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Symptom and Course Heterogeneity of Depressive Symptoms and Prognosis Following Myocardial Infarction

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Abstract

Objective: Previously published findings from the DepreMI cohort suggested that both the course and the type of depressive symptoms following myocardial infarction (MI) are related to prognosis, but did not examine both factors simultaneously. The aim of this re-analysis study was to assess whether MI patients can be empirically classified based on trajectories of cognitive/affective (CA) and somatic/affective (SA) symptoms, and whether these classes differentially predict adverse outcomes.

Methods: Patients with acute MI (n=457) were recruited between 1997 and 2000 and provided (BDI-I) data at baseline, 3, 6 and 12 months. Parallel Processes latent class growth analysis was used to identify latent classes. Patients were followed up until 2007 for all-cause mortality and cardiovascular readmissions.

Results: Three classes were identified: 'low severity': consistently low CA and SA (n=316); 'somatic persistence': consistently low CA and high SA (n=110); and 'overall persistence': high and increasing CA and SA (n=31). After adjustment for gender and the Global Registry of Acute Coronary Events risk score, somatic persistence (HR:1.86; 95% CI: 1.18-2.94; p=0.008), but not overall persistence (HR:1.09.; 95% CI: 0.39-3.03; p=0.87), predicted mortality compared with low severity. Classes were not predictive of non-fatal cardiovascular events.

Conclusions: MI patient classes differed in severity and course of CA and SA depressive symptoms in the post-MI year. Only a class with persistent SA depressive symptoms was associated with increased mortality compared with patients with low severity. This is suggestive of different origins of SA depressive symptoms in MI patients that may explain the differential associations with mortality.

Key words: Depression, depressive symptoms, dimensions, heterogeneity, myocardial infarction, mortality.

Introduction

In patients with an acute myocardial infarction (MI) the prevalence of depression is comparatively high [Thombs et al., 2006] and depression is associated with poor cardiovascular prognosis [Meijer, Conradi, Bos, Thombs, van Melle, & de Jonge, 2011; Meijer et al., 2013a]. Studies on the course of depressive symptoms after MI found that the presence of depressive symptoms is relatively stable during the first year post-MI, although distinct courses could be identified [Kaptein, de Jonge, van den Brink, & Korf, 2006; Martens, Smith, Winter, Denollet, & Pedersen, 2008]. Not only traditional risk factors for depression, such as certain personality traits and the presence of cognitive distortions [Doyle, McGee, Delaney, Motterlini, & Conroy, 2011], but also factors related to heart disease or somatic comorbidity, such as cardiac history [Martens et al., 2008] and diabetes [Murphy et al., 2008], appear to be prominent risk factors for the persistence of depressive symptoms 1 year following acute coronary syndrome (ACS) or coronary artery bypass graft (CABG) surgery.

A previously published study of the Depression after Myocardial Infarction (DepreMI) cohort investigated whether depressive symptom trajectories over 1 year following MI were also of importance for cardiovascular prognosis. This data-driven study by Kaptein et al., [2006] found 5 latent classes, characterized by different longitudinal growth trajectories in depressive symptoms. One group was characterized by the continuous absence of depressive symptoms and four other groups were characterized by 2) mild, 3) moderate, 4) high/decreasing, 5) and high/increasing levels of depressive symptoms. Although all of these groups showed an increased risk of new cardiovascular events during 2.5 years of follow-up compared to the group without symptoms, this increase was only statistically significant for the high/increasing group (4). Thus, the course of depressive symptoms over time appears to hold prognostic information with regard to cardiac risk on top of the quantitative severity of symptoms.

4

Several studies have found that distinct depressive symptom dimensions can be identified with factor analyses in patients with ACS, namely somatic/affective (SA) and cognitive/affective (CA) depressive symptoms. In addition, most, although not all [Frasure-Smith & Lespérance, 2003] of these studies, showed that these symptom dimensions are differentially associated with cardiovascular prognosis [de Jonge et al., 2006a; Smolderen et al., 2009; Martens, Hoen, Mittelhaeuser, de Jonge, & Denollet, 2010; Roest, Thombs, Grace, Stewart, Abbey, & de Jonge, 2011; Bekke-Hansen, Trockel, Burg, & Taylor, 2012]. A recent meta-analysis confirmed that SA depressive symptoms are stronger predictors of mortality and cardiovascular events than CA depressive symptoms [de Miranda Azevedo, Roest, Hoen, & de Jonge, 2014].

It has recently been hypothesized that the effects of depression on cardiovascular prognosis following MI depend on both the course and the type of depressive symptomatology present [Ormel & de Jonge, 2011]. Especially persistent SA depressive symptoms might be predictive of adverse prognosis as these may partly reflect underlying cardiovascular disease processes, like autonomic nervous system dysfunction, and increased inflammation [Ormel & de Jonge, 2011; Poole, Dickens, & Steptoe, 2011].

Both the course and the type of depressive symptoms are important sources of heterogeneity within the depression construct and should ideally be accounted for at the same time. Although Kaptein et al., and de Jonge et al., examined either the association between depressive symptom trajectories and prognosis [Kaptein et al., 2006], or depressive symptom dimensions at baseline and prognosis [de Jonge et al., 2006a], to date, no studies of the DepreMI cohort have combined both aspects in one statistical approach. Such an approach would, in the first place, be very useful to gain insight in how the type and trajectory of symptomatology combine in clinically homogeneous subgroups. In the second place, subgroup-membership would be a very useful determinant in research that seeks to identify

more specific prognostic associations of depressive symptomatology with cardiovascular risk. Another advantage of the current study compared to previously published findings from this cohort [Kaptein et al., 2006; de Jonge et al., 2006a] is the longer follow-up period increasing power to examine endpoints separately.

The first aim of the current re-analysis study was to assess whether MI patients can be classified based on contemporaneous course trajectories on two distinct observed dimensions of depressive symptoms. This was done by use of Parallel Processes latent class growth analysis (PP-LCGA). Next, the relationship of the resulting classes with various characteristics at baseline, and long-term mortality and non-fatal cardiovascular events were assessed. We hypothesized that specific subgroups of patients can be identified based on temporal patterns of SA and CA depressive symptoms. In addition, although we did not have a specific hypothesis about the number and type of underlying classes, we hypothesized that especially patients with persistent, or increasing, SA depressive symptoms, irrespective of their level of CA depressive symptoms, are at risk of adverse outcomes compared to patients without depressive symptoms.

