment for LVEF

The sensitivity analyses with adjustment for LVEF included five studies, and the sample size was roughly 30% smaller than the sample size used in the main analyses. Results of the sensitivity analyses stratified by age and sex groups are available in **Table 5.** In women aged ≤55 years the results were virtually the same as in the models without adjustment for LVEF. In men aged ≤55 years the associations of negative self-image e and indecisiveness with mortality were no longer statistically significant. In women aged between 56 and 69 years, negative self-image was significantly associated with mortality (HR: 1.46). In men aged between 56 and 69 years, dissatisfaction was no longer significantly associated with mortality ($p = .08$). In this subgroup, fatigue also became significantly associated with mortality. In women ≥70 years, adjustment for LVEF explained the association between suicidal ideation and mortality whereas in men ≥70 years old, both dissatisfaction and fatigue remained significantly associated with mortality.

For the 2-way interactions, the pattern of the associations between individual symptoms of depression and all-cause mortality was similar to the main analyses without adjustment for LVEF. In patients' aged ≤55 years, the BDI10 total symptom score was no longer significantly associated with mortality. Reporting work difficulties was no longer significantly associated with mortality in patients aged between 56 and 69 years ($p = .07$). There were no substantial differences in the pattern of the associations across sex subgroups. Results of sensitivity analysis stratified either by sex or age are available in **Table 6**.

(TABLE 5 HERE)

(TABLE 6 HERE)

Sensitivity analyses including adjustment for the remaining depressive symptoms

Results of the sensitivity analyses including statistical adjustment for the remaining depressive symptoms are presented in Supplementary material 3 for the symptoms where a three-way interaction with age and sex was flagged, and at supplementary material 4 (supplementary material) for the symptoms where a two-way interaction with either sex or age was flagged. For the symptoms suicidal ideation, (in women aged 70 years or older) and negative self-image (in men aged 55 years or younger), the association became not statistically significant anymore. For symptoms where a two-way interaction was flagged, changes in estimates also only changed slightly, however changes in statistical significance were more prominent. For the symptoms hopelessness, work difficulties and sadness all the associations became not statistically significant in both sex and age subgroups.

Discussion

This international, multi-level sample derived from an IPD meta-analysis, indicates a substantial degree of heterogeneity in the predictive value of self-reported depressive symptoms associated with all-cause mortality across age and sex subgroups

Interactions of individual depressive symptoms with age and sex differences in relation to all-cause mortality

Three-way interactions with age and sex in relation to all-cause mortality were flagged for the following individual depressive symptoms: suicidal ideation, negative self-image, dissatisfaction, indecisiveness and fatigue.

Two-way interactions with sex in relation to all-cause mortality were flagged for hopelessness and work difficulties. Two-way interactions with age in relation to all-cause mortality were flagged for work difficulties and sadness. A two-way interaction with either sex or age in relation to all-cause mortality was also found for the sum score of the BDI10.

Individual depressive symptoms and mortality according to age and sex differences

There was no three-way interaction between age, sex and BDI10 sum score in predicting all-cause mortality, but there were three-way interactions with specific depressive symptoms. Dissatisfaction, indecisiveness and negative self-image were related to mortality in specific age groups in men, while suicidal ideation was related to mortality in women.

Dissatisfaction was associated with all-cause mortality in men aged 56 years or older, but not in women or younger men. Dissatisfaction was a common symptom (45% of the total sample) with 9% endorsing the moderate/severe category. Bifactor factor analysis of the BDI suggests that dissatisfaction is a somatic/affective symptom that is unrelated to a general depression factor, and that it predicts mortality and recurrent cardiac events(de Miranda Azevedo et al. 2016). Regardless of being a marker of depression or somatic illness, dissatisfaction is a major risk marker in middle-aged and older men. Importantly, interdisciplinary health promotion improves satisfaction in older adults(Wilhelmson, Eklund 2013).

