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Emotional distress as a predictor of statin non-adherence among Swedish first-time myocardial infarction patients, 2006–2013

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ABSTRACT

Background: Emotional distress (depression and anxiety) has been known to affect mortality after a myocardial infarction (MI). One possible mechanism is through medication non-adherence. Few studies have investigated the link between statin adherence and emotional distress, and results are not consistent. We aimed to explore whether emotional distress affects adherence among first-time MI patients younger than 75 years old receiving a prescription for the first time.

Methods: We identified first-MI individuals younger than 75 years from the SWEDEHEART national quality registers discharged with a statin prescription. The main exposure was the anxiety/depression portion of the EQ-5D from Interview 1 (6–10 weeks post-MI) and Interview 2 (12–14 months post-MI). We calculated adherence from the Swedish Prescribed Drugs Register during three observation periods (OP): [1] Interview 1 to Interview 2, [2] one year post Interview 2, and [3] two years post Interview 1.

Results: Emotional distress at Interview 1 was not associated with statin adherence for OP1 (RR: 0.99, 95% CI: 0.98, 1.01). Emotional distress at Interview 2 was associated with lower adherence one year later (RR: 0.95, 95% CI: 0.93, 0.98). Emotional distress at Interview 1 was associated with a small decrease in adherence in the complete OP for adherence (RR: 0.98, 95% CI: 0.96, 0.99).

Conclusion: Emotional distress was marginally, but independently, associated with lower adherence to statin two years after the MI. Our study suggests that emotional distress may be an important factor for long-term statin adherence, and, thus, may play a clinically important role in long-term outcome.

1. Background

Depression and anxiety have both been identified as risk factors for cardiovascular disease. Although the two have different presentations, studies have found an increased prevalence of both in patients who survive a myocardial infarction (MI). In MI survivors, the prevalence of depressive symptoms has been estimated to be approximately 30%, and 20% for major depression as of 2006, though current prevalence is uncertain [1]. There was a similarly high prevalence of anxiety reported in patients with MI, ranging from 30 to 40% [2]. Depression is associated with 50% increased risk of new cardiac events, a doubling in the risk of all-cause mortality, and almost three times increased risk of cardiac mortality [3]. Anxiety has also shown significant association with MI prognosis, with a 36% increased risk of adverse cardiac outcomes [2]. Less is known of the mechanisms by which this type of emotional distress, i.e. depression and anxiety, can affect prognosis, but one hypothesis is that those with emotional distress may be less likely to adhere to evidence-based medication regimens.

There have been several studies on the association between emotional distress and adherence, with most focusing on the entire medication regimen in patients with stable coronary artery disease or in those who have recently suffered an MI. Despite somewhat varied methodology, the results are consistent, generally showing that individuals with depression or anxiety are more likely to not adhere to cardiac medications than those without [4–10]. These studies, however, have not evaluated whether emotional distress affects usage separately depending on type of medication. Different medication may have different side effects, which can affect how emotional distress impacts its adherence.

Statins are prescribed to a majority of MI patients as part of their long-term secondary prevention regimen, and are considered one of the key medications necessary to improve survival and prevent reinfarction. Appropriate adherence to this class of medication has been shown to have the potential for decreasing mortality after an MI by up to 25%

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[11]. However, in part because of a myriad of criticism, both online and among social circles, statins have been shown to suffer from poor adherence rates, reported to be as low as 30% one year later [12]. Because of its importance, statin use is a key area of secondary prevention that may be affected by emotional distress. Few studies investigate this [13–16]. So far all have focused on depression, and results have been conflicting, with significant associations with non-adherence present in three studies, and one showing no association. There is limited data regarding statin adherence in post-MI patients, and what exists is often limited in generalizability. The comprehensive SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) quality registers provide a unique opportunity to investigate emotional distress in first-time MI patients.

The primary objective of the present study is to determine whether symptoms of emotional distress, assessed both after the MI and one year later, affect short- and long-term adherence to statins first prescribed after a first MI among patients aged 74 years old and younger from SWEDEHEART registers. Our secondary goal was to investigate the association between severe emotional distress and diagnosed clinical depression and/or anxiety with statin adherence.