Methods

Participants and procedures

Patients in this re-analysis study were included from the Depression after Myocardial Infarction (DepreMI) study. DepreMI is a naturalistic cohort study evaluating the association of depression after MI with adverse cardiovascular outcomes. Eligible patients admitted for MI at four hospitals in the Netherlands between September 1997 and September 2000 were asked to participate. At least two of the following three criteria for MI had to be met: 1) a documented increase in cardiac enzyme levels, 2) typical electrocardiographic changes, 3) at least 20 minutes of chest pain. Exclusion criteria were the presence of another somatic

disease likely to influence short-term survival, MI during hospital admission for another reason (except unstable angina), and being unable to participate in the study procedures. The ethics committee review board of each participating hospital approved the protocol and all participants signed informed consent. Details of the DepreMI study are described elsewhere [Spijkerman et al., 2005a; Spijkerman, van den Brink, Jansen, Crijns, & Ormel, 2005b]. Previously published reports from the DepreMI study showed that high/increasing depressive symptoms [Kaptein et al., 2006], (incident) depressive episodes following MI [Spijkerman et al., 2006; de Jonge, van den Brink, Spijkerman, & Ormel, 2006b], and baseline SA depressive symptoms [de Jonge et al., 2006a; Meurs, Zuidersma, Dickens, & de Jonge, 2013] predicted cardiovascular prognosis at 2.5 years follow-up. However these studies did not examine contemporaneous course trajectories on different symptom dimensions of depressive symptoms and associations with long-term prognosis (up to 10 years post-MI).

Assessment of depressive symptoms

Depressive symptoms were measured with the Beck Depression Inventory version 1 (BDI-I), a 21-item self-report measure developed to assess the presence and severity of depressive symptoms [Beck, Ward, Mendelson, Mock, & Erbaugh, 1961]. Each item is rated on a 0-3 scale with higher scores reflecting greater severity. The BDI-I has been shown a valid and reliable measure of depressive symptoms in cardiac patients [Davidson et al., 2006]. Depressive symptoms were assessed at baseline (during or shortly following hospitalization, [median and interquartile range in days: 13, 7-31]), and 3 months (median and interquartile range in days: 81, 78-88), 6 months (median and interquartile range in days: 173, 170-179), and 12 months (median and interquartile range in days: 357, 353-361) post-MI.

Previous work in the current baseline sample, together with data from another study (MIND-IT), showed that the BDI-I has a 3-factor structure, consisting of a CA, a SA and an

appetite factor [de Jonge et al., 2006a]. In line with these findings, we constructed a 7-item CA scale (sum of items 3, 5, 6, 7, 8, 9, 14) and a 7-item SA scale (sum of items 10, 11, 15, 16, 17, 20, 21), both with a range of 0-21. Items that loaded on 2 or more factors (items 1, 2, 4, 12, 13) were excluded to optimize scale discrimination. The appetite factor (items 18 and 19) was too small for operationalization in a subscale. The subscale scores were computed for every patient at each of the measurement points.

In DepreMI, 1166 patients were assessed for eligibility. Of those eligible based on the exclusion criteria (882 patients), 528 signed informed consent (59.9%). Of these patients, 71 (13.4%) missed at least one complete BDI-I or had more than 4 missing responses (19% of the items) on the BDI and these patients were excluded from the current study. Of the remaining 457 patients, 304 patients (66.5%) had no missing responses, while 153 (33.5%) had ≤4 missing responses on one or more BDI-I measurements (see supplemental Table 2). Consistent with previous reports [e.g. Kaptein et al., 2006], missing responses were imputed with mean imputation [Rubin, 1987].

Comparison of in- (n=457) and excluded (n=71) patients showed that they did not differ on age (t=0.44, p=0.44) and gender (χ^2=1.03, p=0.31), but that included patients more often had a high (college) education level than excluded patients (16.8% vs. 3.8%; χ^2=6.17; p=0.01). The in- and excluded groups did not differ on a range of health-related factors: previous MI (χ^2=0.11, p=0.74), BMI (t=-0.27; p=0.79); current smoking (χ^2=3.32; p=0.07), hypertension (χ^2=0.12, p=0.72) and diabetes (χ^2=0.63, p=0.43).

Within the included sample, comparison of those with (n=153) and those without (n=304) missing responses on the BDI-I showed that those with missing responses were older, (means: 62.6 years vs. 59.6 years; t=-2.69, p=0.01), were more often female (26.8% vs. 14.8%; χ^2=9.6, p=0.002) and more often lived alone (28.0% vs. 8.7%; χ^2=29.0, p<0.001) than those without missing values. However, the groups did not differ on education (χ^2=0.0,

p=0.99), current smoking (χ^2=2.66, p=0.10), BMI (t=-0.65, p=0.52), hypertension (χ^2=0.85, p=0.36), diabetes (χ^2=0.84, p=0.36) and previous MI (χ^2=0.02, p=0.90).

Demographic and clinical characteristics

Demographic and clinical characteristics were assessed during hospitalization for the index-MI and from hospital charts. Left ventricular ejection fraction (LVEF) was assessed by echocardiography, radionuclide ventriculography, gated single photon emission computed tomography, magnetic resonance imaging, angiography, or clinical assessment. A previous study [Meurs et al., 2013] of this sample calculated Global Registry of Acute Coronary Events (GRACE) risk scores [Eagle et al., 2004]. Variables in the GRACE model include age, history of MI, past or current congestive heart failure, heart rate, systolic blood pressure, serum creatinine, elevated cardiac enzymes, ST-segment depression on electrocardiogram at admission, and no in hospital percutaneous coronary intervention [Meurs et al., 2013]. Educational level and living situation were assessed in an interview 3 months after the index-MI. The presence of an ICD-10 diagnosis of a post-MI depressive episode and current generalized anxiety disorder (GAD) were assessed with the Composite International Diagnostic Interview (CIDI) version 1.1 [Wittchen, 1994] at this time-point. We examined whether classes differed on the presence of GAD since GAD was the most prevalent anxiety disorder and a previous study on this sample showed that GAD was a predictor of adverse outcomes [Roest, Zuidersma, & de Jonge, 2012].

Assessment of adverse outcomes

Data concerning hospital admissions and mortality were obtained up until 31 December 2007 from the Dutch Central Bureau of Statistics by linkage to the municipal personal records database. In line with previous studies in this cohort, hospital readmissions

with ICD-9 codes 410, 411, 413, 414 (ischemic heart disease); 427.1, 427.4, 427.5 (cardiac

arrhythmia); 428, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91,

404.93 (heart failure); 433, 434, 435, 437.0, 437.1 (cerebrovascular disease); and 440, 443.9

(peripheral vascular disease) were included as non-fatal cardiovascular events. End-points of

this study were all-cause mortality and non-fatal cardiovascular events. Only events occurring

between the final BDI-I assessment (12 months post-MI) and 31 December 2007 were

included as adverse outcomes. Information on mortality was missing for 1 patient and

information on cardiovascular readmissions was missing for 22 patients leaving 456 patients

included in the analysis for all-cause mortality and 435 patients for non-fatal cardiovascular

events. The mean follow-up period was 6.5 years (standard deviation [SD]=2.1 years) for all-

cause mortality and 5.6 years (SD=2.7 years) for non-fatal cardiovascular events.

Statistical analyses

The analyses consisted of two parts: first, a subgroup model was constructed and

second, the associations of the resulting subgroups with adverse outcomes were tested.

Before the subgrouping commenced, some preparatory analyses were conducted.