Indecisiveness and *negative self-image* are two symptoms of depression that were associated with an increased risk of all-cause mortality in men 55 years or younger. We hypothesize that indecisiveness could predict failure to make lifestyle changes in younger patients with MI, since they are more likely to adhere to an unhealthy lifestyle. Indecisiveness may also be a marker or determinant of chronic stress in this age group.

Negative self-image has been previously shown to be associated with being overweight in patients with MI (Guiry et al. 1987). The possibility of residual confounding as a function of unhealthy lifestyle and medical comorbidities cannot be discarded.

Suicidal ideation was only associated with an increased risk of all-cause mortality in women aged ≥70 years. Suicidal ideation may reflect a more severe form of depression and therefore should be addressed by clinicians and discussed with their patients. Unfortunately, it was not possible for us to assess whether there was a higher incidence of suicide among women aged ≥70 years, since cause of death was not recorded. Moreover, we cannot exclude the possibility that this symptom might also be an indicator of mortality in men, as it has been stated that men tend to underreport cognitive-affective symptoms of depression such as suicidal ideation (Sigmon et al. 2005).

Age and sex differences: sensitivity analyses including statistical adjustment for LVEF

In the sensitivity analyses including adjustment for LVEF, the association between dissatisfaction and mortality in men aged 56 to 69 years was no longer statistically significant ($p = .08$). The associations of indecisiveness and negative self-image with mortality were also no longer statistically significant in the sensitivity analyses in men aged ≤55 years, and the association between suicidal ideation and all-cause mortality in women aged ≥70 years was also no longer statistically significant. Although the sensitivity analyses suggest that LVEF may help to explain the association between individual symptoms of depression and all-cause mortality in younger men and older women with MI, the sample size was substantially reduced (30% and 42%, respectively) because of missing LVEF data. Therefore, it could be that statistical power in these subgroups was limited. Nonetheless, markers of heart disease severity such as LVEF and Killip class should be routinely included in future studies assessing the association between depressive

symptoms and cardiovascular outcomes.

Frequently reported depressive symptoms and mortality

Fatigue (74%) and work difficulties (62%) were the two symptoms most frequently reported. The 3-way interaction between fatigue, age and sex indicated that fatigue was significantly associated with all-cause mortality in women aged 56-69 years and men ≥70 years. However, the p-values of the association between fatigue and mortality in younger women and younger and middle-aged men were close to .05. In sensitivity analyses adjusting for LVEF, the association between fatigue and all-cause mortality also became statistically significant for men aged between 56 and 69 years. Some have suggested that fatigue should be assessed separately from other depressive symptoms in order to prevent being missed in low depression sum scores (Alsen et al. 2010). Evidence suggests that fatigue can be decreased through moderate aerobic exercise training(Sandor et al. 2014).

Work difficulties revealed significant two-way interactions with age and sex. Yet, in subgroup analyses, work difficulties were significantly associated with all-cause mortality in all patients regardless of age and sex.

Symptoms of general depression factor and mortality

For *hopelessness* and *sadness*, a potential 2-way interaction with age indicated that hopelessness was associated with mortality only in participants that aged ≥56 years. Hopelessness is associated with other risk factors for adverse prognosis, such as lower adherence to cardiac rehabilitation and physical inactivity (Valtonen et al. 2009).

Sadness was significantly associated with an increased risk of all-cause mortality in men, but not in women. It has been suggested that assessing sadness through more items could offer advantages, as this symptom is considered to be rather complex (Fried, Nesse 2015).

