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Impact of pre-admission depression on mortality following myocardial infarction

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Background
The prognostic impact of previous depression on myocardial infarction survival remains poorly understood.

Aims
To examine the association between depression and all-cause mortality following myocardial infarction.

Method
Using Danish medical registries, we conducted a nationwide population-based cohort study. We included all patients with first-time myocardial infarction (1995–2014) and identified previous depression as either a depression diagnosis or use of antidepressants. We used Cox regression to compute adjusted mortality rate ratios (aMRRs) with 95% confidence intervals.

Results
We identified 170 771 patients with first-time myocardial infarction. Patients with myocardial infarction and a previous depression diagnosis had higher 19-year mortality risks (87% *v.* 78%). The overall aMRR was 1.11 (95% CI 1.07–1.15) increasing to 1.22 (95% CI 1.17–1.27) when including use of antidepressants in the depression definition.

Conclusions
A history of depression was associated with a moderately increased all-cause mortality following myocardial infarction.

Declaration of interest
None.

Despite remarkable advances in prevention and prognosis,[1,2] myocardial infarction remains a common life-threatening event and an enormous burden on Western healthcare systems.[2] While the incidence of first-time myocardial infarction has decreased by nearly 50% during the past 25 years,[1] the prevalence of myocardial infarction survivors has increased.[1,3] Patients with depression have an increased risk of myocardial infarction, but the prognostic impact of a history of depression on myocardial infarction remains to be established.[4] However, depression is associated with several factors that could worsen the prognosis following myocardial infarction. These include poor adherence to recommended lifestyle changes and advice relating to secondary prophylactic medications after myocardial infarction,[5] poor social support,[6] low heart rate variability[7] and increased levels of inflammatory markers.[8] Numerous studies have examined the impact of post-admission depression on myocardial infarction mortality, reporting adjusted hazard ratios ranging from 1.33 to 1.53.[4,9] Only two studies have examined the impact of pre-admission depression on myocardial infarction survival.[10,11] Reporting no association with mortality, these two studies had small sample sizes (<600 patients) and relied on patients' anamnesis to confirm previous depression. Trials have shown that antidepressive treatment after myocardial infarction improves survival only for a subgroup of patients with treatment-resistant depression,[12] but not for all patients with depression.[13,14] However, if depression only moderately increases mortality risk, the statistical power of these trials ($n<2500$) may have introduced a type 2 error. We therefore undertook a population-based cohort study to examine how a history of depression influences the mortality of an acute myocardial infarction.

Method

Setting and design

The study period for this nationwide population-based cohort study was 1 July 1995 to 1 February 2014. The Danish National Health Service provides free and universal tax-supported healthcare, guaranteeing unfettered access to general practitioners and hospitals. We linked medical registries using the unique central personal registry number assigned to each Danish citizen at birth and to residents upon immigration.[15] The study was approved by the Danish Data Protection Agency (Record number: 1-16-02-268-14). No approval from an ethics committee or patient informed consent is required for registry-based studies conducted in Denmark.

Patients with myocardial infarction

In Denmark, care for patients with myocardial infarction and other medical emergencies is provided by public hospitals. We used the Danish National Patient Registry (DNPR), covering all Danish hospitals,[16] to identify all patients with a first-time in-patient admission for myocardial infarction during the study period, including registered ST-segment elevation myocardial infarction (STEMI) and non-STEMI. The DNPR contains data on admission and discharge dates and discharge diagnoses from all Danish non-psychiatric hospitals since 1977 and from emergency room and out-patient clinic visits since 1995.[16] Each hospital discharge is assigned one primary diagnosis and up to 19 secondary diagnoses classified according to the ICD-8[17] until the end of 1993 and ICD-10[18] thereafter.[16] We used both primary and secondary diagnoses to identify patients with myocardial infarction.

