Association of Recognized and Unrecognized Myocardial Infarction With Depressive and Anxiety Disorders in 125,988 Individuals

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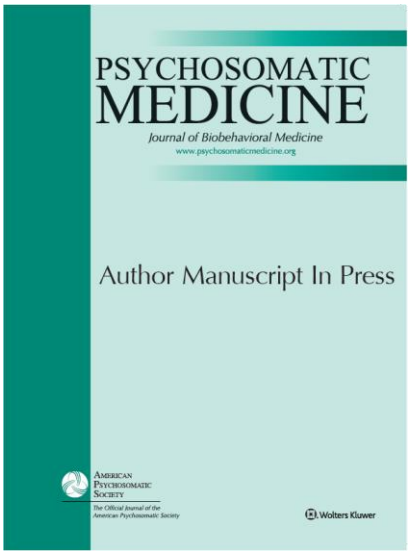

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Association of recognized and unrecognized myocardial infarction with depressive and anxiety disorders in 125,988 individuals: a report of the Lifelines Cohort Study

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Abstract

Objective: No previous study has focused on recognition of myocardial infarction (MI) and the presence of both depressive and anxiety disorders in a large population-based sample. The aim of this study was to investigate the association of recognized MI (RMI) and unrecognized MI (UMI) with depressive and anxiety disorders.

Methods: Analyses included 125,988 individuals enrolled in the Lifelines study. Current mental disorders according to the DSM-IV were assessed with the Mini International Neuropsychiatric Interview. UMI was detected using electrocardiography (ECG) in participants who did not report a history of MI. The classification of RMI was based on self-reported MI history together with either the use of antithrombotic medications or ECG signs of MI. Analyses were adjusted for age, sex, smoking, somatic comorbidities, and physical health-related quality of life as measured by the RAND 36-Item Health Survey in different models.

Results: Participants with RMI had significantly higher odds of having any depressive and any anxiety disorder as compared with participants without MI (depressive disorder: OR=1.86; 95%CI:1.38-2.52; anxiety disorder: OR=1.60; 95%CI:1.32-1.94) after adjustment for age and sex. Participants with UMI did not differ from participants without MI (depressive disorder: OR=1.60; 95%CI:0.96-2.64; anxiety disorder: OR=0.73; 95%CI:0.48-1.11). After additional adjustment for somatic comorbidities and low physical health-related quality of life, the association between RMI with any depressive disorder was no longer statistically significant

(OR=1.18; 95% CI:0.84-1.65), but the association with any anxiety disorder remained (OR=1.27; 95%CI:1.03-1.57).

Conclusions: Recognition of MI appears to play a major role in the occurrence of anxiety, but not depressive, disorders.

Keywords: Myocardial infarction, Depression, Anxiety, Epidemiology.

Abbreviations: AG=agoraphobia; CHD=coronary heart disease; DSM=diagnostic and statistical manual of mental disorders; ECG=electrocardiogram; GAD=generalized anxiety disorder; HRQOL=health-related quality of life; MDD=major depressive disorder; MCS=mental component summary; MINI=mini-international neuropsychiatric interview; MI=myocardial infarction; OR=odds ratio; PCS=physical component summary; PD=panic disorder; RMI=recognized myocardial infarction; SD=standard deviation; UMI=unrecognized myocardial infarction.

Introduction

The relationship between depression and coronary heart disease (CHD) has been extensively investigated, and numerous studies reported an association between both conditions, e.g. (1-4). The prevalence of depression is estimated to be two to three times higher in patients with CHD as compared to the general population (5). In a recent systematic review and meta-analysis, the pooled prevalence estimate of depression (combination of elevated depressive symptoms and depressive disorder) following myocardial infarction (MI) was 29%, with individual study estimates ranging from 9% to 66% (6). Further, depression is associated with an increased risk of mortality in patients with CHD (7-9). Similarly, the prevalence of anxiety appears to be as high as the prevalence of depression in patients with CHD (10). For example, a systematic review reported that the prevalence rate of generalized anxiety disorder (GAD) in patients with CHD was 11% to 14% (11). Anxiety is also predictive of mortality in patients with CHD (12, 13).

