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ORIGINAL ARTICLE

The long-term risk of recognized and unrecognized myocardial infarction for depression in older men

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Background. The association between myocardial infarction (MI) and depression is well described. Yet, the underlying mechanisms are unclear and the contribution of psychological factors is uncertain. We aimed to determine the risk of recognized (RMI) and unrecognized (UMI) myocardial infections on depression, as both have a similar impact on cardiovascular health but differ in psychological epiphenomena.

Method. Participants of the Rotterdam Study, 1823 men aged ⩾55 years, were followed for the occurrence of depression. RMI and UMI were ascertained using electrocardiography and medical history at baseline. We determined the strength of the association of RMI and UMI with mortality, and we studied the relationship of RMI and UMI with depressive symptoms and the occurrence of major depression.

Results. The risk of mortality was similar in men with RMI [adjusted hazard ratio (aHR) 1.71, 95% confidence interval (CI) 1.45–2.03] and UMI (aHR 1.58, 95% CI 1.27–1.97). Men with RMI had on average [unstandardized regression coefficient (*B*) 1.14, 95% CI 0.07–2.21] higher scores for depressive symptoms. By contrast, we found no clear association between UMI and depressive symptoms (*B* 0.55, 95% CI −0.51 to 1.62) in men. Analysis including occurrence of major depression as the outcome were consistent with the pattern of association.

Conclusion. The discrepant association of RMI and UMI with mortality compared to depression suggests that the psychological burden of having experienced an MI contributes to the long-term risk of depression.

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Key words: Depression, epidemiology, myocardial infarction, population based.

Introduction

The increased occurrence of depression after myocardial infarction (MI) is well-recognized in clinical practice (Frasure-Smith *et al.* 1993; Denollet *et al.* 2006; Park *et al.* 2012). In those that experienced MI, the prevalence of depression exceeds 30% (Frasure-Smith *et al.* 1993; Lesperance & Frasure-Smith, 2000). Several biological and pathophysiological pathways including inflammation and endothelial dysfunction might link MI and depression (Tiemeier *et al.* 2003; Harrison *et al.* 2013), but post-MI depression could also occur as a result of illness perception. Alterations in mood can be part of the coping process after surviving a cardiac event, treatment and recovery (Lesperance & Frasure-Smith, 2000).

MI is traditionally described as a clinical syndrome characterized with precordial discomfort and pain. Nevertheless, a substantial proportion of MIs are not clinically recognized by patients or treating physicians (Stokes & Dawber, 1959; de Torbal *et al.* 2006; Leening *et al.* 2012). The available epidemiological, clinical and basic science evidence provides support for a similar ischaemic pathology underlying both recognized (RMI) and unrecognized (UMI) myocardial infarctions (Cabin & Roberts, 1982; Kannel & Abbott, 1984; Barsky *et al.* 1990; Kumar *et al.* 2012; Schelbert *et al.* 2012). Many studies demonstrated that UMI has a similar long-term impact on physical health as RMI. In men, and to a lesser extent in women, both RMI and UMI are associated with increased risk of all-cause mortality, heart failure and sudden death (Schelbert *et al.* 2012; Dehghan *et al.* 2014). In the Rotterdam Study, men with UMI were also at increased risk for dementia, stroke and cerebral small vessel diseases (Ikram *et al.* 2006, 2008; Leening *et al.* 2010; Krijthe *et al.* 2013).

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Whether there is a common mechanism that engenders RMI and clinically UMI remains controversial (Barsky *et al.* 1990). One theory suggests that the cardiac-pain mechanism is the main reason for the difference in the perception of the discomfort (Sheifer *et al.* 2001). A second theory suggests that various humoral and neurological factors together determine whether the symptoms arise from myocardial ischaemia (Cohn *et al.* 2003). Third, despite similar pathophysiology the size, location or duration of the myocardial ischaemia could explain the absence of pain in UMI (Cabin & Roberts, 1982; Cohn *et al.* 2003; Schelbert *et al.* 2012). There is a lack of empirical evidence to supporting any of the above theories and the reported long-term impacts of UMI on physical health suggests that differences in size and duration of ischaemia are unlikely explanations. Finally, psychological factors regarding the recognition and willingness of the patient to seek medical attention have been discussed (Barsky *et al.* 1990).