Confirmatory factor analyses (CFA) with a two-factor model (CA and SA) were conducted

with the BDI-I data at each time-point. In the fitted model, the factors were allowed to

correlate and one loading per factor was fixed to one to set the scale. CFA model estimation

was based on the polychoric item-correlation matrix and done with the robust mean and

variance adjusted Weighted Least Squares (WLSMV) estimator. Model fit was assessed with

the comparative fit index ([CFI]; cut-off: ≥0.90 for adequate fit) and the root mean square

error of approximation ([RMSEA]; cut-off: ≤0.08 for adequate fit). The CFA factor-loadings

and factor correlations were compared across time-points to evaluate model consistency. In

addition, the means and standard deviations of the corresponding subscale scores were

compared and Cronbach's alpha coefficients for ordinal data [Gadermann, Guhn, & Zumbo, 2012] were computed based on polychoric item correlation matrices using the R-package 'psych' [Revelle, 2014].

Next, PP-LCGA was used to identify latent classes based on the longitudinal trajectories on the two separate scales. This technique is an expanded variant of regular LCGA [Muthén 2004] and estimates latent classes based on the growth parameters of two (or more) variables in a bi- or multivariate analysis [Nagin & Tremblay, 2001; Nagin & Odgers, 2010]. This means that in a PP-LCGA model, class-membership is based on the contemporaneous growth of two symptom domains [Nagin & Odgers, 2010]. To identify the optimal subgrouping model, PP-LCGA models with increasing numbers of classes were run and their fit was compared. Model estimation was done with robust Maximum Likelihood estimation. Each analysis was run with 500 initial random starts and 100 final stage optimizations to avoid local maxima. Different sources were used to judge model-fit. First, the Bayesian Information Criterion (BIC) was compared across models, with the lowest value indicating the most useful model. Second, a bootstrapped likelihood ratio test (BLRT) was run to test whether adding the kth class led to a significant increase in model fit compared to the k-1 class model. Third, posterior class probabilities were inspected to make sure that class allocation on the basis of these probabilities would be feasible; probabilities of 0.80 or higher were deemed acceptable. Fourth, model interpretability and usefulness were considered: models with classes that were too small (n<20) to allow for use in further statistical analyses were considered suboptimal. In addition, if adding a class did not lead to a clear increase in (qualitative) class-differentiation or only led to splitting classes into very small subclasses, the less complex model was preferred. After model-selection, posterior class probabilities were used to allocate each patient to his/her most likely class. The resulting categorical

grouping variable was used in consecutive analyses. All latent variable analyses were conducted with Mplus 5 [Muthén & Muthén, 2007].

In the second part of the analyses, classes were compared on demographic and clinical characteristics using Pearson chi-square for categorical variables (80% of cells were required to have an expected frequency of 5 or more) and analyses of variance (ANOVA) for continuous variables. These results were adjusted for multiple testing by applying a Bonferroni adjustment and least-significant pairwise comparison was performed for continuous variables for which the overall ANOVA was significant after Bonferroni correction. Kaplan-Meier survival curves were created and differences between classes for the endpoint were tested using the log rank test. Cox regression analysis was used to compare the separate classes to the class of patients with lowest depressive symptoms. The proportional hazard assumption was tested by examining the log-minus-log survival plots. Analyses were adjusted for gender and the GRACE risk score. In sensitivity analyses we additionally adjusted for the occurrence of cardiovascular events (determined by hospital readmissions) and diagnosis of a depressive episode between 0 and 12 months. Analyses were conducted using SPSS 22 for Windows.

Results

Subscale characteristics

The CFAs (supplemental Figure 1) at each of the time points showed good fit of the two-factor model (CA and SA) to the data with CFI's that ranged from 0.95 to 0.98 and RMSEA's that ranged from 0.039 to 0.064 across the time points (supplemental Table 1). Most factor loadings (especially those on the CA factor) were very stable across time-points with the largest variability for 'sense of punishment' and 'feeling guilty' (max factor loading difference over time: 0.14). On SA, items showed rather stable loadings as well, although the

differences of the factor loadings over time were larger, ranging from 0.07 for 'work inhibition' to 0.30 for 'crying'. Factor covariances/correlations were relatively stable over time (range: 0.65-0.79).

The CA and SA subscales were calculated next and showed consistent psychometric characteristics over time. For CA, the ordinal Cronbach's alpha coefficients ranged from 0.82 to 0.88. The ordinal alpha could not be estimated for CA at 3 months because of empty cells in the polychoric correlation matrix (due to many 0 responses); here the bivariate Cronbach's alpha was 0.70. For SA, the ordinal Cronbach's alpha coefficients ranged from 0.78 to 0.83. This indicated that the internal consistency of each scale was satisfactory, especially given the modest scale lengths (7 items each). Spearman's Correlations between the CA and SA scores were moderate (ρ=0.39-0.49) across time points. At all time-points, mean scale scores were higher for SA (mean scores ranging from 4.0 [SD=3.1] to 4.3 [SD=3.2] than for CA (mean scores ranging from 0.6 [SD=1.5] to 0.7 [SD=1.6]).

Parallel Processes latent class growth analysis

PP-LCGA models with one to seven classes were run (Table 1). BIC's steadily decreased and the BLRT was significant with each class addition, offering no definitive criteria for model-selection. However, the 4-7 class models all had at least one very small class (n<20), making them unsuitable for use in consecutive statistical analyses. Therefore, based on its superior model-fit compared to the 1- and 2-class models and its superior usefulness compared to the 4-7 class models, the 3-class model was selected for use in further analyses.

The 3-class model consisted of classes of patients with either similar or different trajectories on CA and SA (Figure 1). Class 1 ('low severity') showed low levels of CA and SA at all time-points. Class 2 ('somatic persistence') showed low levels of CA at all time-

points and persisting high levels of SA over time. Class 3 ('overall persistence') showed high levels of both CA and SA that increased over time. Adding a quadratic term to the 3-class model did not improve model-fit (BIC=14253), suggesting that a model with linear growth-trajectories was optimal.

Class-characteristics

Classes differed significantly on age, gender, living situation, GRACE score, prevalence of post-MI depression, current GAD, and treatment by a health care worker for psychological complaints (Table 2). All groups differed significantly from each other on age (p's ranging from p<.001- 0.018), with mean age being highest for patients in class 2 (somatic persistence) and lowest for patients in class 3 (overall persistence). Also, patients in classes 2 and 3 were significantly more likely to be female than patients in class 1 (low severity) (class 2 versus class 1 p<0.001; class 3 versus class 1 p=0.03) and patients in class 2 were more likely to live alone than patients in class 1 (p<0.001). Patients in class 2 had a significantly higher GRACE score compared with patients in classes 1 (p=0.002) and 3 (p=0.001). Prevalence of post-MI depression was elevated in classes 2 (p<0.001) and 3 (p<0.001) versus class 1. Additionally, prevalence of current GAD was highest in class 3 (p<0.001 compared with class 1 and p=0.03 compared with class 2), but prevalence in class 1 was lower than in class 2 (p<0.001). Patients in class 3 were most likely to receive treatment by a health care worker for psychological complaints but prevalence did not differ significantly from class 2 (p=0.19) while both classes differed significantly from class 1 (p<0.001).