Ischaemic heart disease was the leading cause of burden of disease worldwide in 2010 (14). (Acute) MI is defined as myocardial necrosis resulting from myocardial ischemia (15, 16). Symptoms of myocardial ischemia include, amongst others, chest pain, and upper extremity, jaw, or epigastric discomfort (15). Yet, MI symptoms can also be minor, atypical (e.g. fatigue, dizziness), or non-existent, and therefore MI can go undetected. This phenomenon is known as silent MI or unrecognized MI (UMI) and can be detected using an electrocardiogram (ECG) (17, 18). In studies in younger individuals of the general population (i.e. mean age < 60 years), the prevalence of UMI ranged between 0.3 – 0.5% (17). The prevalence of UMI in older individuals (i.e. mean age > 60 years) ranged between 3.4 - 6.4% (17). In addition, ample research has shown that UMI is a predictor of adverse medical outcomes (e.g. (19-21).

Different theories exist on how MI may lead to depression and anxiety. The aetiology of post-MI depression and anxiety may be mainly psychological, due to the experience of a stressful life event, threatening one's health, well-being, and working life (5) and these reactive symptoms may range from adaptive to pathological (22). On the other hand, depression and anxiety may also result from physiological pathways, including inflammation (23-25), and autonomic imbalance (25).

Investigating the association between UMI and depressive or anxiety disorders might provide novel insights regarding the aetiology of post-MI depressive and anxiety disorders. To our knowledge, the association between UMI and anxiety disorders has not been studied before. One previous study in individuals aged 55 years or older, investigated the association between UMI and recognized MI (RMI) with depressive disorder (19). In this study only men with RMI, and not men with UMI, were at increased risk of developing depressive disorder compared to men without MI (19).

The aim of the current study was to investigate the association of RMI and UMI with depressive and anxiety disorders in a large population sample. Based on results of a previous study (19), we hypothesized that the odds of having depressive and anxiety disorders were significantly increased in participants with RMI when compared with participants without MI, but that the odds were not increased in participants with UMI.

Methods

Study design and participants

Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. Baseline data were collected between 2006 and 2013 (26). The Lifelines study sample has been shown to be broadly representative of the population in the north of the Netherlands (27). The Lifelines study is approved by the medical ethical committee of the University Medical Center Groningen, The Netherlands. Written informed consent was obtained after the procedure and methods of the study were explained to participants. In the current study, we excluded participants younger than 18 years (n=15,549). We also excluded 2,932 participants who received a Mini-international neuropsychiatric interview (MINI) focusing on past year mental disorders instead of current mental disorders. Participants were allowed to refuse participation in the MINI interview and participants who did not have an assessment of depressive and anxiety disorders (n=23,260) were also excluded; the latter number included 2,600 elderly participants with a Mini Mental State Examination score < 26 or who were unable to fill out questionnaires. Participants without a MINI assessment were more likely to be male (42.7% versus 41.3%, p<.001) and older (47.1[SD=15.5] versus 44.2 [SD=12.6] (p<0.001)), compared to participants with a MINI assessment.

Assessment of RMI and UMI

A previous publication assessed the prevalence of RMI and UMI in the Lifelines cohort (20). During the baseline visit, a 12-lead ECG was recorded. All ECG data were initially automatically processed using the WelchAllyn CardioPerfect software (version 1.6.2.1105). Potential abnormal ECGs were examined by an interventional cardiologist and classified as MI or no MI, based on "any Q wave in leads V2–V3 ≥ 0.02 s or QS complex in leads V2 and V3. Q wave ≥0.03 s and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF or V4–V6 in any two leads of a contiguous lead grouping (I, aVL; V–V6; II, III, aVF). R wave ≥0.04 s in V1–V2 and R/S ≥ 1 with a concordant positive T wave in absence of conduction defect" (20).

Questions on medical history and drug use were included in the baseline Lifelines questionnaire. The classification of RMI was based on the combination of self-reported medical history of MI together with ECG signs of MI, or self-reported history of MI together with use of antithrombotic medications (20). UMI was diagnosed in participants who did not report a history of MI but who had ECG signs suggestive of MI. Other participants were classified as not having had MI. After recognition of UMI the general practitioner of the participant was informed.