To test the impact of RMI and UMI in the present study population, we first compared the association of RMI and UMI with mortality in men and women (note, mortality has been studied in a slightly different sample of the Rotterdam Study previously; Dehghan *et al.* 2014). By definition, the awareness of having survived a life-threatening health event is absent in persons with UMI. This characteristic of UMI provides us with the opportunity to explore the potential role of psychological mechanisms underlying the relationship between MI and depression, but only if the long-term impact can be established and if depression can be assessed independently of help-seeking behaviour. In this case our approach provides us with the unique opportunity to disentangle the pathophysiological from the psychological mechanisms in the association between MI and depression.

The main aim of our study was to determine the relationship of RMI and UMI with depression in older persons. If MI would cause depression mainly due to psychological mechanisms, we would expect that individuals, who are unaware of having had an MI, are not at risk of developing depression. Indeed we hypothesized that RMI but not UMI is associated with an increased risk of depression.

Method

The study was part of the Rotterdam Study, a population-based cohort designed to study the occurrence and determinants of diseases (Hofman *et al.* 2013). In 1990, all residents aged $\geqslant$55 years of Ommoord, a district in Rotterdam, The Netherlands, were invited to participate. Informed consent to retrieve information from treating physicians was obtained from all participants. The medical ethics committee approved the study according to the Wet Bevolkingsonderzoek-Population Study Act executed by the Ministry of Health, The Netherlands.

In the Rotterdam Study, four examination rounds took place. In each round, participants underwent home interviews and subsequent physical examinations at the research centre. During the second examination (1993–1995), 4940 persons were interviewed for depressive symptoms. This round constituted the baseline for the current study (Luijendijk *et al.* 2008). We excluded 461 persons without electrocardiography, due to technical problems, or lack of personnel to operate the electrocardiography device. Another 23 persons were excluded because they withdrew informed consent. We excluded persons with a Mini Mental State Examination (MMSE) score of $\leqslant$26 at baseline (n = 287) (Folstein *et al.* 1975), no valid information on the MMSE (n = 129), and bipolar disorder (n = 3). In total, 4037 participants were eligible with a valid electrocardiography and evaluation of depressive symptoms. These participants were followed from baseline to occurrence of major depression (MDD), death, loss to follow-up, or the end of the study (1 January 2010).

History of MI

MI status was assessed as described in detail previously (Leening *et al.* 2012). In short, at the research centre visit, a 10-s 12-lead electrocardiogram was recorded using an ACTA Gnosis IV electrocardiography recorder (Esaote Biomedica, Italy) at a sampling frequency of 500 Hz and scored digitally.

Electrocardiograms were processed by the Modular Electrocardiogram Analysis System (MEANS; http://www.telelab.nl/doc/kors_ane09.pdf) to obtain electrocardiogram measurement and interpretation (van Bemmel *et al.* 1990). Two research doctors blinded for other clinical information validated the electrocardiograms selected by MEANS. The diagnosis of MI using MEANS is mainly driven by pathological Q waves and auxiliary criteria, such as QR ratio and R-wave progression. ST-T changes were not considered as criteria for MI by MEANS, but were taken into account by the clinicians validating and ascertaining the diagnosis of MI. A senior cardiologist, ascertained the final diagnosis of MI. Assessment of clinically RMI was done as reported previously (Leening *et al.* 2012). A history of RMI was defined by self-reported MI confirmed by clinical data (GP records, and Nationwide Medical Registry), and confirmed or not confirmed with electrocardiogram characteristics matching MI (Leening *et al.* 2012). A history of UMI included all participants without documentation or self-reported MI, but with electrocardiogram characteristics matching MI (Leening *et al.*

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2012). All UMIs were therefore Q-wave MIs. Persons without indication of MI on electrocardiography and no medical documentation of an earlier MI constituted the reference group (Leening *et al.* 2012).

Vital status

The information on vital status is collected continuously, on a weekly basis from the Central Register of Population of Rotterdam. The follow-up for mortality started from the assessment of depression until loss to follow-up or 5 September 2013 (mean follow-up 13.9 years) (Leening *et al.* 2012; Dehghan *et al.* 2014).