Clinical implications

To date, it has been reported that psychotherapy and psychopharmacological interventions (i.e. antidepressants) have a small but clinically significant effect on decreasing depressive symptomatology in patients with CHD (Baumeister, Hutter & Bengel 2014). Overall, receiving anti-depressant treatment did not show to efficiently improve medical prognosis in patients with CHD. However, secondary analyses of clinical depression trials in patients with CHD suggest that prognosis improves when depression improves (Carney, Freedland 2017). Regardless of improving medical prognosis, depressive symptoms should always be treated when necessary, as they provide substantial suffering for the individual. Moreover, future studies should assess whether interventions focused on treating cognitive symptoms. To our knowledge there are no studies assessing whether solely modifying negative self-

image and indecisiveness could be improve medical prognosis in younger men. Findings from a meta-analysis suggested that stand-alone cognitive-behavior therapy for self-image significantly improves negative self-image (Jarry, Ip 2005). This intervention includes a combination of cognitive restructuring, self-monitoring and psychoeducation aimed at dysfunctional cognitions, with the objective to improve exposure, response prevention and desensitization of the participant in the way that the individual progressively stops experiencing a negative view of himself or herself. Our findings could serve as a framework for future researchers who aim to tailor new symptom-specific interventions. Moreover, the predictive models including the complete sample, as opposed to models based on subsamples that adjusted for LVEF, may be more generalizable.

Limitations

Findings of the present study should be interpreted in the light of its limitations. Although a previous study investigated the validity of the BDI10 (Denollet et al. 2010), the literature on this instrument is scarce. In the present study, only the original 21-item BDI was assessed, therefore we had to manually reduce the number of items and the response categories in order to compute the BDI10 sum score, which is a limitation of the study.

Another important limitation of the study was the lack of adjustment for body mass index (BMI). BMI was not measured at every study and therefore we did not adjust for it in the predictive models. Moreover, missing data for individual symptoms of depression had already been imputed for a large parcel of the sample using mean imputation. For this reason, we could not use more sophisticated techniques for addressing missing data.

We did not formulate a hypothesis prior to assessing the predictive value of individual symptoms of depression. This could lead to chance findings due to the problem of multiple testing. Due to the exploratory nature of the present study, we did not use any correction for multiple testing, as these could be rather conservative for our purposes. Therefore, findings of the present study should be interpreted with care and further replicated before definitive conclusions are made.

Conclusions

Findings from the present study suggest that men and women from different age groups are differentially affected by symptoms of depression. Although adjustment for LVEF helped to explain the association in younger men and older women, adjusting for LVEF did not seem to change the pattern of the associations in middle-aged patients or in older men. Future research needs to account for large heterogeneity in the predictive value of individual depressive symptoms among post-MI patients.

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Table 1: Individual studies characteristics

First author. year	Country and start baseline assessment (year)	N	Age (mean, sd)	Male (%)	History of MI (%)	Diabetes (%)	Smoking (%)	LVEF ≤ 40%	Median and IQR	Incidence of endpoint (%)	Mean follow-up time (years)
Lane, 2001	United Kingdom, 1997	288	62.7 (11.5)	75	22	12	43	N/A	Median: 2 IQR: 3	13	2.7
Berkman, 2003	USA, 1996	2848	60.8 (12.3)	58	26	32	31	28	Median: 6 IQR: 6	12	2.3
Lauzon, 2003	Canada, 1996	552	60.2 (12.2)	79	21	16	40	N/A	Median: 2 IQR: 4	6	1.0
Spijkerman, 2005	The Netherlands, 1997	499	60.7 (11.7)	81	14	10	53	23	Median: 2 IQR: 3	22	7.3
Van Melle, 2007	The Netherlands, 1999	1814	61.0 (11.6)	78	13	12	48	25	Median: 2 IQR: 3	15	6.0
Parakh, 2008	USA, 1995	280	64.9 (12.1)	57	31	35	29	30	Median: 1 IQR: 2	54	6.6

Denollet, 2010	The Netherlands, 2003	498	59.6 (11.6)	78	14	14	38	15	Median: 2 IQR: 3	8	3.8
Combined sample	Various	6773	61.0 (12.0)	69	20	22	39	25	Median: 4 IQR: 6	15	3.8

*ACM: All-cause mortality; IQR: Inter-quartile range; MI: Myocardial Infarction; N/A: Not applicable.