Depressive and anxiety disorders

Current depressive, i.e. major depressive disorder (MDD) or dysthymia, and anxiety disorders, i.e. panic disorder (PD) with or without agoraphobia (AG), AG without PD, social anxiety disorder and GAD were assessed through the MINI 5.0.0 at baseline. The MINI is a systematic interview and is administered for assessing depressive and anxiety disorders based on the diagnostic and statistical manual of mental disorders version IV (DSM-IV) (28). Dichotomous

items assessing the presence or absence of symptoms were used. The MINI has been found to be a valid and reliable interview and showed a good diagnostic concordance with the Structured Clinical Interview for DSM-III-R (28). Trained research assistants performed the MINI assessment.

Physical health-related quality of life

Health-related quality of life (HRQOL) was assessed through the RAND 36-Item Health Survey (RAND-36) (29). The RAND-36 consists of items distributed across eight scales on physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health. Each domain is scored from 0 to 100 with higher scores reflecting better health. The domain scores were standardized by linear z-score transformation to have a mean of 50 and a standard deviation (SD) of 10 in the US general population. The physical component summary (PCS) and the mental component summary (MCS), were constructed from these eight domains using recommended scoring algorithms. The PCS primarily reflects measures of physical functioning, pain, and role limitations caused by physical health problems while the MCS primarily reflects measures of emotional well-being and role limitations caused by emotional problems (30). The RAND-36 has been validated in the general population and across patient groups suffering from different medical conditions (31). In order to prevent overlap with depressive and anxiety disorders, only the PCS, and not the MCS, was used in the present study.

Statistical analysis

Descriptive statistics were reported for all variables. We checked for significant differences between participants with no MI, RMI, and UMI using ANOVA and chi-square tests, for continuous and nominal variables, respectively. In case the overall test was statistically significant, we examined which groups differed significantly from each other in post-hoc comparisons.

Logistic regression analyses were conducted to assess the association between the status of the MI and the occurrence of depressive and anxiety disorders. Odds ratios (ORs) were used to represent the risk of having any depressive and any anxiety disorder associated with MI status. For this purpose, two dummy variables of MI were included in the models, with "no MI" as reference category. The reference category was switched to "UMI" in order to directly compare the odds of depressive and anxiety disorders between RMI and UMI.

Five models were used to assess the association between MI status and the occurrence of depressive and anxiety disorders. In model 1, adjustment for age and sex was performed. In model 2, additional adjustment for self-reported history of somatic diseases related to MI (diabetes, kidney disease and heart failure) and smoking ("Do you currently smoke or have you smoked in the past month?") was performed. In model 3, additional adjustment for PCS was performed. Covariates were chosen based on previous literature. Diabetes, kidney disease, heart failure, smoking and physical HRQOL showed a significant association with depressive and anxiety symptoms in several previous studies (32-40) and may reflect a higher somatic burden in participants with RMI compared to participants with UMI. Depressive and anxiety disorders are

often comorbid (41). Models 4 and 5 present results for post-hoc analyses in which comorbidity of depressive and anxiety disorders was taken into account by adding comorbid anxiety or depressive disorder diagnoses.

All analyses were conducted using SPSS 25.0 (IBM Corp., Armonk, NY, USA) and significance level was set at .05 (two-tailed).

Results

The total sample for the current study included 125,988 participants (58.8% women) aged between 18 and 93 years (mean=44.3 years; standard deviation [SD]=12.6 years). Of the total sample 4,292 (3.4%) were classified as having any depressive disorder and 12,425 (9.9%) as having any anxiety disorder. RMI was present in 1068 (0.8%) participants and UMI in 346 (0.3%) participants.