Depression

At baseline, all participants were screened for depression with the validated Dutch versions of the Centre for Epidemiologic Studies Depression (CES-D) scale (Beekman *et al.* 1997), or the Hospital Anxiety and Depression Scale (HADS-D; Bjelland *et al.* 2002). The reliability of these questionnaires was tested formally: Cronbach alphas were 0.82 and 0.83, respectively. The CES-D consists of 20 items related to assess depressive symptoms. All symptoms were self-rated on a 0–3 scale, dependent upon the frequency of the experienced symptom (Breslau, 1985). Participants could score from 0 up to 60. The HADS-D consists of seven items measuring depressive symptoms. Again, participants rated the symptoms on a 0–3 scale. Standardized *z* score of the CES-D and HADS-D scores at baseline was used to control for the severity of depressive symptoms and adjust for pre-existing depressive symptoms.

During first and second follow-up assessments (at the examination rounds in 1997–1999 and 2002–2004) the CES-D Scale was used to determine depressive symptoms.

From 1993 to 2010, participants were followed for the occurrence of MDD, which was determined from two sources of information as described previously (Luijendijk *et al.* 2008). At follow-up examinations all participants who scored $\geqslant 16$ on the CES-D scale (Beekman *et al.* 1997), were invited to the research centre for a semi-structured clinical interview to diagnose depressive disorders. A trained clinician diagnosed depression according to the Diagnostic and Statistical Manual of Mental Disorders, 4th revised edition (DSM-IV) by using the Dutch version of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Piyavhatkul *et al.* 2008). Second, medical records of general practitioners were continuously monitored for occurrence of an episode of MDD from baseline onward (mean follow-up 12.5 years). Considering the information about possible MDD provided by the psychiatric interviews and medical records, we defined the occurrence of MDD episodes as the first event that chronologically occurred in one of the two data sources (*note*, all record retrievals were blinded for prior episodes). The occurrences inferred from the different data sources were consistent (Luijendijk *et al.* 2008). However, one assessment (SCAN) was repeatedly cross-sectional and the other assessment reflects continuous monitoring, thus such comparison must be interpreted carefully to account for the different assessment methods.

Covariates

Potential confounders were selected on the basis of prior knowledge (Frasure-Smith *et al.* 1993; Denollet *et al.* 2006). Marital status, education, smoking, and alcohol use were assessed at baseline during the home interview. Education was classified as low, intermediate, or high. Participants were classified as never married or divorced, married, and widowed. Smoking habits were classified as never, past, or current smoker and, similarly, alcohol consumption was classified as never, past, or current consumer. The MMSE was used to measure cognitive performance (Folstein *et al.* 1975).

Blood pressure was measured twice in the sitting position at the right upper arm with a random-zero sphygmomanometer. The average of these consecutive measurements was calculated. Diabetes was considered present if fasting plasma glucose was $\geqslant 7.0$ mmol/l, non-fasting glucose or an oral glucose tolerance test result of $\geqslant 11.1$ mmol/l, or if the participant used blood glucose-lowering medication (Dehghan *et al.* 2007). A history of stroke was defined as a self-reported stroke verified by medical records (Wieberdink *et al.* 2012). Height and weight were measured without heavy clothing to calculate body mass index (BMI).

Data analysis

First, we determined the relative mortality risk of participants with RMI and UMI using Cox proportional hazard regression analyses. These analyses were adjusted for age, level of education, smoking status, alcohol consumption, history of stroke, diabetes, systolic blood pressure, and baseline depressive symptoms. Results of previous studies suggested sex difference in the prognosis of RMI and UMI (Dehghan *et al.* 2014). Moreover, the interaction term of history of MI with sex and mortality was statistically significant ($p < 0.05$). Therefore we stratified all analyses by sex.