All-cause mortality

91 (20.0%) patients died during the follow-up period. For 40 of these patients (44.0%) the cause of death was cardiac in nature. According to the log rank test, there was a significant difference in survival among the classes (p=0.001). In unadjusted analyses, patients with persistent SA symptoms (class 2) were at increased risk of all-cause mortality compared with patients with low depressive symptoms (class 1) (Hazard Ratio [HR]: 2.14; 95% CI: 1.39-3.29; p=0.001). Overall persistent depressive symptoms (class 3) were not significantly associated with survival (HR: 0.77; 95% CI: 0.28-2.13; p=0.62). Also after adjustment for gender and GRACE score only somatic persistence was an independent predictor of mortality compared with low depressive symptoms (Table 3 and Figure 2).[1] Results did not change after additional adjustment for the presence of cardiovascular events and presence of a depressive episode between 0 and 12 months after the index MI.

Non-fatal cardiovascular events

117 (26.9%) patients had at least 1 non-fatal cardiovascular related readmission during the follow-up period. The log rank test did not show a statistically significant difference between the classes on this endpoint (p=0.63). In unadjusted analyses, neither patients with persistent SA symptoms (class 2) (HR: 0.93; 95% CI: 0.59-1.47; p=0.76) or patients with overall persistent depressive symptoms (class 3) (HR: 1.33; 95% CI: 0.69-2.57; p=0.39) were at a statistically significant increased risk of non-fatal cardiovascular events compared with patients with low depressive symptoms (class 1). Associations remained non-significant after adjustment for gender and GRACE score (Table 3). Also, adjustment for the presence of cardiovascular events and presence of a depressive episode between 0 and 12 months after the index MI did not change the results.

Discussion

To our knowledge, this re-analysis study of the DepreMI cohort is the first study that examined whether MI patients can be empirically classified based on concurrent course trajectories of depressive symptom dimensions. While previous reports of the DepreMI cohort showed the existence of different depressive symptom dimensions at baseline [de Jonge et al., 2006a] and different trajectories of depressive symptoms in the post-MI year [Kaptein et al., 2006], the PP-LCGA conducted in this study combined these two sources and confirmed that MI patients differ on severity and course of CA and SA depressive symptoms. The largest underlying class consisted of patients without depressive symptoms (low severity), followed by patients with persistent SA depressive symptoms only (somatic persistence). Relatively few patients (6.8%) were classified as having overall persistence (high and increasing CA and SA symptoms). Consistent with our hypothesis, the subgroup of patients in the somatic persistence class was at an increased risk of all-cause mortality at follow-up, compared with patients with low severity, after adjustment for sex and GRACE score. However, patients in the overall persistence class (who also experienced SA symptoms) were not at an increased risk of all-cause mortality, which was unexpected, especially with regard to the previously published finding by Kaptein et al., [2006a], who found that particularly patients with high and increasing levels of depressive symptoms were at risk of cardiovascular events. Finally, we found no significant associations between the different classes and recurrent non-fatal cardiovascular events.

By use of PP-LCGA, the current study confirms the existence of different types of depressive symptoms in patients with ACS, which was proposed in the model by Ormel & de Jonge [2011], that are accompanied by differences in demographic characteristics, medical characteristics, and measures of psychopathology. Patients in the somatic persistence class were more likely to be older women with a high GRACE score, unlike patients in the overall persistence class who were relatively young and had the lowest mean GRACE score. On the

other hand, the prevalence of a Killip score ≥ 2 suggests that these patients were more likely to have clinical signs of heart failure. Patients with overall persistence were more likely to have comorbid GAD and to receive treatment from a health care worker than patients with somatic persistence, although this difference was not statistically different for treatment by a health care worker.

Ormel & de Jonge [2011] suggested that SA depressive symptoms and CA depressive symptoms may have different etiologies [Ormel & de Jonge, 2011]. Results provided by the PP-LCGA in the current study additionally suggest that SA depressive symptoms in MI patients with SA depressive symptoms only, may have a different origin than SA depressive symptoms in patients who experience both CA and SA depressive symptoms. Potentially, SA depressive symptoms in patients with overall persistence reflect "typical depression", originating from a combination of vulnerability factors and stressful life events [Ormel & de Jonge, 2011]. Atherosclerotic processes and systemic inflammation might lead to sickness behavior that can account for the reporting of SA depressive symptoms in patients with somatic persistence [Ormel & de Jonge, 2011; Poole et al., 2011].

Contrary to our expectations we did not find a significant relationship between the somatic persistence, or the overall persistence class, with non-fatal cardiovascular events. This finding appears to be in contrast with previously published studies of this cohort [Kaptein et al., 2006 and de Jonge et al., 2006a], although these studies did not separate non-fatal from fatal cardiovascular events. Also, although a study that combined data from DepreMI with data from another study found a significant association between depressive symptoms and non-fatal cardiovascular events, this association was weaker compared with the associations found for mortality [Zuidersma, Conradi, van Melle, Ormel, de Jonge, 2013]. In addition, our findings are also in line with meta-analyses that showed that depressive symptoms following MI are a stronger predictor of mortality than cardiovascular events

[Meijer et al., 2011; Meijer et al., 2013a], suggesting that the potential effect of depression on medical illness is not specific for heart disease. On the other hand, it could also be that depressive symptoms are only predictive of specific events, such as (acute) ischemic events, or that only specific depressive symptoms, excluded from our study, are related to non-fatal cardiac events, or that depressive symptoms are predictive of non-fatal cardiovascular events at short-term but not at long-term follow-up.

Interestingly, the somatic persistence class remained an independent predictor of all-cause mortality after adjustment for GRACE score. As mentioned above, potential mediators of this association include inflammation and adverse health behaviors. However, since it is impossible to completely rule out a potential confounding effect of the medical condition in observational research [Meijer, Zuidersma, & de Jonge, 2013b], this association may still be the result of underlying heart disease, in which persistent SA depressive symptoms reflect general somatic complaints originating from the medical condition. Future research is needed in order to determine whether depression is an actual causal risk factor for heart disease, or only a risk marker [Meijer et al., 2013b; Hare, Toukhsati, Johansson, & Jaarsma, 2014]. To this end, research should go beyond simple models and take into account, amongst others, the heterogeneity of the depression construct and differences between individuals [de Jonge & Roest, 2012]. Previous studies in psychiatric patients for example showed that major depressive disorder is associated with more somatic symptoms in females [Schuch, Roest, Nolen, Penninx, & de Jonge, 2014] and in patients with comorbid medical conditions [Yates et al., 2007]. In addition, several studies have shown that depressive symptom presentation differs quantitatively and qualitatively across MI patients and psychiatric patients [Martens et al., 2006; Groenewold et al., 2013] and that the BDI-I can pick up somatic symptoms unrelated to depression [Delisle et al., 2012a; Delisle, Beck, Ziegelstein, & Thombs, 2012b]. The latter could be investigated in more detail in future studies by using item response theory

to compare the item-endorsement patterns on depression scales and compare them across different clinical groups [e.g. Wanders, Wardenaar, Kessler, Penninx, Meijer, & de Jonge, 2015].