Depression

We used the DNPR[16] and the Danish Psychiatric Central Research Register (DPCR)[19] to identify all diagnoses of depression prior to admission for myocardial infarction. The DPCR is a nationwide registry with records of all psychiatric admissions and, from 1995, also out-patient treatment at psychiatric departments in Denmark. All diagnoses in the DPCR are registered by

psychiatrists. Furthermore, we obtained information on depression severity (classified as mild, moderate or severe) using ICD-10 codes.[18] Patients with more than one severity code were assigned the most severe code. The positive predictive values of data in the DPCR have been reported previously and found to be high for severe depression (83%) but somewhat lower for moderate (76%) and mild depression (65%).[20] Because many patients with depression are managed in primary care only and hence not included in hospital registries, we sought to increase completeness of the depression diagnosis by including redeemed prescriptions for antidepressants in our analyses. We grouped patients into six categories based on depression diagnoses and antidepressant use: (a) no diagnosis of depression and $\leqslant 1$ redeemed prescription for antidepressants before the myocardial infarction/index date (reference group), (b) no diagnosis of depression, >1 redeemed prescription with former use of the antidepressant, (c) no diagnosis of depression, >1 redeemed prescription with current use of the antidepressant, (d) a prior depression diagnosis and $\leqslant 1$ redeemed prescription, (e) a prior depression diagnosis, >1 redeemed prescription with former use of the antidepressant, and (f) a prior depression diagnosis, >1 redeemed prescription with current use of the antidepressant. We defined 'current users' as patients having redeemed a prescription for antidepressants within 90 days before the index date. 'Former users' redeemed their last prescription more than 90 days before the myocardial infarction/index date.

Patient characteristics

We used the complete medical history available in the DNPR[16] to ascertain the presence of non-psychiatric comorbidities and the DPCR[19] to identify psychiatric comorbidity. Both in-patient and out-patient diagnoses were used to identify comorbidity. Information on use of medications <90 days prior to myocardial infarction/index date was retrieved from the Danish Registry of Medicinal Product Statistics,[21] which has recorded all prescriptions redeemed in community pharmacies, according to the Anatomical Therapeutic Chemical (ATC) classification system, since 1995.[21] The following medications were included: antidepressants, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), anxiolytics/hypnotics, antipsychotics, statins, low-dose aspirin, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists, beta blockers, diuretics and non-steroidal anti-inflammatory drugs. Data on socioeconomic variables (income, employment and education) were retrieved from the Integrated Database for Labour Market Research.[22] ICD and ATC codes used in the study are provided in online Table DS1.

Outcome

We used the Danish Civil Registration System to obtain information on all-cause mortality.[15] This registry has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[15] We also examined immediate causes of deaths using data from the Danish Register of Causes of Death[23] (data available through 31 December 2012). We estimated cardiovascular and non-cardiovascular mortality in myocardial infarction patients with and without depression (defined as any diagnosis or >1 prescription of antidepressant before the index date). Moreover, we specifically examined deaths caused by arrhythmia, venous thromboembolism, stroke, myocardial infarction and heart failure.

Statistical analysis

We characterised the myocardial infarction cohort according to age group, gender, calendar year interval, individual comorbidities, use of medication and socioeconomic status. We followed all patients from hospital admission date until death, emigration, or 1 September 2014, whichever came first. We used the Kaplan–Meier estimator to visually present the cumulative mortality during follow-up and to compute mortality risks at 1 year, 5 years, 10 years, 15 years and 19 years after myocardial infarction for patients with and without a pre-myocardial infarction depression diagnosis. We used Cox proportional hazards regression models to compute hazard ratios as a measure of the mortality rate ratio (MRR) comparing patients with myocardial infarction with and without a depression diagnosis from the DNPR or DPCR. Use of antidepressants was not included in this analysis. To increase the sensitivity of depression, we also conducted several analyses combining depression diagnoses and use of antidepressants. In the models, we adjusted for gender, age group, income, employment, calendar year interval and the individual comorbidities listed in Table 1 and online Table DS2. The proportional hazard assumption was assessed using log–log plots and found valid. We repeated the analysis on depression diagnoses stratifying by gender, age group, myocardial infarction type (STEMI or non-STEMI), comorbidity (cardiovascular and other), medication use and socioeconomic factors.