Second, we studied whether RMI and UMI are associated with depressive symptoms with linear regression. The models were adjusted for baseline depressive symptoms in order to correct for pre-existing depression. The Generalized Estimating Equation (GEE) approach was

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Table 1. *Baseline characteristics of the study population (N = 4037)*

	History of myocardial infarction					
	Men (*N* = 1823)			Women (*N* = 2214)		
	No MI (*N* = 1488)	RMI (*N* = 220)	UMI (*N* = 115)	No MI (*N* = 2057)	RMI (*N* = 53)	UMI (*N* = 104)
Age, years, mean (S.D.)	67.6 (6.9)	69.8 (6.5)	70.1 (7.2)	68.2 (7.6)	74.3 (8.7)	71.8 (7.9)
Depressive symptoms at baseline, score, mean (S.D.)[a]	4.3 (4.7)	4.9 (4.9)	4.3 (5.6)	5.4 (5.9)	7.2 (5.7)	6.1 (5.9)
Smoking status						
Never smoker, *n* (%)	132 (8.9)	11 (5.1)	7 (6.4)	944 (48)	23 (46)	58 (56.9)
Past smoker, *n* (%)	1041 (70.6)	167 (77)	78 (71.6)	658 (33.5)	21 (42)	28 (27.5)
Current smoker, *n* (%)	302 (20.5)	39 (18)	24 (22)	363 (18.5)	6 (12)	16 (15.7)
Alcohol consumption						
Never consumer, *n* (%)	82 (5.5)	26 (11.9)	3 (2.6)	293 (14.5)	14 (27.5)	19 (19)
Past consumer, *n* (%)	100 (6.8)	23 (10.6)	11 (9.6)	345 (17.1)	10 (19.6)	24 (24)
Current consumer, *n* (%)	1299 (87.7)	169 (77.5)	101 (87.8)	1378 (68.4)	27 (52.9)	57 (57)
MMSE, score, mean (S.D.)	28.2 (1.2)	28.2 (1.2)	28.1 (1.4)	28.1 (1.3)	27.9 (1.1)	28.2 (1.3)
BMI, kg/m^2, mean (S.D.)	25.8 (2.9)	26.2 (3.1)	26.3 (3.2)	26.6 (3.9)	27.4 (4.5)	27.6 (4.5)
Systolic blood pressure, mmHg, mean (S.D.)	139.8 (21.6)	138.4 (20.4)	146.3 (21)	140 (21.9)	134.1 (19.2)	146.3 (23.4)
Blood pressure-lowering medication, *n* (%)	274 (19.4)	81 (39.3)	22 (20.2)	521 (26.4)	18 (37.5)	30 (30.3)
History of cardiovascular diseases, *n* (%)	80 (5.4)	205 (93.2)	99 (86.1)	61 (3)	50 (94.3)	86 (82.7)
History of stroke, *n* (%)	39 (2.6)	13 (5.9)	7 (6.1)	32 (1.6)	4 (7.5)	3 (2.9)
History of CABG, *n* (%)	36 (2.5)	59 (27.6)	0 (0)	9 (0.4)	8 (15.4)	0 (0)
History of PCI, *n* (%)	10 (0.7)	12 (5.6)	0 (0)	6 (0.3)	4 (7.7)	1 (1)
Diabetes mellitus, *n* (%)	121 (8.1)	40 (18.2)	17 (16.5)	162 (7.9)	7 (13.2)	11 (10.6)
Highest education attained						
Low education, *n* (%)	282 (19)	59 (26.78)	26 (23.2)	729 (35.5)	27 (50.9)	35 (34)
Intermediate education, *n* (%)	935 (63)	131 (59.5)	67 (59.8)	1209 (58.9)	25 (47.2)	61 (59.2)
High education, *n* (%)	268 (18)	30 (13.6)	19 (17)	113 (5.5)	1 (1.9)	7 (6.8)
Marital status						
Never married or divorced, *n* (%)	57 (4.6)	9 (5.6)	6 (7)	249 (14.3)	4 (11.1)	7 (8.1)
Married or living together, *n* (%)	1055 (84.7)	140 (86.4)	66 (76.7)	970 (55.7)	14 (38.9)	41 (47.7)
Widowed, *n* (%)	133 (10.7)	13 (8)	14 (16.3)	522 (30)	18 (50)	38 (44.2)

RMI, Recognized myocardial infarction; UMI, unrecognized myocardial infarction; MMSE, Mini Mental State Examination; BMI, body mass index; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Table presents complete data, missing values are not imputed here.