Characteristics of participants according to MI status

Table 1 shows the baseline characteristics for the entire sample, and for participants without MI, those with UMI and those with RMI. Statistically significant differences across MI groups were found for age ($p<.001$), sex ($p<.001$), diabetes ($p<.001$), kidney disease ($p<.001$), heart failure ($p<.001$), PCS ($p<.001$), PD without AG ($p=0.021$), and AG without PD ($p=0.001$). When comparing UMI versus RMI in post-hoc comparisons, individuals with RMI were more likely to be older ($p<.001$), male ($p<.001$), and be diagnosed with diabetes ($p=0.009$) and heart failure ($p<.001$) compared with participants with UMI. In addition, participants with RMI had worse physical HRQOL as indicated by a lower PCS ($p<.001$) than participants with UMI. Finally,

participants with RMI were more likely to be diagnosed with AG without PD than participants with UMI (p=0.041) (see **Table 1)**.

Comparisons of participants with UMI and RMI with participants without MI for any depressive disorder

The odds of any depressive disorder were not significantly higher in participants with UMI versus participants without MI in any of the models (p=0.07-0.22) (see **Table 2**).

When adjusting for sex and age only (model 1), participants with RMI were at increased risk of any depressive disorder (OR=1.86; 95% CI: 1.38-2.52; p<.001) compared with participants without MI, but this association lost statistical significance after adjustment for somatic comorbidities and smoking in the second model (OR=1.38; 95% CI: 0.99-1.93; p=0.056). In the third model, younger age, female sex, smoking, diabetes, heart failure, and low physical HRQL (i.e. higher PCS was a protective factor) were statistically significant predictors of any depressive disorder **(Table 2)**.

Comparisons of participants with UMI and RMI with participants without MI for any anxiety disorder

The odds of any anxiety disorder were not significantly higher in participants with UMI versus participants without MI in any of the models (p=0.14-0.19) (see **Table 3**).

The odds of having any anxiety disorder were statistically significantly increased in participants with RMI as compared with participants without MI (OR= 1.60; 95%CI: 1.32-1.94;

p <.001) after adjustment for sex and age. This association reduced in strength but remained statistically significant after further adjustment for somatic comorbidities and smoking in model 2 (OR= 1.39; 95% CI: 1.13-1.71; p=0.002) and PCS in model 3 (OR= 1.27; 95% CI: 1.03-1.57; p=0.027). Other statistically significant predictors of any anxiety disorder in model 3 were younger age, female sex, smoking, diabetes, heart failure, and low physical HRQL (i.e. higher PCS was a protective factor) (**Table 3**).

Direct comparison of RMI and UMI in the association with any depressive and any anxiety disorder

Table 4 compares participants with RMI to participants with UMI in the association with any depressive and any anxiety disorder. No differences were found for RMI versus UMI in the association with any depressive disorder. However, participants with RMI were more likely to be diagnosed with any anxiety disorder compared to participants with UMI after adjustment for sex and age (OR= 2.20; 95% CI: 1.38-3.50; p=0.001) in model 1, and additional adjustment for diabetes, kidney disease, heart failure, smoking (OR= 1.86; 95% CI: 1.15-3.01; p=0.012) (model 2) and PCS (OR= 1.76; 95% CI: 1.09-2.87; p=0.022) (model 3).

Post-hoc analyses

Because the associations between MI statuses appeared to be qualitatively different for the endpoints of depressive and anxiety disorders respectively, post-hoc analyses adjusted for the presence of comorbid anxiety or depressive disorders. After adding comorbid anxiety disorder to the variables already included in model 2, participants with UMI were more likely to be diagnosed with any depressive disorder than participants without MI (OR= 1.83; 95% CI: 1.02-

3.28; p= 0.042) (**table 5,** model 4). Yet, there was no statistically significant difference between UMI and RMI (p=0.23). The association between UMI and any depressive disorder was no longer statistically significant after addition of the PCS in model 5 (OR= 1.73; 95% CI: 0.96-3.13; p= 0.071).

Participants with RMI were more likely than participants without MI and participants with UMI, to be diagnosed with any anxiety disorder after adding comorbid depressive disorder in model 4 (see **Table 5**). These associations between RMI and any anxiety disorder remained statistically significant after addition of the PCS in model 5 (RMI versus no MI: OR= 1.29; 95% CI: 1.03-1.62; p=0.029; RMI versus UMI: OR= 2.02; 95% CI: 1.20-3.41; p=0.008) (**Table 5**).