This re-analysis study has several methodological strengths compared to the previously published reports of the DepreMI cohort that examined the course and type of depressive symptoms with adverse prognosis [e.g. Kaptein et al., 2006; de Jonge et al., 2006a], including a longer follow-up period, and a differentiation in (all-cause) mortality and non-fatal cardiovascular events as endpoints. Another important strength of the current study is the use of PP-LCGA to empirically classify patients on contemporaneous course trajectories of CA and SA depressive symptoms. The finding that SA depressive symptoms were predictive in the somatic persistence class, but not in the overall persistent class, exemplifies the added value of PP-LCGA to examine the associations between classes of persons and prognosis, instead of merely associations between symptom dimensions and adverse outcomes. The PP-LCGA resulted in a 3 class solution, while Kaptein et al., [2006] previously identified a 5 class solution on this sample. Potential reasons for this difference is that we distinguished courses on CA and SA depressive symptoms instead of overall depressive symptoms and used somewhat different criteria for selection, i.e. smallest class should include more than 20 persons. The different class solution might also be partly responsible for differences found in associations between classes and prognosis when comparing our results to the findings reported in Kaptein et al., [2006].

Another strength of the current study is the multivariable adjustment for GRACE score, which is a well-validated risk score for mortality after MI [Eagle et al., 2004]. The GRACE score is a composite score and the use of this mortality risk score is therefore especially suited in our study, since the classes differed in sample size and the number of patients included in the subgroup reflecting patients with high and increasing SA and CA was

relatively small. Still, power to detect statistically significant associations was reduced for this class, which is a limitation of the study. However, the finding that only 6.8% of MI patients had elevated CA depressive symptoms and were thereby classified to the overall persistence class, while 34.8% of patients were included in the somatic persistence class, suggests that the majority of evidence in the literature on this topic probably reflects the poor cardiovascular prognosis of patients with increased SA depressive symptomatology only. Previously published findings of the DepreMI cohort were not adjusted for GRACE score [e.g. Kaptein et al., 2006; de Jonge et al., 2006a] but were adjusted for LVEF, Killip class and previous MI. Notably, when we replaced GRACE score with these variables, results are comparable (data not shown). Yet, although we adjusted for GRACE score we did not adjust for specific risk factors of other potential causes of death, which is another limitation of this study since a significant number of patients died from other causes than cardiac disease.

Although we used a composite measure for mortality risk, the sample size still posed a restriction to the number of other covariates that could be included in the model. For example we did not take treatment of depressive symptoms into account. Thirty percent of patients in the overall persistence class received psychosocial or pharmacological treatment, which may have influenced their prognosis since some observational studies have suggested that selective serotonin reuptake inhibitors might reduce subsequent cardiovascular morbidity and mortality, although this has not yet been shown in a randomized controlled trial [Taylor et al., 2005; Pizzi, Rutjes, Costa, Fontana, Mezzetti, & Manzoli, 2011]. In addition, information on treatment for depression, or on other variables besides hospital admissions and mortality, was not available during the follow-up period. Also, depressive symptom trajectories were not assessed after the first year post-MI, therefore there is a lack of information on whether these symptoms persisted or not, which might influence study outcomes.

Another important limitation of the current study is the exclusion of BDI-I items that loaded on both the CA and the SA factor, i.e. sadness, pessimism, dissatisfaction, social withdrawal, and indecisiveness. This may be especially problematic since the core symptom "sadness" was excluded. In addition, several symptoms were excluded that have previously been used to create measures of anhedonia and hopelessness, for which specific associations were found with adverse cardiovascular outcomes following ACS [Davidson et al., 2010; Denollet, Freedland, Carney, de Jonge, & Roest, 2013]. Exclusion of these items might be another explanation for the slightly different results in the current study compared with previously published findings of this sample [Kaptein et al., 2006]. Finally, differences between those who provided the needed BDI data and those who did not could have led to some selection bias.

In summary, this re-analysis study shows that post-MI patients can be grouped in different classes based on severity and course of SA and CA depressive symptoms. These differences are additionally reflected by differences in demographic variables, and medical and psychological factors. Compared with patients with low depressive symptoms, only a subgroup of patients characterized by merely persistent SA depressive symptoms was at an increased risk of all-cause mortality. Our results are suggestive of different origins of SA depressive symptoms in MI patients with only SA depressive symptoms and patients with both SA and CA depressive symptoms, which may explain the differential associations with all-cause mortality.

References

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J (1961). An inventory for

measuring depression. *Archives of General Psychiatry, 4,* 561-571. doi:

10.1001/archpsyc.1961.01710120031004

Bekke-Hansen S., Trockel, M., Burg, M. M., & Taylor, C. B. (2012). Depressive symptom

dimensions and cardiac prognosis following myocardial infarction: results from the

ENRICHD clinical trial. *Psychological Medicine, 42,* 51-60. doi:

10.1017/S0033291711001000

Davidson, K. W., Burg, M. M., Kronish, I. M., Shimbo, D., Dettenborn, L., … Rieckmann, N.

(2010). Association of anhedonia with recurrent major adverse cardiac events and

mortality 1 year after acute coronary syndrome. Archives of General Psychiatry, 67,

480-488. doi: 10.1001/archgenpsychiatry.2010.36

Davidson, K. W., Kupfer, D. J., Bigger, J. T., Califf, R. M., Carney, R. M., … Suls, J. M.;

National Heart, Lung, and Blood Institute Working Group. Assessment and treatment

of depression in patients with cardiovascular disease: National Heart, Lung, and

Blood Institute Working Group Report. (2006). *Psychosomatic Medicine, 68,* 645-650.

doi: 10.1097/01.psy.0000233233.48738.22

de Jonge, P., Ormel, J., van den Brink, R. H., van Melle, J. P., Spijkerman, T. A., … Schene,

A. H. (2006a). Symptom dimensions of depression following myocardial infarction

and their relationship with somatic health status and cardiovascular prognosis.

American Journal of Psychiatry, 163, 138-144. doi:

http://dx.doi.org/10.1176/appi.ajp.163.1.138

de Jonge, P., van den Brink, R. H., Spijkerman, T. A., & Ormel, J. Only incident depressive

episodes after myocardial infarction are associated with new cardiovascular events. (2006b) *Journal of the American College of Cardiology, 48,* 2204-2208. doi: http://dx.doi.org/10.1016/j.jacc.2006.06.077

de Jonge, P., & Roest, A. M. (2012). Depression and cardiovascular disease: the end of simple models. *British Journal of Psychiatry, 201,* 337-338. doi: 10.1192/bjp.bp.112.110502

de Miranda Azevedo, R., Roest, A. M., Hoen, P. W., & de Jonge, P. (2014). Cognitive/affective and somatic/affective symptoms of depression in patients with heart disease and their association with cardiovascular prognosis: a meta-analysis. *Psychological Medicine, 27,* 1-15. doi: 10.1017/S0033291714000063

Delisle, V. C., Abbey, S. E., Beck, A. T., Dobson, K. S., Dozois, D. J., … Thombs B. D. (2012a). The influence of somatic symptoms on Beck Depression Inventory scores in hospitalized postmyocardial infarction patients. *Canadian Journal of Psychiatry, 57,* 752-758.