[a] Centre for Epidemiologic Studies Depression Scale/Hospital Anxiety and Depression Scale *z* score.

used to estimate the pooled effect of RMI and UMI on repeatedly assessed depressive symptoms. The interaction term of history of MI with sex and depressive symptoms was statistically significant ($p < 0.05$).

All analyses related to the association between RMI/UMI and depressive symptoms were tested using two models. The first model was adjusted for age and baseline depressive symptoms. The second model was additionally adjusted for level of education, marital status, smoking status, alcohol consumption, BMI, history of stroke, diabetes mellitus, and systolic blood pressure.

Third, we assessed the association between RMI/UMI and MDD using Cox proportional hazard regression analyses. These analyses included two models with the same covariates in those testing depressive symptoms described above. The Breslow Generalized Wilcoxon test was used to compare the hazard curves of RMI and UMI.

Multiple imputations were used in order to account for missing data on potential confounding variables. Smoking status was missing in 2.9%, marital status in 16.9%, BMI in 3.5%, alcohol consumption in 1.4%, systolic blood pressure in 1.5%, and education in 0.3% of the participants. All analyses were rerun in the complete case and five imputed datasets. In this paper we present the data on the imputed data. All analyses were performed using IBM SPSS Statistics v. 21 (IBM Corp., USA).

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Results

Baseline characteristics of 4037 participants are presented in Table 1. The mean age of men was 68.1 years (S.D. = 6.9) and women were on average 68.5 years (S.D. = 7.7). Of the men, 12.3% (n = 220) had a RMI, 6.3% (n = 115) an UMI and 81.4% (n = 1488) had no evidence of a MI. Of the women, 2.4% (n = 53) had had a RMI, 4.7% (n = 104) had had an UMI and 92.9% (n = 2057) were free of MI. In total, 273 persons had a RMI, of these 138 had electrocardiographic evidence of MI. The remaining 135 RMI cases were identified by clinical records and therefore represent non-Q-wave MIs.

First, we assessed the mortality risk of RMI and UMI (Table 2). In men, the average follow-up was 13.1 years (23 846 person-years) during which 943 men died. RMI and UMI were associated with an increased risk of mortality: RMI [hazard ratio (HR) 1.71, 95% confidence interval (CI) 1.45–2.03]; UMI (HR 1.58, 95% CI 1.27–1.97). In women, the average follow-up was 13.9 years (32 438 person-years) during which time 825 women died. Women with RMI (N = 53) had a higher mortality risk (HR 1.81, 95% CI 1.33–2.46). However, there was no association between UMI (N = 104) and mortality risk in women (HR 0.99, 95% CI 0.77–1.30).

Next, we studied the association between RMI and UMI and repeated assessments of depressive symptoms after a mean of 3.8 and 8.5 years The mean CES-D score at the first and second follow-up assessment was 4.2 (S.D. = 6.7) and 6.7 (S.D. = 7.7), respectively. In men (Table 3), RMI predicted higher scores of depressive symptoms at the first (B 1.05, 95% CI 0.16–1.95) and second (B 1.29, 95% CI 0.07–2.52) assessment. UMI was not associated with depressive symptoms at the first (B 0.79, 95% CI −0.34 to 1.97), or second (B 0.54, 95% CI −1.14 to 2.21) assessment. In the combined analysis of the two assessments, we observed that RMI (B 1.14, 95% CI 0.07–2.21) but not UMI (B 0.55, 95% CI −0.51 to 1.62) was associated with more depressive symptoms. In women (Table 4), RMI was not significantly associated with depressive symptoms in the first (B−1.37, 95% CI −3.64 to 0.90) or in the second (B 1.48, 95% CI −1.94 to 4.89) assessment. Moreover, there were no significant associations in the combined analysis of the two depressive symptoms assessments (B−0.86, 95% CI −3.13 to 1.42). UMI was not associated with depressive symptoms in any analysis. For this reason we restricted the additional analysis on occurrence of MDD in men only.