Sensitivity analyses

We performed a variety of sensitivity analyses to test the robustness of the estimates. First, we analysed patients according to the registry in which the first diagnosis of depression was recorded (DNPR or DPCR), as the depression diagnosis has been validated only in the DPCR. Second, we restricted our analysis to depression diagnoses made 90 days and 1, 2, and 3 years before the index date to detect any temporal effect of the timing of first depression diagnosis. Third, we fitted five additional multivariable models as follows: (a) additional adjustment for education as these data were not available for all patients; (b) additional adjustment for use of anxiolytics/hypnotics and (c) antipsychotics as these drugs may in part serve as a proxy for depression, (d) additional adjustment for cardiovascular diseases and drugs that may represent intermediate steps between depression and post-myocardial infarction mortality,[24] and (d) omitting diabetes, stroke and hypertension from the model, as these covariates potentially could also represent intermediate steps in the association examined. Finally, to detect any temporal changes in the impact of depression, we analysed each calendar year interval separately. All analyses were performed using Stata, version 14.

Results

Patient characteristics

Overall, 171 200 patients with a first-time myocardial infarction were identified during the study period. We excluded 138 patients with no follow-up time, 11 patients with missing data on age, and 280 patients with missing data on income and employment. After these exclusions, 170 771 patients with myocardial infarction were available for analysis, of which 6015 (3.5%) had a previous depression diagnosis. Median follow-up time was 1460 days (25–75th percentiles: 283–3251 days) for patients without a depression diagnosis and 855 days (25–75th percentiles: 88–2215 days) for patients with a previous diagnosis. Median age was 71 years for patients without a previous depression diagnosis and 72 years for patients with a previous depression diagnosis. All comorbidities and use of medication were more common among patients with myocardial infarction with a previous depression diagnosis and among current users of antidepressants (Table 1 and online Table DS2).

Table 1 Characteristics of myocardial infarction patients with and without a prior depression diagnosis

	n (%)	
	No depression 164 756 (96.5)	Previous depression 6015 (3.5)
Age, years		
<40	2624 (1.6)	86 (1.4)
40–59	36 211 (22.0)	1225 (20.4)
60–79	83 043 (50.4)	3000 (49.9)
⩾80	42 878 (26.0)	1704 (28.3)
Women	61 170 (37.1)	3375 (56.1)
Calendar year interval		
1995–1999	41 759 (25.4)	1075 (17.9)
2000–2004	49 930 (30.3)	1739 (28.9)
2005–2009	42 159 (25.6)	1735 (28.8)
2010–2014	30 908 (18.8)	1466 (24.4)
Comorbidity		
Hypertension	33 474 (20.3)	1717 (28.6)
Atrial fibrillation/atrial flutter	13 909 (8.4)	633 (10.5)
Stroke	13 766 (8.4)	840 (14.0)
Cancer	19 058 (11.6)	893 (14.9)
Obesity	6094 (3.7)	447 (7.4)
Diabetes	18 235 (11.1)	909 (15.1)
Chronic pulmonary disease	17 147 (10.4)	1131 (18.8)
Chronic kidney disease	5981 (3.6)	320 (5.3)
Peptic ulcer	10 983 (6.7)	751 (12.5)
Illicit drug/alcohol/smoking abuse	6764 (4.1)	1470 (24.4)
Dementia	3390 (2.1)	618 (10.3)
Medication <90 days prior to MI/index date		
Antidepressants	14 140 (8.6)	3190 (53.0)
SSRIs	9415 (5.7)	1799 (29.9)
TCAs	2500 (1.5)	597 (9.9)
Anxiolytics/hypnotics	28 677 (17.4)	2585 (43.0)
Antipsychotics	4153 (2.5)	1220 (20.3)
Statins	20 033 (12.2)	861 (14.3)
Low-dose aspirin	36 396 (22.1)	1630 (27.1)
ACE/ARBs	34 370 (20.9)	1318 (21.9)
Beta blockers	26 121 (15.9)	1028 (17.1)
Diuretics	44 760 (27.2)	2051 (34.1)
NSAIDs	23 162 (14.1)	949 (15.8)
Income		
Low	39 263 (23.8)	1438 (23.9)
Intermediate	41 782 (25.4)	1886 (31.4)
High	41 057 (24.9)	1743 (29.0)
Very high	42 654 (25.9)	948 (15.7)
Employment		
Employed	43 637 (26.5)	719 (12.0)
Early retirement: receiving sickness, disability or early retirement benefits	4147 (2.5)	168 (2.8)
Unemployed	21 040 (12.8)	1276 (21.2)
State pensioner	95 932 (58.2)	3852 (64.0)
Education		
Basic education, primary school	65 947 (40.0)	2811 (46.7)
Youth education, high school or similar	48 043 (29.2)	1512 (25.1)
Higher education	17 034 (10.3)	599 (10.0)
Unknown	33 732 (20.5)	1093 (18.2)