Delisle, V. C., Beck, A. T., Ziegelstein, R. C., & Thombs, B. D. (2012b). Symptoms of heart disease or its treatment may increase Beck Depression Inventory Scores in hospitalized post-myocardial infarction patients. *Journal of Psychosomatic Research, 73,* 157-162. doi: 10.1016/j.jpsychores.2012.07.001

Denollet, J., Freedland, K. E., Carney, R. M., de Jonge, P., & Roest, A. M. (2013). Cognitive-affective symptoms of depression after myocardial infarction: different prognostic importance across age groups. *Psychosomatic Medicine, 75,*701-8. doi: 10.1097/PSY.0b013e31829dbd36

Doyle, F., McGee, H., Delaney, M., Motterlini, N., & Conroy, R. (2011). Depressive

vulnerabilities predict depression status and trajectories of depression over 1 year in persons with acute coronary syndrome. *General Hospital Psychiatry, 33*, 224-231. doi: 10.1016/j.genhosppsych.2011.03.008

Eagle, K. A., Lim, M. J., Dabbous, O. H., Pieper, K. S., Goldberg, R. J., … Fox, K. A.; GRACE Investigators. (2004). A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *Journal of the American Medical Association, 291*, 2727-2733. doi: 10.1001/jama.291.22.2727

Frasure-Smith, N., & Lespérance F. (2003). Depression and other psychological risks following myocardial infarction. *Archives of General Psychiatry, 60*, 627-636. doi: 10.1001/archpsyc.60.6.627

Gadermann, A.M., Guhn, M., & Zumbo, B.D. (2012). Estimating ordinal reliability for Likert-type and ordinal item response data: a conceptual, empirical, and practical guide. *Practical Assessment, Research & Evaluation*, *17,* 1-13.

Groenewold, N. A., Doornbos, B., Zuidersma, M., Vogelzangs, N., Penninx, B. W., … de Jonge, P. (2013). Comparing cognitive and somatic symptoms of depression in myocardial infarction patients and depressed patients in primary and mental health care. *PLoS One, 8,* e53859. doi: 10.1371/journal.pone.0053859

Hare, D. L., Toukhsati, S. R., Johansson, P., & Jaarsma, T. (2014). Depression and cardiovascular disease: a clinical review. *European Heart Journal, 35,* 1365-1372. doi: 10.1093/eurheartj/eht462

Kaptein, K. I., de Jonge, P., van den Brink, R. H., & Korf, J. (2006). Course of depressive

symptoms after myocardial infarction and cardiac prognosis: a latent class analysis.

Psychosomatic Medicine, 68, 662-668. doi: 10.1097/01.psy.0000233237.79085.57

Martens, E. J., Denollet, J., Pedersen, S. S., Scherders, M., Griez, E., … Appels, A. (2006).

Relative lack of depressive cognitions in post-myocardial infarction depression.

Journal of Affective Disorders, 94, 231-237. doi:

http://dx.doi.org/10.1016/j.jad.2006.04.023

Martens, E. J., Hoen, P. W., Mittelhaeuser, M., de Jonge, P., & Denollet, J. (2010). Symptom

dimensions of post-myocardial infarction depression, disease severity and cardiac

prognosis. *Psychological Medicine, 40,* 807-814. doi: 10.1017/S0033291709990997

Martens, E. J., Smith, O. R., Winter, J., Denollet, J., & Pedersen, S. S. (2008). Cardiac history,

prior depression and personality predict course of depressive symptoms after

myocardial infarction. *Psychological Medicine, 38,* 257-264. doi:

http://dx.doi.org/10.1017/S0033291707001377

Meijer, A., Conradi, H. J., Bos, E. H., Anselmino, M., Carney, R. M., … de Jonge, P. (2013a).

Adjusted prognostic association of depression following myocardial infarction with

mortality and cardiovascular events: individual patient data meta-analysis. *British

Journal of Psychiatry, 203*, 90-102. doi: 10.1192/bjp.bp.112.111195

Meijer, A., Conradi, H. J., Bos, E. H., Thombs, B. D., van Melle, J. P., & de Jonge, P. (2011).

Prognostic association of depression following myocardial infarction with mortality

and cardiovascular events: a meta-analysis of 25 years of research. *General Hospital

Psychiatry, 33,* 203-216. doi: 10.1016/j.genhosppsych.2011.02.007

Meijer, A., Zuidersma, M., & de Jonge, P. (2013b). Depression as a non-causal variable risk

marker in coronary heart disease. *BMC Medicine, 11,* 130. doi: 10.1186/1741-7015-

11-130

Meurs, M., Zuidersma, M., Dickens, C., & de Jonge, P. (2013). Examining the relation

between post myocardial infarction depression and cardiovascular prognosis using a

validated prediction model for post myocardial mortality. International Journal of

Cardiology, 167, 2533-2538. doi: 10.1016/j.ijcard.2012.06.042

Murphy, B. M., Elliott, P. C., Worcester, M. U., Higgins, R. O., Le Grande, … Goble, A. J.

(2008). Trajectories and predictors of anxiety and depression in women during the 12

months following an acute cardiac event. *British Journal of Health Psychology, 13,*

135-153. doi: 10.1348/135910707X173312

Muthén, B. O. (2004) Latent variable analysis: Growth mixture modeling and related

techniques for longitudinal data. In: Kaplan D., (editor), *Handbook of quantitative*

methodology for the social sciences (pp. 345-368)*. Newbury Park, CA: Sage

Publications.

Muthén, L. K., & Muthén, B. O. (1998-2007). *Mplus user's guide. 5th ed.* Los Angeles, CA:

Muthén & Muthén.

Nagin, D. S., & Odgers, C. L. (2010). Group-based trajectory modeling in clinical research.

Annual Review of Clinical Psychology, 6, 109-138. doi:

10.1146/annurev.clinpsy.121208.131413

Nagin, D. S., & Tremblay, R. E. (2001). Analyzing developmental trajectories of distinct but

related behaviors: a group-based method. *Psychological Methods, 6,* 18-34. doi:

10.1037/1082-989X.6.1.18

Ormel, J., & de Jonge, P. (2011). Unipolar depression and the progression of coronary artery

disease: toward an integrative model. *Psychotherapy and Psychosomatics, 80,* 264-

274. doi: 10.1159/000323165

Pizzi, C., Rutjes, A. W., Costa, G. M., Fontana, F., Mezzetti, A., & Manzoli, L. (2011). Meta-

analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. *American Journal of Cardiology, 107*, 972-979. doi: 10.1016/j.amjcard.2010.11.017

Poole, L., Dickens, C., & Steptoe, A. (2011). The puzzle of depression and acute coronary syndrome: reviewing the role of acute inflammation. *Journal of Psychosomatic Research, 7,* 61-68. doi: 10.1016/j.jpsychores.2010.12.009

Revelle, W. (2014). Package 'psych'(version 1.4.8.11). Retrieved from http://cran.rproject.org/web/packages/psych/psych.pdf (January 20, 2015)

Roest, A. M., Thombs, B. D., Grace, S. L., Stewart, D.E., Abbey, S. E., & de Jonge, P. (2011). Somatic/affective symptoms, but not cognitive/affective symptoms, of depression after acute coronary syndrome are associated with 12-month all-cause mortality. *Journal of Affective Disorder, 131*, 158-163. doi: 10.1016/j.jad.2010.11.018

Roest, A. M., Zuidersma, M., & de Jonge, P. (2012). Myocardial infarction and generalised anxiety disorder: 10-year follow-up. *British Journal of Psychiatry, 200*, 324-329. doi: 10.1192/bjp.bp.111.103549.