In an additional sensitivity analysis we explored the relationship of RMI and UMI with the occurrence of MDD. Men were followed up for 11.8 years ± 4.71 S.D. (21 664 person years). In total, 52 men (10 of those with RMI but only three of those with UMI) developed MDD during follow-up. We calculated occurrence of MDD during follow-up and cannot present point prevalence data. Men with a history of RMI were at increased risk of developing MDD (HR 2.18, 95% CI 1.04–4.57), but not those with an UMI (HR 0.99, 95% CI 0.77–1.30). The difference between the risk of RMI and UMI was statistically significant (p = 0.024).

We repeated the analyses (see Supplementary material) excluding RMI cases that did not meet electrocardiography criteria for prior Q-wave MI, to reduce possible misclassification and bias by persons (over) reporting symptoms. In these analyses, the effect estimates were very similar. However, due to loss of statistical power the effect was no longer statistically significant.

Table 2. *Recognized (RMI) and unrecognized (UMI) myocardial infarction and all-cause mortality risk with Cox regression (N = 4037)*

	All-cause mortality	
	HR (95% CI)	p value
Men (n = 1823)		
RMI (n = 220)		
Multivariate adjusted[a]	1.71 (1.45–2.03)	<0.001
UMI (n = 115)		
Multivariate adjusted[a]	1.58 (1.27–1.97)	<0.001
Women (n = 2214)		
RMI (n = 53)		
Multivariate adjusted[a]	1.90 (1.39–2.61)	<0.001
UMI (n = 104)		
Multivariate adjusted[a]	0.99 (0.77–1.30)	0.99

HR, Hazard ratio; CI, confidence interval.

1768 (943 men) of 4037 person died during 56 284 person-years of follow-up.

[a] Multivariate adjusted: additionally adjusted for age, level of education, smoking status, alcohol consumption, history of stroke, diabetes mellitus and systolic blood pressure.

Discussion

Men with RMI or UMI had an increased mortality risk in this population-based study, as demonstrated previously (Dehghan *et al.* 2014). However, the risks of RMI and UMI for depression did not correspond to the mortality risks. Whereas men with RMI had an increased risk to develop depression, men with UMI were at similar risk of developing depression compared to persons without MI. In line with other studies, we confirmed a much weaker association

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Table 3. *The longitudinal association of recognized (RMI) or unrecognized (UMI) myocardial infarction with depressive symptoms in men (N = 1823)*

		Depressive symptoms						
		First assessment ($n = 1471$)[a]			Second assessment ($n = 1113$)[a]		Combined analysis ($n = x$, with 2584 observations)	
Exposure	n	B (95% CI)	p value	n	B (95% CI)	p value	B (95% CI)	p value
RMI								
Adjusted for age and baseline depressive symptoms[b]	159	0.92 (0.29 to 1.81)	0.043	102	1.26 (0.04 to 2.48)	0.043	1.06 (−0.09 to 2.13)	0.052
Multivariate adjusted[c]	159	1.05 (0.16 to 1.95)	0.021	102	1.29 (0.07 to 2.52)	0.039	1.14 (0.07 to 2.21)	0.037
UMI								
Adjusted for age and baseline depressive symptoms[b]	84	0.85 (−0.33 to 2.04)	0.16	51	0.50 (−1.18 to 2.18)	0.56	0.62 (−0.44 to 1.67)	0.25
Multivariate adjusted[c]	84	0.79 (−0.40 to 1.97)	0.19	51	0.54 (−1.14 to 2.21)	0.53	0.55 (−0.51 to 1.62)	0.31

CI, Confidence interval.

Analysis were performed with linear regression and Generalized Estimating Equations.

[a] Centre for Epidemiologic Studies Depression Scale mean score (S.D.). **First assessment**: RMI 4.2 (7.9), UMI 3.8 (6.5), no MI 2.9 (5.3). **Second assessment**: RMI 6.7 (8.1), UMI 5.4 (5.9), no MI 5.1 (6.3).

[b] Model adjusted for age and baseline depression (corrected for baseline depressive symptoms).