MI, myocardial infarction; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants, ACE/ARBs, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; NSAIDs, non-steroidal anti-inflammatory drugs.

Mortality

Throughout the follow-up period, the mortality risks were higher among patients with myocardial infarction with a previous depression diagnosis than among those without a previous depression diagnosis (33% *v.* 26% at 1 year and 87% *v.* 78% at 19 years, Fig. 1 and online Table DS3). Adjusted MRRs (aMMRs) were increased for depression diagnoses overall (1.11, 95% CI 1.07–1.15). Consistent with this overall finding but without any trend, aMMRs were increased for mild (1.11, 95% CI 1.02–1.21), moderate (1.14, 95% CI 1.07–1.21) and severe previous depression diagnoses (1.15, 95% CI 1.05–1.26) (Table 2). Using patients without a previous depression diagnosis and without antidepressant use as the reference, the aMRR was 1.29 (95% CI 1.26–1.32) for current users of antidepressants without a depression diagnosis (no difference between TCA users and SSRI users) and 1.22 (95% CI 1.17–1.27) for current users with a previous depression diagnosis (slightly higher risk for TCA users compared with SSRI users) (Table 3).

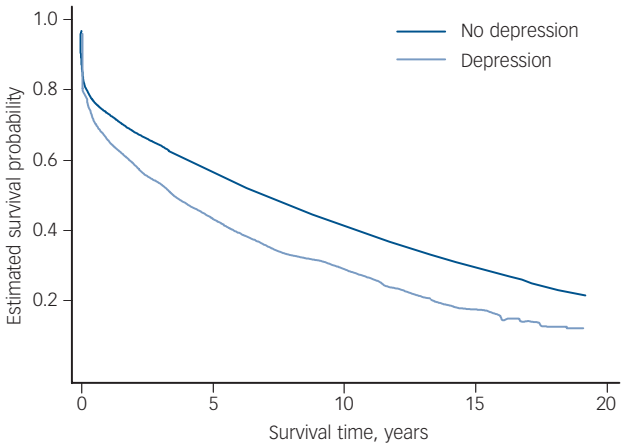

Fig. 1 Kaplan–Meier survival curve for patients with myocardial infarction with and without a depression diagnosis.

We identified no notable modification of the effect found in the overall results on depression diagnoses (hazard ratio = 1.11) within strata of myocardial infarction type, age group, gender, comorbidity, medication use, income, employment and education (Table 4 and online Figs DS1–5). However, the effect of depression was not present in a few strata (SSRI use, antipsychotic use, illicit drug use, dementia and unemployed). In cause-specific analyses, patients with myocardial infarction with previous depression had higher non-cardiovascular mortality and moderately higher cardiovascular mortality than patients without previous depression (Table 5).