2. Methods

2.1. Data sources

Data were obtained from the SWEDEHEART collection of national quality registers for cardiovascular disease, which includes approximately 90% of all MIs in Sweden [17]. For this study we utilized two of SWEDEHEART's sub-registers: RIKS-HIA (Register of Information and Knowledge about Swedish Heart Intensive Care Admissions) and SEPHIA (Secondary Prevention after Heart Intensive Care Admission). The RIKS-HIA register includes patients who have had an MI in Sweden and records information regarding the episode, such as relevant data on medical history, admission, symptom onset, in-hospital treatments provided, and discharge information, including medications prescribed. The SEPHIA register began in 2005, and as of 2014, coverage was approximately 80% [18]. Only individuals aged 74 years and younger are eligible to participate. Those who enroll are interviewed on two occasions: approximately 6–10 weeks (Interview 1) and 12–14 months (Interview 2) after the MI event.

SWEDEHEART data were linked to the Swedish Prescribed Drugs Register, which includes information on dispensed medications, and National Patient Register, which records all inpatient and outpatient hospital visits, with the exception of primary care visits. This study was conducted with approval from the regional ethics committee in Uppsala, Sweden (Dnr: 2013/478).

2.2. Sample and observation periods

We selected individuals with a first MI who had received a first-time statin prescription at discharge. To exclude participants who had previously received a statin prescription, we removed those with registered statin use upon admission, as well as those who had a record of a statin pickup prior to the MI event. This was done to ensure that we could evaluate a homogeneously statin-naïve population not been previously exposed to potential side effects or with issues of non-adherence. We also excluded individuals who did not participate in SEPHIA.

We used three observation periods (OP) for adherence: 1) from Interview 1 (approximately 6–10 weeks after the MI) to Interview 2 (approximately 12–14 months after the MI), 2) the year following Interview 2, and 3) two years after Interview 1, or the complete OP for adherence (Fig. 1). Number of days in the each period was calculated based on time between recorded interview dates or the end date stipulated by the study design. The first included patients who had their first follow up after the MI before January 1, 2013. This resulted in a sample of 15,154 participants after excluding individuals who died or had missing data on exposure, outcome, or any of the confounders. The second and complete OPs included individuals who had the first interview after the MI before January 1, 2012 to ensure all participants had the respective follow-up time's worth of recorded refills, which resulted in a sample of 10,674 and 12,357, respectively, after excluding those who died or had missing values on any of the study covariates. Appendix 1 shows a flowchart of the number of individuals excluded and those with missing values.

2.3. Outcome

To calculate statin adherence, we used the medication possession ratio (MPR) measure:

$$MPR = \frac{Number\ of\ pills\ obtained}{Number\ of\ days\ in\ OP}$$

For this study data on dosage was missing; therefore, we assumed that each individual was prescribed one statin pill per day as has been reported true for approximately 98% of prescriptions [19]. For OP 1, we measured adherence for the time between each patient's follow-up interviews, approximately one year after the MI event. We calculated the time between those two dates and calculated the number of pills distributed during this period. The reimbursement system in Sweden allows individuals to refill prescriptions for up to a three-month's supply at a time. Because of this we had to account for any leftover pills dispensed immediately after the MI and before Interview 1. We used the amount of surplus medication they had obtained and added it to the number of pills for our time period of interest. If individuals did not have enough pills to cover the initial MI-Interview 1 period, we did not add or subtract from their adherence calculation. Fig. 2 shows sample calculations for two hypothetical patients. This same process was repeated for the second and complete OPs. To be considered adherent, individuals had to have taken out pills covering > 80% of the days, which is the usual convention for cardiovascular medication adherence studies [11]. Lastly, some patients got a supply of their daily medications automatically sent to them from their pharmacy every 14 days. We excluded these individuals as they could artificially increase adherence [19].

During Interview 2, participants reported whether or not they regularly took a variety of medications prescribed at discharge, including statins. Although interviewers may have this information written on each participant's chart, interviewers were to ask and write down the patient's answer. We used this variable to compare adherence calculated from the pharmacy register with self-reported adherence.