[c] Multivariate adjusted: additionally adjusted for level of education, marital status, body mass index, smoking status, alcohol consumption, and history of stroke, diabetes mellitus and systolic blood pressure.

between UMI and survival in women (de Torbal *et al.* 2006). This has been attributed to the increased likelihood of lead-placement artifacts due to breast tissue (Murabito *et al.* 1993). Therefore, the results of the association between UMI and depression in women are hard to interpret.

A history of RMI conveyed a long-term increased risk of both depressive symptoms and MDD in men. Many studies of cardiovascular disease and depression focused on the prognostic value of short-term incidence of depression in patients shortly after the diagnosis of MI (Frasure-Smith *et al.* 1993; Thombs *et al.* 2006; Larsen, 2013). One such study reported that patients with heart disease have 45% more depressive symptoms compared to those without heart disease (Polsky *et al.* 2005). The long-term risk of psychological distress in post-MI patients as well as depression in patients with cardiovascular disease have previously been studied for follow-up periods of 5–8 years (Drory *et al.* 2002; Polsky *et al.* 2005). The present study addresses a period of 11 years after experiencing MI. In men, RMI was associated with an increased risk of MDD that remained elevated even over a long period. However, in men UMI was not associated with depressive symptoms or occurrence of MDD, although it was a risk factor for mortality. This discrepancy in the risks of UMI for mortality and depression, compared to RMI, can be explained in multiple ways.

First, previous studies have suggested that patients with UMI may have less severe symptoms and mostly do not consult physicians (Barsky *et al.* 1990; Stern, 2005). Others have argued that, the size of myocardial tissue damage underlying UMI may also be less severe (Lumley *et al.* 1997). Yet, our study showed that in men, UMI was almost as predictive of mortality as RMI. This suggests that the underlying pathology is of equal severity.

Second, it is conceivable that the mortality risk of RMI and UMI are similar only due to the medical interventions and behavioural changes occurring after RMI. Successful treatment of RMI certainly decreases mortality risk (Steg *et al.* 2012). However, it is questionable whether treating MI successfully has a strong impact on the risk of depression (Ravven *et al.* 2013).

Third, depression may also be an adverse effect of the treatment of RMI. Patients with RMI are more often treated with interventions such as percutaneous coronary intervention to restore the coronary blood flow and the tissue perfusion (Steg *et al.* 2012). These procedures have been associated with increased risk

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Table 4. *The longitudinal association of recognized (RMI) or unrecognized (UMI) myocardial infarction with depressive symptoms in women (N = 2214)*

		Depressive symptoms							
		First assessment (*n* = 1831)[a]			Second assessment (*n* = 1506)[a]		Combined analysis (*n* = *x*, with 3337 observations)	
Exposure	*n*	*B* (95% CI)	*p* value	*n*	*B* (95% CI)	*p* value	*B* (95% CI)	*p* value
RMI								
Adjusted for age and baseline depressive symptoms[b]	36	−1.11 (−3.37 to 1.16)	0.34	19	1.24 (−2.20 to 4.68)	0.48	−0.73 (−3.0 to 1.54)	0.53
Multivariate adjusted[c]	36	−1.37 (−3.64 to 0.90)	0.24	19	1.48 (−1.94 to 4.89)	0.40	−0.86 (−3.13 to 1.42)	0.46
UMI								
Adjusted for age and baseline depressive symptoms[b]	84	0.12 (−1.38 to 1.62)	0.87	62	0.57 (−1.37 to 2.50)	0.57	0.23 (−1.18 to 1.64)	0.75
Multivariate adjusted[c]	84	−0.04 (−1.54 to 1.46)	0.96	62	0.39 (−1.54 to 2.33)	0.69	0.12 (−1.30 to 1.54)	0.87

CI, Confidence interval.

Analysis were performed with linear regression and generalized estimating equations.

[a] Centre for Epidemiologic Studies Depression Scale mean score (S.D.). **First assessment**: RMI 5.2 (8.2), UMI 5.9 (8.2), no MI 4.9 (7.2). **Second assessment**: RMI 10.2 (9.2), UMI 9.1 (8.4), no MI 7.6 (8.3).

[b] Model adjusted for age and baseline depression (corrected for baseline depressive symptoms).