Sensitivity analyses

The results were robust in the analysis restricted to patients registered in the DNPR and the DPCR, respectively. When the analysis was restricted to patients with a recent depression diagnosis (90 days, 1, 2, and 3 years prior to the myocardial infarction/index date), the association was stronger than the overall estimates (online Table DS4). In an analysis restricted to patients with either STEMI or non-STEMI, the results were consistent with the overall estimates (Table 4). When the model was extended to also adjust for education, use of anxiolytics/hypnotics, use of antipsychotics and cardiovascular diseases and drugs, the results were robust. Omitting diabetes, stroke and hypertension from the multivariate model did not change the results (online Table DS4). Finally, results were robust when stratifying by calendar year interval (online Table DS5).

Discussion

In this nationwide cohort study of patients with first-time myocardial infarction, previously diagnosed depression was an

Table 2 Nineteen-year mortality estimates in patients with myocardial infarction with and without a prior depression diagnosis, overall and by depression severity

	Mortality rate per 1000 person-years (95% CI)	Crude mortality rate ratio (95% CI)	Adjusted mortality rate ratio (95% CI)[a]
No depression	104.2 (103.6–104.9)	1.0 (reference)	1.0 (reference)
Depression overall[b] ($n = 6015$)	168.1 (162.9–173.5)	1.43 (1.38–1.47)	1.11 (1.07–1.15)
Mild depression[c] ($n = 798$)	209.2 (192.2–227.6)	1.63 (1.50–1.77)	1.11 (1.02–1.21)
Moderate depression[c] ($n = 1778$)	170.3 (160.4–180.9)	1.37 (1.29–1.46)	1.14 (1.07–1.21)
Severe depression[c] ($n = 768$)	179.2 (163.9–196.0)	1.45 (1.32–1.58)	1.15 (1.05–1.26)

a. Adjusted for age group, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking misuse, dementia, income, employment and calendar year interval.
b. Including all ICD codes for depression.
c. Specific ICD-10 codes provided in online Table DS1.

Table 3 Nineteen-year mortality rate ratios in patients with myocardial infarction according to presence of a depression diagnosis and use of antidepressants before the index date

	Crude mortality rate ratio (95% CI)	Adjusted mortality rate ratio (95% CI)[a]
No prior depression diagnosis		
No use ($n = 138\,405$)	1.0 (reference)	1.0 (reference)
Former use ($n = 13\,184$)	1.14 (1.11–1.17)	1.06 (1.04–1.09)
Current use ($n = 13\,167$)	1.79 (1.76–1.83)	1.29 (1.26–1.32)
Selective serotonin reuptake inhibitors ($n = 8782$)	1.91 (1.86–1.96)	1.30 (1.27–1.33)
Tricyclic antidepressants ($n = 2348$)	1.59 (1.52–1.67)	1.27 (1.21–1.33)
Prior depression diagnosis		
No use ($n = 1348$)	1.28 (1.19–1.36)	1.01 (0.95–1.08)
Former use ($n = 1522$)	1.17 (1.10–1.26)	1.10 (1.02–1.18)
Current use ($n = 3145$)	1.83 (1.76–1.91)	1.22 (1.17–1.27)
Selective serotonin reuptake inhibitors ($n = 1771$)	1.93 (1.82–2.04)	1.17 (1.11–1.24)
Tricyclic antidepressants ($n = 592$)	1.78 (1.62–1.95)	1.34 (1.22–1.47)

a. Adjusted for age group, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking misuse, dementia, income, employment and calendar year interval.