2.4. Exposure

To characterize emotional distress, we used the European Quality of Life Five Dimensions questionnaire (EQ-5D). This instrument consists of five questions, each with a three-item ordinal response scale. The five questions are designed to measure mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [20]. We utilized the anxiety/depression dimension, which consists of the following three alternatives: “1: I am not anxious or depressed,” “2: I am anxious or depressed to some extent,” and “3: I am extremely anxious or depressed” [20]. Overall, the EQ-5D has shown to have good reliability and validity in over 60 studies of cardiovascular disease [21]. The anxiety/depression dimension has shown moderate associations with established measures of depression and anxiety, such as the Mini International Neuropsychiatric Interview, the Beck Anxiety Inventory, and the Beck Depression Inventory [22–27]. Additionally, one study found that individuals with both anxiety and depression were more likely to report some anxiety or depression on the EQ-5D than those with anxiety or major depressive disorder alone. However, those with only anxiety or depression were

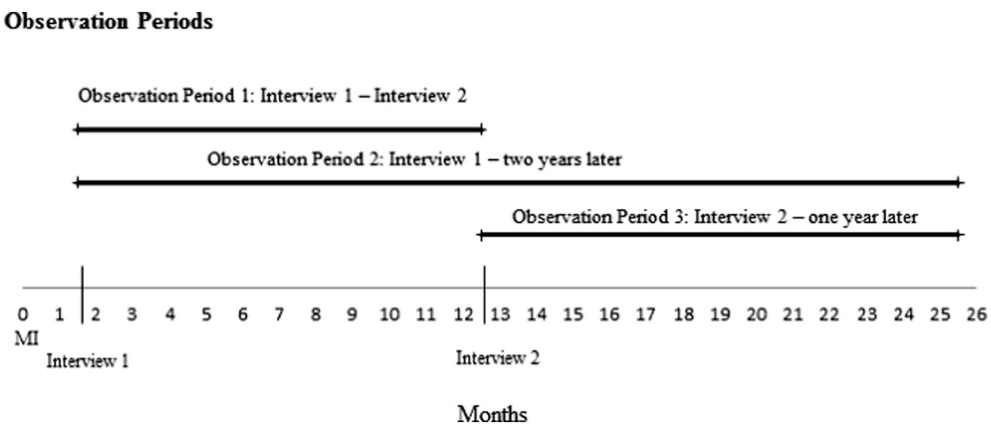

Fig. 1. Observation periods for statin adherence. Interview 1 was conducted approximately 6–10 weeks after the index MI; Interview 2 was conducted approximately 12–14 months after the index MI. Therefore, the length of observation period 1 varies by individual.

more likely to report some anxiety or depression in the EQ-5D than individuals without either of these conditions [25]. The EQ-5D questions were administered twice, both during Interview 1 and Interview 2. Responses from Interview 1 were used as the main exposure for OP 1 and the complete OP for adherence; whereas Interview 2 was used for OP 2. For the primary analysis, we combined the second and third response categories to compare individuals who had any emotional distress versus none.

2.5. Secondary analyses

To investigate the effect of severe anxiety and depression, we created two additional exposure variables. First, we combined the first and second EQ-5D categories to compare severe emotional distress to those who report mild or none. Second, we looked into whether having a clinical diagnosis 6 months prior to the myocardial infarction would yield the same results as self-reported emotional distress. To do this, we extracted International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes from the National Patient Register. We extracted codes "F30-39: Mood [affective] disorders" and "F40-48: Neurotic, stress-related and somatoform disorders" to account for clinical diagnoses of depression and anxiety. This register covers only diagnoses made within specialized care, and thus excludes any diagnoses from primary care.

2.6. Confounders

We chose confounders based on previous literature and psychological (E.O. and J.W.) and cardiologic (C.H.) expertise. Potential confounders identified were as follows: age, sex, employment status (employed, retired, other), smoking status (never smoker, former smoker, current smoker), diabetes (yes, no), BMI (underweight, normal weight, overweight, obese), hypertension (yes, no), history of stroke (yes, no), cholesterol levels, left ventricular ejection fraction (normal,