Rubin, D. B. (1987). *Multiple Imputation for Nonresponse in Surveys.* New York: John Wiley & Sons.

Schuch, J. J., Roest, A. M., Nolen, W. A., Penninx, B. W., & de Jonge, P. (2014). Gender differences in major depressive disorder: results from the Netherlands study of depression and anxiety. *Journal of Affective Disorders, 156,* 156-163. Doi: 10.1016/j.jad.2013.12.011

Smolderen, K. G., Spertus, J. A., Reid, K. J., Buchanan, D. M., Krumholz, H. M., … Chan, P. S. (2009). The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. *Circulation.*

Cardiovascular Quality and Outcomes, 2, 328-337. doi:

10.1161/CIRCOUTCOMES.109.868588

Spijkerman, T., de Jonge, P., van den Brink, R. H., Jansen, J. H., May, J. F., … Ormel, J.

(2005a). Depression following myocardial infarction: first-ever versus ongoing and

recurrent episodes. *General Hospital Psychiatry, 27,* 411-417. doi:

http://dx.doi.org/10.1016/j.genhosppsych.2005.05.007

Spijkerman, T. A., van den Brink, R. H., Jansen, J. H., Crijns, H. J., & Ormel, J. (2005b).

Who is at risk of post-MI depressive symptoms? *Journal of Psychosomatic Research,*

58, 425-432. doi: http://dx.doi.org/10.1016/j.jpsychores.2005.02.005

Spijkerman, T. A., van den Brink, R. H., May, J. F., Winter, J. B., van Melle, J. P., … Ormel,

J. (2006). Decreased impact of post-myocardial infarction depression on cardiac

prognosis? *Journal of Psychosomatic Research, 61*, 493-499. doi:

http://dx.doi.org/10.1016/j.jpsychores.2006.02.016

Taylor, C. B., Youngblood, M. E., Catellier, D., Veith, R. C., Carney, R. M., … Jaffe, A. S.;

ENRICHD Investigators. (2005). Effects of antidepressant medication on morbidity

and mortality in depressed patients after myocardial infarction. *Archives of General*

Psychiatry, 62, 792-798. doi: 10.1001/archpsyc.62.7.792

Thombs, B. D., Bass, E. B., Ford, D. E, Stewart, K. J., Tsilidis, K. K., … Ziegelstein, R. C.

(2006). Prevalence of depression in survivors of acute myocardial infarction. *Journal*

of General Internal Medicine, 21, 30-38. doi: 10.1111/j.1525-1497.2005.00269.x

Wanders, R. B. K., Wardenaar, K. J., Kessler, R. C., Penninx, B. W., Meijer, R. R., & de

Jonge, P. (2015). Differential reporting of depressive symptoms across distinct

clinical subpopulations: What DIFference does it make? *Journal of Psychosomatic*

Research, 78, 130-136. doi: 10.1016/j.jpsychores.2014.08.014

Wittchen, H. U. (1994). Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *Journal of Psychiatric Research, 28,* 57-84. doi: http://dx.doi.org/10.1016/0022-3956(94)90036-1

Yates, W. R., Mitchell, J., John Rush, A., Trivedi, M., Wisniewski, S. R., … Gaynes, B. N. (2007). Clinical features of depression in outpatients with and without co-occurring general medical conditions in STAR*D: confirmatory analysis. *Primary Care Companion to the Journal of Clinical Psychiatry, 9,* 7-15.

Zuidersma, M., Conradi, H. J., van Melle, J. P., Ormel, J., & de Jonge, P (2013). Self-reported depressive symptoms, diagnosed clinical depression and cardiac morbidity and mortality after myocardial infarction. International Journal of Cardiology, 167, 2775-2780. doi: 10.1016/j.ijcard.2012.07.002

Footnotes

[1] Results for the association between depressive symptom classes and outcome were not adjusted for age, since age is included in the GRACE score. When analyzing the data using age as a covariate instead of the GRACE score, or in addition to the GRACE score, the results did not differ.

Table 1. Parallel Processes latent class growth analysis with the cognitive/affective and somatic/affective subscales across time points

	DF	BIC[1]	BLRT	Smallest class size, n (%)	Range of posterior class probabilities
1-class	12	16127	-	-	-
2-class	17	14838	<.001	42 (9.3%)	0.986-0.997
3-class[2]	**22**	**14251**	**<.001**	**31 (6.8%)**	**0.937-0.975**
4-class	27	14003	<.001	13 (2.8%)	0.924-0.999
5-class	32	13866	<.001	12 (2.6%)	0.861-0.998
6-class	37	13772	<.001	11 (2.4%)	0.964-0.999
7-class	42	13664	<.001	11 (2.4%)	0.862-0.998

BIC=Bayesian Information Criterion; BLRT=Bootstrapped Likelihood Ratio Test; DF=degrees of freedom;.

[1]All model estimations based on robust maximum likelihood (MLR). BIC and BLRT are fit indices that can be used for model selection, the lowest BIC indicates the preferred model, and the BLRT tests whether adding an additional class leads to a significant increase in model fit compared to the previous model.

[2]The 3- class model was selected for use in further analyses based on model-fit (BIC and BLRT) compared to the 1- and 2-class models and the number of patients in the smallest class (≥ 20).

Table 2. Comparison of the classes obtained with Parallel Processes latent class growth analysis

	Total N=457	Class 1 Low severity N=316	Class 2 Somatic persistence N=110	Class 3 Overall persistence N=31	Test statistic	Effect size	p
Demographic characteristics							
					F statistic	Eta squared	
Age, years *mean (SD)*	61 (11.4)	60 (11.0)^a	63 (12.0)^b	55 (11.0)^c	7.2	0.03	0.001*
					χ^2	Cramer's V	
Female gender, *n (%)*	86 (18.8)	38 (12.0)^a	40 (36.4)^b	8 (25.8)^b	32.7	0.27	<.001*
Living alone, *n (%)*	68 (15.1)	33 (10.7)^a	29 (26.6)^b	6 (19.4)^{ab}	16.4	0.19	<.001*
Primary school only, *n (%)*	80 (18.4)	44 (14.8)	30 (28.3)	6 (20.0)	9.6	0.15	0.008
Clinical characteristics							
					F statistic	Eta squared	
Body mass index, *mean (SD)*	26.7 (3.9)	27.0 (4.0)	26.4 (4.0)	25.5 (2.7)	2.3	0.01	0.10
CPK, *mean (SD)* [1]	1327 (1452.7)	1368 (1270.5)	1265 (1859.5)	1138 (1580.4)	4.3	0.02	0.014
CPK-MB, *mean (SD)* [1]	119 (131.1)	125 (123.0)	106 (137.7)	105 (179.0)	4.4	0.02	0.013
GRACE score, *mean (SD)* [2]	106 (28.0)	104 (25.9)^a	114 (33.0)^b	95 (24.2)^a	7.6	0.03	0.001*
					χ^2	Cramer's V	
Anterior site of MI, *n (%)*	145 (31.7)	93 (29.4)	37 (33.6)	15 (48.4)	4.9	0.10	0.085
Cardiovascular events between 0 and 12 months, *n (%)*	96 (21.0)	67 (21.2)	21 (19.1)	8 (25.8)	0.7	0.04	0.71
Current smoking, *n (%)*	203 (51.5)	134 (49.4)	51 (52.0)	18 (72.0)	4.7	0.11	0.097
Diabetes, *n (%)*	44 (9.6)	26 (8.2)	13 (11.8)	5 (16.1)	2.8	0.08	0.24
Family history of cardiovascular disease, *n (%)*	174 (38.1)	127 (40.2)	32 (29.1)	15 (48.4)	5.8	0.11	0.06