Table 2. Prevalence and internal consistency of depressive symptoms (N= 6,773)

Depression symptom (BDI10)	**Mild (score 1)**	**Moderate - severe (2)**	**Item-rest correlation**	**Alpha if item deleted**
Sadness	29%	8%	0.583	0.803
Hopelessness	20%	9%	0.608	0.801
Sense of failure	10%	7%	0.519	0.812
Self-dislike	19%	5%	0.568	0.807
Suicidal ideation	6%	1%	0.346	0.827
Negative self-image	12%	6%	0.464	0.816
Dissatisfaction	36%	9%	0.612	0.799
Indecisiveness	20%	11%	0.481	0.814
Work difficulties	39%	23%	0.510	0.811
Fatigue	52%	22%	0.457	0.815

Table 3. Subgroup analyses of depressive symptoms and mortality according to both age and sex.

Depressive symptom (BDI10)	**≤55 years**		**56-69 years**		**≥70 years**	
	Women N = 539	**Men N = 1,738**	**Women N = 721**	**Men N = 1,727**	**Women N = 701**	**Men N = 938**
Suicidal ideation	0.57 (0.16-2.01) p = .384	1.31 (0.74-2.35) p = .350	0.94 (0.42-2.06) p = .702	0.59 (0.28-1.24) p = .169	**1.58 (1.03-2.43) p = .037**	1.23 (0.73-2.07) p = .433
Negative self-image	0.68 (0.40-1.18) p = .173	**1.53 (1.06-2.21) p = .022**	1.31 (0.94-1.81) p = .108	1.26 (0.94-1.69) p = .120	1.23 (0.96-1.57) p = .088	1.23 (0.93-1.63) p = .144
Dissatisfaction	1.19 (0.75-1.89) p = .457	1.14 (0.83-1.58) p = .410	1.30 (0.94-1.80) p = .109	**1.35 (1.07-1.71) p = .011**	1.06 (0.84-1.33) p = .590	**1.34 (1.10-1.63) p = .003**
Indecisiveness	0.87 (0.56-1.38) p = .567	**1.53 (1.15-2.04) p = .003**	0.74 (0.55-1.01) p =.063	1.14 (0.92-1.42) p = .222	1.07 (0.88-1.31) p = .485	1.04 (0.87-1.25) p = .635
Fatigue	1.49 (0.94-2.35) p = .087	1.36 (0.97-1.91) p = .066	**1.54 (1.09-2.15) p = .012**	1.21 (0.96-1.52) p = .105	1.07 (0.86-1.32) p = .538	**1.45 (1.20-1.74) p < .001**

*Significant associations marked in **bold** ($p < .05$).

Table 4. Subgroup analyses of depressive symptoms and mortality according to either age or sex

	Age groups			**Sex**	
Depressive symptom (BDI10)	**≤55 years N = 2,277**	**56-69 years N = 2,448**	**≥70 years N = 1,639**	**Women N = 1,961**	**Men N = 4,403**
Total symptom score	**1.20 (1.01-1.42); p=. 040**	**1.16 (1.02-1.36); p = .005**	**1.25 (1.13-1.38); p < .001**	1.11 (0.99-1.24); p = .062	**1.31 (1.19-1.44); p < .001**
Hopelessness	1.22 (0.95-1.57); p= .119	**1.26 (1.04-1.53); p = .017**	**1.24 (1.08-1.43); p = .002**		
Work difficulties	**1.37 (1.09-1.73); p =. 007**	**1.25 (1.06-1.48); p = .007**	**1.29 (1.14-1.47); p < .001**	**1.22 (1.05-1.42); p = .009**	**1.33 (1.19-1.50); p < .001**
Sadness				0.94 (0.79-1.11); p = .486	**1.24 (1.07-1.30); p = .004**

*Significant associations marked in **bold** ($p < .05$).