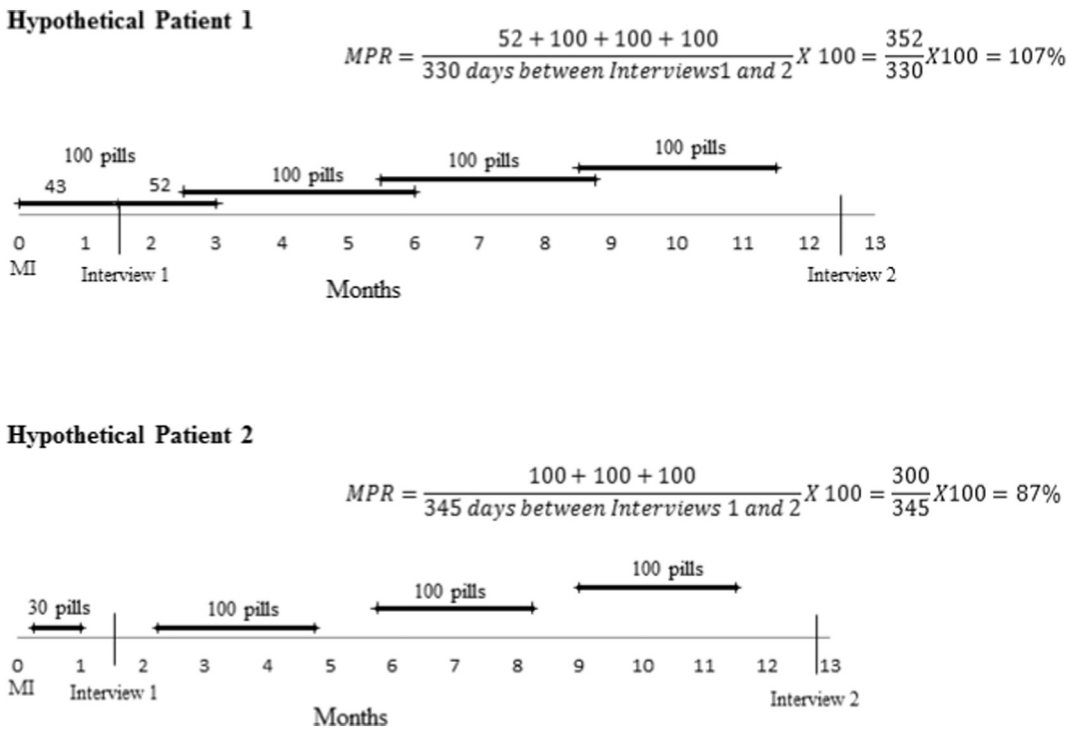

Fig. 2. Sample Medication Possession Ratio (MPR) calculation for two hypothetical patients. The denominator consists of the number of days in Observation Period 1 (from Interview 1 to Interview 2). Hypothetical Patient 1 picked up 100 pills immediately after discharge and 43 days later was interviewed for the first time (Interview 1). This means that at the time of Interview 1, the patient had 52 pills leftover from the first dispensation, which were added to the calculation of the MPR during the observation period. Hypothetical patient 2 also picked up pills after his MI, but these were not enough to cover the entire period before Interview 1; therefore, no pills were added to the observation period calculation.

reduced, not measured), medications prescribed at discharge, and country of birth (Sweden, other). Discharge medications consisted of anticoagulants, angiotensin II receptor blockers (ARB), angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium antagonists, digitalis, diuretics, nitrates, other antiplatelets, and other lipid lowering agents.

2.7. Statistical analyses

All statistical analyses were done on SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.3.2 (Vienna, Austria). Chi-square and *t*-tests were done on all baseline measures. We calculated the tetrachoric correlation coefficient for self-reported statin use and calculated adherence. For the primary analyses, we utilized propensity score matching procedures to balance confounders. We first calculated propensity scores with logistic regression. We then performed a one-to-one match without replacement using a caliper equal to 0.2 times the standard deviation of the logit of the propensity score. This was done for each of the three OPs. We ensured balancing of the data by comparing absolute standardized differences of the means between those with emotional distress and those without emotional distress, as well as the variance ratio for continuous variables [28].

After matching we ended up with a sample of 5288 matched pairs (n = 10,576) for OP 1, resulting in 4578 unmatched participants. Of these, 236 were from the emotional distress group and the remainder came from the no emotional distress group. In the OP 2 group there were 3306 matched pairs (n = 6612) and 4062 unmatched individuals, of which 72 belonged to the emotional distress group. From the total 12,357 sample pertaining to the complete OPs, we got 4341 matched pairs (n = 8682) and 3675 unmatched participants, of which 185 were from the emotional distress group.