Discussion

To our knowledge, the current study is the first to examine the association between RMI, UMI, and depressive and anxiety disorders in a large population sample. Compared to participants without MI, those with RMI, but not those with UMI, were at increased risk of anxiety disorders. This association remained statistically significant after adjustment for age, sex, smoking, somatic comorbidities, and physical HRQOL. Regarding depressive disorders, the odds were significantly increased in participants with RMI, but not in participants with UMI, compared to participants without MI after adjustment for age and sex. Yet, after further adjustment for smoking, diabetes, kidney disease, heart failure, and physical HRQOL the association between RMI and depressive disorders was no longer statistically significant.

Our results differ from the only other study that examined the association between RMI and UMI with depressive disorders. This previous study found that in 1823 elderly men, RMI, but not UMI, was a significant predictor of depressive disorder. The authors concluded that a psychological, rather than a physiological pathway, is likely to be responsible for the increased risk of depressive disorders in patients with MI (19). The difference in findings may be explained by the inclusion of physical HRQOL as a covariate in our study. While there was a trend for statistical significance for the association between RMI and depressive disorders after adjustment for age, sex, smoking, and somatic comorbidities (OR: 1.38; 95% CI: 0.99-1.93; p=0.056), the OR reduced substantially after inclusion of physical HRQOL in the model (OR: 1.18; 95% CI: 0.84-1.65; p=0.34). These results suggest that the association between MI and depressive disorders is explained by reduced quality of life, especially in patients with RMI who may have more severe cardiac disease. In concordance with Jovanova et al., (19) we found no evidence for an association between UMI and depressive disorders in our main analysis. However, after adjustment for comorbid anxiety disorders, participants with UMI, and not those with RMI, were at increased risk of depressive disorders. Again, this association reduced to a trend for statistical significance after adjustment for physical HRQOL (OR: 1.73; 95% CI: 0.96-3.13; p=0.071). Yet, these results tentatively suggest that individuals who are not aware of having experienced MI might be at increased risk of depressive disorder, and this association is at least partly explained by reduced quality of life. Future research should replicate the current findings and could examine whether physiological mechanisms may mediate the association between UMI and depressive disorders specifically.

Recognition of MI appears to be a prerequisite in order to increase the risk of anxiety disorders in individuals with MI. When comparing RMI to UMI after full adjustment for covariates, participants with RMI were at increased risk of anxiety disorders both compared to participants without MI and participants with UMI. AG without PD was twice as common in the group of individuals with RMI versus individuals with UMI. Our results therefore suggest that recognition of MI is particularly strongly related to AG without PD. It could well be possible that participants who have experienced MI are more likely to avoid certain situations or places (one of the key symptoms of AG). The current study used DSM-IV criteria for AG, meaning that participants could only meet the criteria for AG when their anxiety concerned places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in *the event of having an unexpected or situationally predisposed panic attack or panic-like symptoms* (42). In DSM-5 individuals can meet criteria for AG also when they fear or avoid situations because of other incapacitating or embarrassing symptoms (43). This suggests that the prevalence of AG may be even higher in individuals with RMI when DSM-5 criteria are used, if a person's fear concerns for example cardiac symptoms or recurrent MI. In this respect, it is important to note that individuals who meet DSM-5 criteria for AG have shown to be severely and persistently impaired (44).

The present study has important strengths. The large sample of 125,988 participants enabled us with enough statistical power to examine the association between UMI and RMI with current depressive and anxiety disorders according to the DSM, in a population sample. Yet, because of the focus on point prevalence rates of DSM-IV mental disorders, the numbers for any current depressive disorder and current individual anxiety disorders were still quite low. Other

studies examining the prevalence of depression in individuals with MI generally used depressive symptom questionnaires, which inflated the prevalence rate of depression (6, 45). When compared to other studies using interviews to assess current mental disorders, the prevalence rates found in the current study appear to be valid. For example, the prevalence rate of MDD in the current study was comparable to the 30-day prevalence rate of MDD in population samples from high-income countries included in the World Mental Health surveys (46). Future research is warranted to study associations between the specific anxiety disorders and heart disease (10) and to replicate our findings for the association between RMI and AG.