History of cardiovascular disease, *n (%)*[3]	94 (20.6)	58 (18.4)	29 (26.4)	7 (22.6)	3.3	0.09	0.19
Hypercholesterolemia, n (%)	164 (35.9)	118 (37.3)	35 (31.8)	11 (35.5)	1.1	0.05	0.58
Hypertension, *n (%)*	125 (27.4)	85 (26.9)	35 (31.8)	5 (16.1)	3.1	0.08	0.21
Invasive treatment of index MI, *n (%)*[4]	115 (29.3)	75 (28.3)	30 (30.0)	10 (35.7)	0.7	0.04	0.70
Killip class ≥2, *n (%)*	61(14.1)	33 (11.1)	20 (18.9)	8 (26.7)	8.0	0.14	0.018
LVEF <40%, *n (%)*	108 (23.7)	71 (22.5)	26 (23.6)	11 (35.5)	2.6	0.08	0.27
Psychopathology							
BDI score at baseline, *mean (SD)*	7 (5.5)	4 (3.0)	11 (5.3)	14 (5.9)			
BDI score at 3 months, *mean (SD)*	7 (5.8)	4 (2.9)	11 (4.6)	19 (7.3)			
BDI score at 6 months, *mean (SD)*	6 (5.9)	4 (2.8)	11 (4.9)	18 (5.7)			
BDI score at 12 months, *mean (SD)*	7 (6.1)	4 (3.1)	11 (4.3)	20 (8.7)			
Generalized anxiety disorder *n (%)*	25 (6.0)	6 (2.1)[a]	11 (10.6)[b]	8 (26.7)[c]	33.9	0.29	<.001*
Post-MI depression *n (%)*	63 (15.2)	14 (5.0)[a]	38 (36.5)[b]	11 (36.7)[b]	70.3	0.41	<.001*
Treatment by a health care worker, *n* (%)	44 (10.1)	15 (5.0)[a]	20 (18.9)[b]	9 (30.0)[b]	30.4	0.27	<.001*
Prognosis							
All-cause mortality, *n (%)*	91 (20.0)	53 (16.8)	34 (31.2)	4 (12.9)	11.6	0.16	0.003
Non-fatal cardiovascular events, *n (%)*	117 (26.9)	83 (27.1)	24 (24.0)	10 (34.5)	1.3	0.05	0.53

BDI= Beck Depression Inventory; CABG= coronary artery bypass graft; CPK= creatine phosphokinase; LVEF= left ventricular ejection fraction; MI= myocardial infarction; PCI= percutaneous coronary intervention.

*p value significant after Bonferroni adjustment (0.05 divided by 24 tests (p<0.002)). Means and frequencies with differing superscripts within rows are significantly different at p<.05 in post-hoc analyses.

[1] Log-transformations of CPK were used in analysis

[2] Brown-Forsyth F-ratio is reported

[3] history of MI, cerebral vascular disease or peripheral vascular disease

[4] PCI or CABG

Table 3. Associations between the depressive symptom classes and adverse outcomes[1]

	All-cause mortality			cardiovascular readmissions		
	HR	95% CI	p	HR	95% CI	p
Class 2: Somatic persistence[2]	1.86	1.18-2.94	0.008	0.97	0.61-1.56	0.91
Class 3: Overall persistence[2]	1.09	0.39-3.03	0.87	1.51	0.78-2.93	0.22
Female gender	0.90	0.53-1.50	0.68	0.81	0.48-1.36	0.42
GRACE score	1.03	1.02-1.04	<.001	1.01	1.00-1.02	0.02

[1]Analyses were performed on n=449 patients for all-cause mortality and 429 patients for the non-fatal cardiovascular events since 6 cases had missing data on GRACE score and 1 case was dropped for all-cause mortality as an endpoint because it was censored before the earliest event took place.
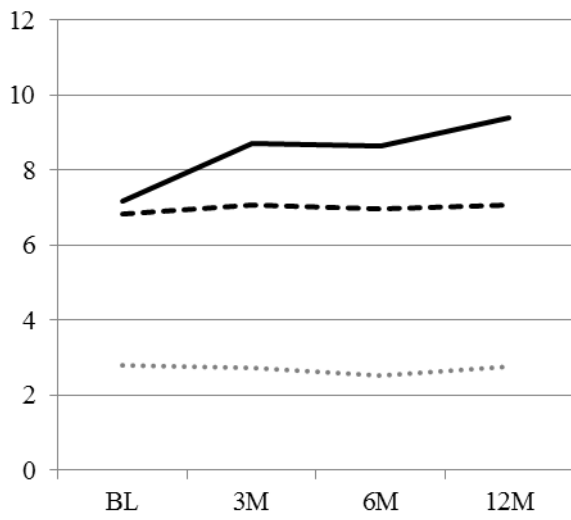
[2]Class 1 (low severity) was used as reference group.

Figure 1. Contemporaneous growth trajectories for the 3-class Parallel Processes latent class growth analysis classes
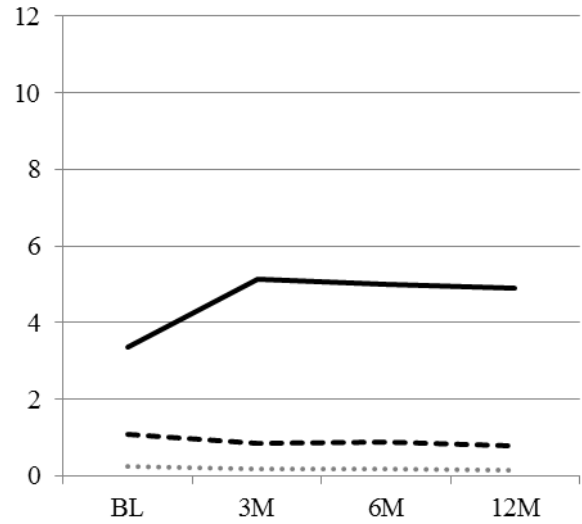
Somatic/affective   **Cognitive/affective**

Time points   Time points

Figure 2. Associations between the depressive symptom classes and all-cause mortality