Table 5. Sensitivity subgroup analyses of depressive symptoms and mortality according to both age and sex including adjustment for LVEF ≤ 40% (three-way interactions)

Depressive symptom (BDI10)	**≤55 years**		**56-69 years**		**≥70 years**	
	Women **N = 394**	**Men** **N = 1210**	**Women** **N = 502**	**Men** **N = 1252**	**Women** **N = 467**	**Men** **N = 685**
Suicidal ideation	0.62 (0.17-2.28) p = .476	1.07 (0.49-2.31) p = .863	1.19 (0.56-2.51) p = .653	0.43 (0.18-1.02) p = .057	1.45 (0.84-2.51) p = .185	1.32 (0.77-2.28) p = .339
Negative self-image	0.84 (0.46-1.54) p = .577	1.44 (0.92-2.26) p = .111	**1.46 (1.00-2.09) p = .047**	1.24 (0.90-1.70) p = .184	1.29 (0.97-1.71) p = .083	1.32 (0.98-1.77) p = .067
Dissatisfaction	1.03 (0.57-1.86) p = .914	0.98 (0.67-1.43) p = .927	1.22 (0.85-1.74) p = .282	1.26 (0.97-1.65) p = .085	1.02 (0.77-1.36) p = .861	**1.46 (1.15-1.86) p = .002**
Indecisiveness	0.93 (0.55-1.55) p = .787	1.29 (0.91-1.83) p = .152	0.77 (0.55-1.08) p = .126	1.24 (0.98-1.56) p = .063	1.05 (0.82-1.35) p = .669	1.09 (0.89-1.35) p = .376
Fatigue	1.47 (0.88-2.48) p = .139	1.12 (0.77-1.63) p = .548	**1.48 (1.04-2.12) p = .031**	**1.31 (1.01-1.69) p = .039**	1.19 (0.92-1.55) p = .186	**1.45 (1.18-1.78) p = .001**

*Significant associations marked in **bold** (p < .05).

Table 6. Subgroup analyses of depressive symptoms and mortality according to either age or sex including adjustment for LVEF ≤ 40%(two-way interactions)

	Age groups			**Sex**	
Depressive symptom (BDI10)	**≤55 years N = 1,604**	**56-69 years N = 1,754**	**≥70 years N = 1,152**	**Women N = 1,363**	**Men N = 3,147**
Total symptom score	1.07 (0.87-1.33); p = .503	**1.16 (1.01-1.33); p = .033**	**1.31 (1.17-1.48); p < .001**	1.12 (0.98-1.28); p = .108	**1.29 (1.16-1.44); p < .001**
Hopelessness	1.01 (0.73-1.39); p = .954	**1.26 (1.02–1.56); p = .035**	**1.31 (1.11-1.54); p = .001**		
Work difficulties	**1.37 (1.05-1.77); p = .017**	1.18 (0.99-1.42); p = .070	**1.27 (1.10-1.47); p = .001**	**1.21 (1.02-1.44); p = .029**	**1.29 (1.13-1.47); p < .001**
Sadness				0.91 (0.74-1.12); p = .389	**1.24 (1.05-1.45); p < .001**

*Significant associations marked in **bold** (p < .05).

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Supplementary material 1. Univariable models of clinical covariates predicting all-cause mortality

Clinical covariate	**Risk**
History of MI	2.60 (2.27 – 2.96); p < .001
Aspirin use	0.46 (0.40 – 0.54); p < .001
Beta-blocker use	0.54 (0.47 – 0.62);p < .001
Smoking	0.63 (0.55 – 0.73);p < .001
Diabetes	2.32 (2.02 – 2.65);p < .001