Table 4 Nineteen-year mortality rate ratios in patients with myocardial infarction with and without a prior depression diagnosis, by type of myocardial infarction

	Crude mortality rate ratio (95% CI)	Adjusted mortality rate ratio (95% CI)[a]
Non-ST segment elevation myocardial infarction		
No depression ($n = 46\,349$)	1.0 (reference)	1.0 (reference)
Depression overall[b] ($n = 1774$)	1.50 (1.41–1.59)	1.15 (1.08–1.23)
Mild depression[c] ($n = 250$)	1.81 (1.54–2.12)	1.20 (1.02–1.40)
Moderate depression[c] ($n = 585$)	1.36 (1.21–1.52)	1.16 (1.03–1.30)
Severe depression[c] ($n = 235$)	1.50 (1.26–1.78)	1.16 (0.97–1.38)
ST-segment elevation myocardial infarction		
No depression ($n = 20\,295$)	1.0 (reference)	1.0 (reference)
Depression overall[b] ($n = 728$)	1.49 (1.33–1.67)	1.08 (0.96–1.21)
Mild depression[c] ($n = 108$)	1.89 (1.44–2.47)	1.12 (0.85–1.47)
Moderate depression[c] ($n = 252$)	1.36 (1.12–1.66)	1.07 (0.87–1.30)
Severe depression[c] ($n = 108$)	1.24 (0.90–1.70)	1.01 (0.74–1.39)

a. Adjusted for age group, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking misuse, dementia, income, employment, and calendar year interval.
b. Including all ICD codes for depression.
c. Specific ICD-10 codes provided in online Table DS1.

adverse prognostic factor for all-cause mortality, independent of depression severity and type of myocardial infarction. The association was strongest for recent depression and for current users of antidepressants, indicating that active depression exacerbates its adverse prognostic influence on post-myocardial infarction mortality. The association was overall consistent with the analysis on depression diagnoses in the strata of age, gender, comorbidity, medication use, or socioeconomic status.

Only two studies have examined the effect of pre-admission depression on mortality following myocardial infarction.[10,11] Neither of these studies reported any association with mortality. However, one study had only 4 months of follow-up,[11] and both studies had small sample sizes, selective inclusion of patients from specific hospitals, and assessed depression by self-report questionnaires and medical chart review. Other studies on the association between depression and mortality following myocardial infarction have focused on post-myocardial infarction depression (i.e. detecting the depression after admission for myocardial infarction). Two recent meta-analyses with post-myocardial infarction depression as the exposure reported

Table 5 Cardiovascular and non-cardiovascular mortality in patients with myocardial infarction with and without previous depression, 1995–2012

	Mortality rate per 1000 person-years (95% CI)		Adjusted mortality rate ratio (95% CI)[b]
	No depression ($n = 138\,405$)	Depression[a] ($n = 32\,366$)	
All-cause mortality	110.3 (109.5–111.1)	193.5 (190.8–196.2)	1.19 (1.17–1.21)
Cardiovascular mortality	41.0 (40.5–41.5)	71.1 (69.4–72.7)	1.15 (1.11–1.18)
Arrhythmia	3.7 (3.5–3.8)	6.1 (5.6–6.6)	1.12 (1.02–1.23)
Venous thromboembolism	0.7 (0.7–0.8)	1.3 (1.1–1.5)	1.19 (0.96–1.46)
Myocardial infarction	12.0 (11.7–12.2)	25.8 (24.9–26.9)	1.15 (1.10–1.21)
Stroke	3.5 (3.3–3.6)	6.3 (5.8–6.8)	1.16 (1.05–1.27)
Heart failure	7.2 (7.0–7.4)	13.0 (12.3–13.7)	1.19 (1.11–1.27)
Non-cardiovascular mortality	48.2 (47.7–48.7)	91.2 (89.4–93.1)	1.25 (1.22–1.29)

a. Including all patients with ICD codes for depression or more than one prescription of an antidepressant before the index date.
b. Adjusted for age group, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking misuse, dementia, income, employment and calendar year interval.