A limitation of this study is that the prevalence of UMI may be underestimated, and cases with UMI missed, because of the use of ECG to detect UMI, instead of for example ultra-low-dose computed tomography. In general, ECG has shown modest sensitivity and reasonable specificity in identifying UMI (47). However, there is no reason to believe that participants with undetected UMI are more likely to have AG, therefore it is unlikely that a higher number of UMI cases would have changed the direction of the findings. In addition, we did not have adequate statistical power to examine interactions with sex. However, in sensitivity analysis we did not find suggestions for any sex differences in the association between MI status and depressive and anxiety disorders (p values interaction effects ranged between 0.12 and 0.74) (see Tables S1-S2, Supplemental Digital Content, for analyses stratified by sex). Another limitation of this study is that the cross-sectional design does not allow inference on the direction of the association between recognition of MI and the occurrence of depressive and anxiety disorders. Although the results suggest that a psychological pathway is responsible for the increased risk of anxiety in patients with MI, reverse causality cannot be ruled out, since anxiety and depression have been

shown to predict CHD onset in initially disease-free individuals (48-50). The lack of a positive association between UMI and increased risk of anxiety disorders may also be explained by increased help-seeking in anxious individuals leading to an increased chance of MI diagnosis in those individuals, and a decreased risk of anxiety disorders in individuals with UMI. On the other hand, this does not explain the high prevalence of AG, which is characterized by avoidance behaviour, in participants with RMI. Further, adjustment for left-ventricular ejection fraction, an important marker of heart disease severity, was not performed, as this variable has not been measured in Lifelines. Left-ventricular ejection fraction is related to depression in patients with MI, especially in men (51, 52), and partly accounts for the associations with adverse cardiac outcomes (52). Finally, the difference in the prevalence of somatic comorbidities between participants with UMI and RMI may be explained by further diagnostic testing in participants with RMI, while those comorbidities may also be present in participants with UMI. Yet, if this is the case we do not expect this to affect our results since we found very few significant associations for UMI in the prediction of anxiety or depressive disorders.

This study confirms the previously reported association between MI and anxiety disorders, and the risk of AG may be particularly increased following MI diagnosis. Of the anxiety disorders, AG is one of the least studied (53). The present results could stimulate further research into interventions for anxiety disorders, including AG, in patients with CHD, as has been argued before in a systematic review (10). On the other hand, future research could take a lifespan approach. The onset of anxiety disorders often lies in adolescence (44, 54). Ideally, studies would use a longitudinal design, examining bidirectional processes between cardiovascular parameters and anxiety, taking psychiatric and medical treatments into account

(55). For clinical practice these results argue for (more) awareness of potential AG and avoidance behaviour in patients who suffered MI. Addressing these avoidance behaviours may improve patients' quality of life and potentially their cardiac prognosis.

In summary, this study showed that recognition of the (stressful) event appears to play a major role in the occurrence of anxiety, but not depressive, disorders in individuals with MI. More research, using a lifespan perspective, is warranted to examine whether recognition of MI is especially important for the development and/or recurrence of AG.

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Conflict of interest

None.

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Table 1. Characteristics of participants in total sample and according to MI status