Supplementary material 2. Three-way interaction models

Item	**Interaction term**
Sadness X Sex X Age	1.00 (0.98 – 1.02); P = .625
Hopelessness X Sex X Age	1.01 (0.99 – 1.03); P = .384
Sense of failure X Sex X Age	0.99 (0.97 – 1.01); P = .406
Self-dislike X Sex X Age	0.99 (0.98 – 1.02); P = .996
Suicidal ideation X Sex X Age^2	**1.00 (0.99 – 1.00); P = .065**
Negative self-image X Sex X Age	**0.98 (0.96 – 1.00); P = .127**
Dissatisfaction X Sex X Age	**1.01 (0.99 – 1.03); P = .170**
Indecisiveness X Sex X Age	**0.99 (0.97 – 1.00); P = .145**
Work difficulties X Sex X Age	0.99 (0.98 – 1.01); P = .683
Fatigue X Sex X Age	**1.02 (1.00 – 1.04); P = .020**

*Potentially relevant interactions are marked in **bold;** following previous recommendations, a confidence level of .20 was used when screening for interactions.

Supplementary material 3. Subgroup analyses of depressive symptoms and mortality according to both age and sex, including statistical adjustment for the remaining individual symptoms of depression.

Depressive symptom (BDI10)	**≤55 years**		**56-69 years**		**≥70 years**	
	Women **N = 539**	**Men** **N = 1,738**	**Women** **N = 721**	**Men** **N = 1,727**	**Women** **N = 701**	**Men** **N = 938**
Suicidal ideation	0.72 (0.19-2.70) p = .628	0.98 (0.52-1.84) p = .954	0.89 (0.39-2.03) p = .791	**0.47** **(0.22-0.99)** **p = .047**	1.48 (0.94-2.32) p = .089	1.06 (0.62-1.82) p = .825
Negative self-image	0.65 (0.37-1.14) p = .134	1.31 (0.87-1.96) p = .192	1.33 (0.93-1.89) p = .116	1.19 (0.93-1.89) p = .116	1.18 (0.91-1.52) p = .199	1.13 (0.85-1.52) p = .390
Dissatisfaction	1.13 (0.66-1.92) p = .659	0.85 (0.58-1.25) p = .404	1.29 (0.90-1.86) p = .169	**1.31** **(1.00-1.71)** **p = .046**	0.98 (0.76-1.25) p = .865	**1.25** **(1.01-1.54)** **p = .033**
Indecisiveness	0.81 (0.49-1.32) p = .395	**1.44** **(1.02-2.03)** **p = .036**	**0.58** **(0.41-0.82)** **p =.002**	1.03 (0.81-1.31) p = .798	1.01 (0.82-1.26) p = .892	0.87 (0.71-1.06) p = .162
Fatigue	1.69 (0.99-2.88) p = .056	1.23 (0.85-1.77) p = .270	**1.66** **(1.15-2.40)** **p = .007**	1.12 (0.87-1.44) p = .353	1.03 (0.82-1.30) p = .766	**1.43** **(1.17-1.74)** **p < .001**

*Significant associations marked in **bold** (p < .05).

Supplementary material 4. Subgroup analyses of depressive symptoms and mortality according to either age or sex, including statistical adjustment for the remaining individual symptoms of depression.

	Age groups			**Sex**	
Depressive symptom (BDI10)	**≤55 years N = 2,277**	**56-69 years N = 2,448**	**≥70 years N = 1,639**	**Women N = 1,961**	**Men N = 4,403**
Hopelessness	1.18 (0.85-1.66) p= .313	1.24 (0.97-1.57) p = .092	1.14 (0.95-1.35) p = .147		
Work difficulties	1.27 (1.94-1.70) p = . 118	1.18 (1.96-1.46) p = .111	1.15 (0.99-1.35) p = .070	1.17 (0.97-1.41) p = .091	1.15 (0.99-1.33) p = .061
Sadness				0.81 (0.67-0.98) p = .036	1.02 (1.86-1.21) p = .814

*Significant associations marked in **bold** ($p < .05$).