increased relative risks for all-cause mortality (1.23, 95% CI 1.15–1.31[9] and 1.80, 95% CI 1.50–2.15[4]). Thus, these studies generally found higher estimates compared with our study. This may be explained by lack of adjustment for essential covariates included in our study (for example alcohol misuse and socioeconomic status). Furthermore, the stronger association in studies of post-myocardial infarction depression may be confounded by severity of myocardial infarction, i.e., the likelihood of detecting important depressive symptoms (for example fatigue, disturbed sleep and poor appetite) may be higher after severe cases of myocardial infarction and hence would lead to stronger association with mortality. In post-myocardial infarction depression studies that did adjust for myocardial infarction severity (Killip class or left ventricular ejection fraction), the association with mortality was attenuated by 25% after adjustment,[9] further supporting this notion. By contrast, we based our depression exposure on physician-diagnosed depression prior to admission for myocardial infarction. This strict definition of depression explains the discrepancy between depression prevalence in our cohort (3.5%) and that of previously reported studies (approximately 20%).[25] However, when we also included use of antidepressants in the definition, the prevalence increased to 19% (Table 3).

Several underlying pathophysiological mechanisms have been suggested to link depression to increased mortality in patients with myocardial infarction, and the causality is likely to be multifactorial. Evidence for a biological pathway suggests that depression is associated with hyperactivity of the hypothalamic–pituitary–adrenocortical axis with increased cortisol levels,[26] which can lead to elevation of blood pressure, increased plasma volume, hyperinsulinaemia, hyperglycaemia, insulin resistance and dyslipidaemia.[27] It is unlikely that the increased mortality can be attributed to the antidepressive treatment itself as treatment with SSRIs has been shown to lower cortisol and insulin resistance.[28] Moreover, clinical trials have shown no[13,14] or a slightly positive effect[12] of SSRI treatment on mortality. Depression has also been associated with disturbances in cardiac autonomic tone including elevated heart rate and low heart rate variability.[29] These factors may exacerbate heart failure in the course of myocardial infarction and are associated with post-myocardial infarction mortality.[30] A behavioural pathway suggests that patients with a depression diagnosis are less likely to adopt a healthy lifestyle (for example, regarding physical activity and smoking) and dietary recommendations, and are less likely to adhere to recommended secondary prophylactic medication than patients without depression.[5] Clinical pathways may include metabolic syndrome[31] leading to increased risk of cardiovascular diseases such as stroke and heart failure.[24]

Limitations

Several issues should be considered when interpreting our results. This is the first nationwide study of the association between pre-admission depression and all-cause mortality following myocardial infarction. Its main strength is its large population-based design within a tax-supported, uniformly organised healthcare system with independently and prospectively recorded hospital and prescription history, and with complete follow-up for all patients. This setting reduces the risk of selection biases.[32] One study limitation is reliance on routine hospital discharge diagnoses, which may contain coding errors. However, the positive predictive value of myocardial infarction diagnoses in the DNPR has been examined previously and found to exceed 95%.[16,33]

Misclassification because of underreporting of depression diagnoses from primary care has most likely biased the estimates based only on depression diagnoses towards the null. This is supported by the increased mortality in analyses including antidepressants in the depression definition. In these analyses, however, increased mortality may be because of prescribing of antidepressants for more severe conditions than depression (such as cancer pain). Another concern is that the depression diagnosis has been validated only in the DPCR;[20] however, we obtained similar results when we separately analysed individuals with depression identified from the DNPR and from the DPCR. The observational nature of our study renders it vulnerable to unmeasured confounding. Specifically, we lacked information on smoking. However, we did adjust for chronic pulmonary disease as a proxy for smoking and for socioeconomic status and alcohol misuse, which are likely to mimic the distribution of smoking.

Implications

We found that depression diagnosed prior to myocardial infarction was an adverse prognostic factor for post-myocardial infarction mortality. The association was stronger in patients with recent depression or current use of antidepressants, but was not influenced by depression severity or type of myocardial infarction. Our findings merit clinical attention to myocardial infarction patients with a previous depression diagnosis or with current use of antidepressants. The clinical pathways responsible for increased mortality in these patients need further clarification to allow prevention of specific high-risk conditions.

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