Characteristics*	**Total (N=125,988)**	**No MI N= 124,574**	**UMI N= 346**	**RMI N= 1,068**	**Overall, p**	**UMI vs. no MI, p**	**RMI vs. no MI, p**	**UMI vs. RMI, p**
Age, *mean (SD)*	44.3 (12.6)	44.1 (12.5)	54.2 (12.4)	60.8 (10.8)	<.001	<.001	<.001	<.001
Female sex, *n (%)*	74,062 (58.8)	73,656 (59.1)	173 (50.0)	233 (21.8)	<.001	0.001	<.001	<.001
Smoking, *n (%)*	25,951 (21.3)	25,681 (21.3)	75 (22.2)	195 (18.6)	0.10	-	-	-
Diabetes, *n (%)*	2940 (2.3)	2,760 (2.2)	30 (8.7)	150 (14.1)	<.001	<.001	<.001	0.009
Kidney disease, *n (%)*	648 (0.5)	630 (0.5)	1 (0.3)	17 (1.6)	<.001	0.58	<.001	0.065
Heart failure, *n (%)*	878 (0.7)	661 (0.5)	5 (1.5)	212 (20.2)	<.001	0.020	<.001	<.001
PCS, *mean* (*SD*)	52.9 (7.5)	52.9 (7.5)	51.0 (8.1)	48.0 (9.5)	<.001	<.001	<.001	<.001
Any depressive disorder, *n (%)*	4292 (3.4)	4,230 (3.4)	16 (4.7)	46 (4.3)	0.12	-	-	-
MDD, *n (%)*	2858 (2.3)	2,818 (2.3)	10 (2.9)	29 (2.7)	0.45	-	-	-
Dysthymia, *n (%)*	1434 (1.2)	1,411 (1.2)	6 (1.8)	17 (1.6)	0.20	-	-	-
Any anxiety disorder, *n (%)*	12,425 (9.9)	12,283 (9.9)	23 (6.6)	119 (11.1)	0.050	-	-	-
GAD, *n (%)*	5,457 (4.3)	5,403 (4.3)	13 (3.8)	41 (3.8)	0.63	-	-	-
SAD, *n (%)*	1,165 (0.9)	1,156 (0.9)	1 (0.3)	8 (0.7)	0.39	-	-	-
PD without AG, *n (%)*	2,904 (2.3)	2,886 (2.3)	2 (0.6)	16 (1.5)	0.021	0.032	0.076	0.19

PD with AG, *n (%)*	1,008 (0.8)	997 (0.8)	2 (0.6)	9 (0.8)	0.89	-	-	-
AG without PD, *n (%)*	4,089 (3.2)	4,024 (3.2)	9 (2.6)	56 (5.2)	0.001	0.51	<.001	0.041

AG= agoraphobia; GAD= generalized anxiety disorder; MDD=major depressive disorder; MI=myocardial infarction; PCS=physical component summary; PD=panic disorder; SAD=social anxiety disorder; SD=standard deviation; RMI=recognized myocardial infarction; UMI=unrecognized myocardial infarction.

*Missing values: smoking (n=4,082); diabetes (n=307); kidney disease (n=6,334); heart failure (n=1,664); PCS (n=375); any depressive disorder (n=505); any anxiety disorder (n=1).

ANOVA and chi-square tests were used for continuous and nominal variables respectively.

Table 2. Association between UMI and RMI with any depressive disorder

	Model 1			Model 2			Model 3		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
MI status									
No MI (reference category)	-			-			-		
UMI	1.60	0.96-2.64	0.070	1.49	0.87-2.57	0.15	1.41	0.82-2.44	0.22
RMI	1.86	1.38-2.52	<.001	1.38	0.99-1.93	0.056	1.18	0.84-1.65	0.34
Covariates									
Age	0.991	0.989-0.993	<.001	0.993	0.990-0.996	<.001	0.987	0.985-0.990	<.001
Female sex	1.77	1.65-1.89	<.001	1.83	1.70-1.97	<.001	1.68	1.56-1.81	<.001
Smoking				2.26	2.11-2.42	<.001	2.12	1.98-2.27	<.001
Diabetes				1.88	1.57-2.24	<.001	1.47	1.23-1.76	<.001
Kidney disease				1.56	1.07-2.26	0.020	1.31	0.90-1.90	0.17
Heart failure				2.30	1.71-3.08	<.001	1.75	1.30-2.35	<.001
PCS							0.949	0.946-0.952	<.001

CI=confidence interval; MI=myocardial infarction; OR=odds ratio; PCS=physical component summary; RMI=recognized myocardial infarction; UMI=unrecognized myocardial infarction.

Logistic regression analyses were conducted to assess the association between the status of the MI and the occurrence of any depressive disorder.