[c] Multivariate adjusted: additionally adjusted for level of education, marital status, body mass index, smoking status, alcohol consumption, and history of stroke, diabetes mellitus and systolic blood pressure.

of depressive symptoms because of the intensity of the treatment procedure (Park *et al.* 2012). Further, drugs used for blood-pressure and heart-rate control, such as beta-blockers, may worsen depressive symptoms (Steg *et al.* 2012). However, we accounted for antihypertensive use and previous cardiac interventions at baseline to control for this effect.

Fourth, our results suggest that in men psychological factors contribute to the development of depression after MI. Although it remains difficult to disentangle psychological mechanisms from the pathophysiological mechanism underlying both MI and depression, we argue that psychological mechanisms are key to the different risk patterns of RMI and UMI in men. Due to improved clinical management of clinical MI, the survival has improved substantially, yet patients with MI often experience the event as life threatening (Ladwig *et al.* 1994). Further, frightening events impact not only the survivors' health, but also their families and working life (Wiles, 1998). These resulting lifestyle changes contribute to the psychological reaction following the MI experience and often resulting in depression (Lloyd & Cawley, 1982). Clinical studies of MI patients demonstrated that the psychological distress related to health problems makes men particularly vulnerable to depression (Drory *et al.* 2002).

We did not observe any relationship between RMI or UMI with depressive symptoms in women. Only 53 women but 220 men had RMI at baseline, thus our analysis were underpowered in women. Moreover, we found no relationship between UMI and mortality in women, suggesting that this event does not signal pathophysiological change or that there is possible misclassification of UMI in women. Some studies reported a low accuracy of electrocardiography diagnostics in older women (Murabito *et al.* 1993). In this light the association of UMI with both mortality and depression was consistent.

Depression is an established risk factor for coronary heart disease (Lesperance *et al.* 1996) and may thus contribute to the occurrence of MI. Although we corrected for baseline depressive symptoms, reverse causality could in theory influence the observed association between RMI and depression (Trivedi, 2004). The Rotterdam Study started with screening for depression during 1993, this assessment constitutes the baseline of our study and no prior assessments were conducted.

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A limitation of our study is the possible misclassification of UMI. The definition of UMI heavily relies on the presence of pathological Q waves, therefore most non-Q-wave MIs remained undetected. Second, electrocardiogram evidence of a previous MI can disappear over time (Sheifer *et al.* 2001). This again could lead to misclassification of UMI and thereby lower the effect estimates. Third, the known history of RMI might introduce assessment bias towards MDD diagnosis. In contrast, individuals with UMI have less specific symptomatology and mostly seek no medical care thus may avoid MDD medical diagnosis. However, the systematic approaches we used to ascertain events of MDD minimize the possibility of these biases (Luijendijk *et al.* 2008). Fourth, due to the observational nature of the study design presence of residual confounding cannot be ruled out.

Our study has several strengths. It is based on a large well-described population-based cohort with a long follow-up. Data were gathered prospectively and without prior knowledge of MI status. Participants were monitored continuously during follow-up for the occurrence of depression and diagnoses were made by clinical interviews according to DSM-IV criteria. We used different data sources and approaches to collect and validate MDD (Luijendijk *et al.* 2008).

Furthermore, detailed information on RMI was collected and validated from the medical records of the participants (Leening *et al.* 2012). Importantly, when we restricted the cases with RMI to those with electrocardiography-verified changes (excluding those with clinical symptoms only) the results did not change. This suggest that possible misclassification cannot explain our findings. Possibly, persons (over)reporting more symptoms (without pathology) do not account for the observed association and did not bias the effect estimates (see Macleod *et al.* 2002, for example).

In conclusion, RMI and UMI are both associated with a higher mortality risk in men. However, only men with RMI had a higher likelihood of depression during follow-up. Although pathophysiological differences between UMI and RMI may also explain this discrepancy, our results are consistent with the hypothesis that the psychological burden of experiencing MI contributes to the long-term risk of depression after MI. We can only carefully speculate about clinical implication as future studies must confirm this results and the underlying mechanisms but our findings suggest that effective long-term prevention of post-MI depression should address the psychological impact of experiencing an MI.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291716000544.

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Declaration of Interest

None.

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