Table 3. Association between UMI and RMI with any anxiety disorder

	Model 1			Model 2			Model 3		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**p**
MI status									
No MI (reference category)	-			-			-		
UMI	0.73	0.48-1.11	0.14	0.75	0.48-1.16	0.19	0.72	0.47-1.12	0.14
RMI	1.60	1.32-1.94	<.001	1.39	1.13-1.71	0.002	1.27	1.03-1.57	0.027
Covariates									
Age	0.994	0.993-0.996	<.001	0.996	0.994-0.997	<.001	0.993	0.991-0.994	<.001
Female sex	1.83	1.76-1.91	<.001	1.88	1.80-1.97	<.001	1.80	1.73-1.89	<.001
Smoking				1.73	1.66-1.81	<.001	1.67	1.60-1.75	<.001
Diabetes				1.56	1.39-1.75	<.001	1.36	1.21-1.53	<.001
Kidney disease				1.35	1.05-1.72	0.018	1.22	0.95-1.56	0.12
Heart failure				1.50	1.21-1.85	<.001	1.27	1.03-1.58	0.027
PCS							0.968	0.966-0.971	<.001

CI=confidence interval; MI=myocardial infarction; OR=odds ratio; PCS=physical component summary; RMI=recognized myocardial infarction; UMI=unrecognized myocardial infarction.

Logistic regression analyses were conducted to assess the association between the status of the MI and the occurrence of any anxiety disorder.

Table 4. RMI versus UMI in the association with any depressive and any anxiety disorder

	Model 1			Model 2			Model 3		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
	Any depressive disorder								
MI status									
UMI (reference)	-			-			-		
No MI	0.63	0.38-1.04	0.070	0.67	0.39-1.15	0.15	0.71	0.41-1.22	0.22
RMI	1.12	0.65-2.10	0.60	0.93	0.49-1.74	0.81	0.83	0.44-1.58	0.58
	Any anxiety disorder								
UMI (reference)	-			-			-		
No MI	1.37	0.90-2.10	0.14	1.34	0.86-2.07	0.19	1.39	0.90-2.15	0.14
RMI	2.20	1.38-3.50	0.001	1.86	1.15-3.01	0.012	1.76	1.09-2.87	0.022

CI=confidence interval; MI=myocardial infarction; OR=odds ratio; PCS=physical component summary; RMI=recognized myocardial infarction; UMI=unrecognized myocardial infarction.

Covariates included in model 1: age and sex.

Covariates included in model 2: age, sex, diabetes, kidney disease, heart failure, and smoking.

Covariates included in model 3: age, sex, diabetes, kidney disease, heart failure, smoking, and PCS.

Logistic regression analyses were conducted to assess the association between the status of the MI and the occurrence of any depressive or any anxiety disorder.

Table 5. MI status and the association with any depressive and anxiety disorder after adjustment for depressive and anxiety disorder comorbidity (post-hoc analyses)

	Model 4			Model 5		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
	Any depressive disorder					
MI status						
UMI vs. no MI	1.83	1.02-3.28	0.042	1.73	0.96-3.13	0.071
RMI vs. no MI	1.21	0.85-1.73	0.30	1.04	0.72-1.49	0.85
RMI vs. UMI	0.66	0.34-1.30	0.23	0.60	0.30-1.20	0.15
	Any anxiety disorder					
UMI vs. no MI	0.65	0.40-1.04	0.074	0.64	0.40-1.02	0.062
RMI vs. no MI	1.37	1.09-1.71	0.007	1.29	1.03-1.62	0.029
RMI vs. UMI	2.11	1.25-3.56	0.005	2.02	1.20-3.41	0.008

CI=confidence interval; MI=myocardial infarction; OR=odds ratio; PCS=physical component summary; RMI=recognized myocardial infarction; UMI=unrecognized myocardial infarction.

Covariates included in model 4: age, sex, diabetes, kidney disease, heart failure, and smoking, and comorbid depressive or anxiety disorder depending on outcome.

Covariates included in model 5: age, sex, diabetes, kidney disease, heart failure, smoking, comorbid depressive or anxiety disorder depending on outcome, and PCS.

Logistic regression analyses were conducted to assess the association between the status of the MI and the occurrence of any depressive or any disorder.