Once we achieved balancing of the covariates, we calculated relative risks using a modified Poisson regression [29] with robust error variances. This same regression method was used for all secondary analyses, with the exception that we simply adjusted for all confounders that were used in the propensity score calculation. All regressions were done using Proc GENMOD in SAS. We utilized multiple imputation procedures to investigate the impact of the exclusion of incomplete cases on the main results. Imputations of study covariates, excluding the adherence outcome, for each OP were conducted in R using the *mice* package [30]. Analysis and pooling of imputed results were done using Proc GENMOD and Proc MIANALYZE in SAS.

3. Results

Our total sample in OP 1 consisted of 15,154 individuals, of which 11.8% were not adherent (< 80% coverage) to statins during the period approximately one year after discharge (n = 1782). Primary nonadherence in this sample was small: 4.32% of non-adherent individuals never picked up a single pill (n = 77). In OP2, 21.2% were not adherent (n = 2266), and 17.6% were not adherent two years after discharge (n = 2178).

Approximately 36% and 32% of individuals reported emotional distress at Interview 1and Interview 2, respectively. Of those reporting emotional distress at Interview 1, 57.9% also reported emotional distress at Interview 2. During Interview 1, 35.5% of individuals with no anxiety and/or depression diagnoses reported some symptoms of emotional distress. Of those with a diagnosis, 70.9% reported emotional distress to some extent. During Interview 2, 31.7% of individuals without a diagnosis of depression and/or anxiety reported no emotional distress, and 67.8% of those with a diagnosis reported emotional distress on the EQ-5D. As previously mentioned, these proportions do not include individuals who received a diagnosis from their primary care provider.

Table 1 describes the characteristics prior to discharge for the OP 1 sample. Non-adherent patients more frequently reported emotional

Table 1
Characteristics of the Observation Period 1[a] sample among individuals aged 74 years old and younger with a first myocardial infarction participating from the SWEDEHEART cohort.

Variable	Total sample (n = 15,154)	Adherence		p-Value
		No n = 1782 (11.8%)	Yes n = 13,485 (88.1%)	
Emotional distress				**0.0007**
Yes	5524 (36.4)	714 (40.1)	4810 (36.0)	
No	9630 (63.6)	1068 (59.9)	8562 (64.0)	
Age (mean)	60.7 (8.8)	60.7 (9.2)	60.7 (8.8)	0.99
Sex				< **0.0001**
Male	11,437 (75.5)	1249 (70.1)	10,188 (76.2)	
Female	3717 (24.5)	533 (29.9)	3184 (23.8)	
Country of birth				< **0.0001**
Sweden	12,932 (85.3)	1457 (81.8)	11,475 (85.8)	
Other	2222 (14.7)	325 (18.2)	1897 (14.2)	
Employment status				**0.003**
Employed	7701 (50.8)	858 (48.1)	6843 (51.2)	
Retired	6530 (43.1)	787 (44.2)	5743 (42.9)	
Other	923 (6.1)	137 (7.7)	786 (5.9)	
Smoking status				< **0.0001**
Never smoker	5110 (33.7)	588 (33.0)	4522 (33.8)	
Former smoker	4748 (31.3)	483 (27.1)	4265 (31.9)	
Current smoker	5296 (35.0)	711 (39.9)	4585 (34.3)	
Diabetes				0.31
Yes	954 (6.3)	122 (6.9)	832 (6.2)	
No	14,200 (93.7)	1660 (93.1)	12,540 (93.8)	
BMI				< **0.0001**
Underweight (< 18.5)	110 (0.7)	33 (1.8)	77 (0.6)	
Normal weight (18.5–24.9)	4603 (30.4)	618 (34.7)	3985 (29.8)	
Overweight (25.0–29.9)	7138 (47.1)	805 (45.2)	6333 (47.4)	
Obese (30 or greater)	3303 (21.8)	326 (18.3)	2977 (22.3)	
Hypertension				0.18
Yes	4603 (30.4)	566 (31.8)	4037 (30.2)	
No	10,551 (69.6)	1216 (68.2)	9335 (69.8)	
History of stroke				0.36
Yes	250 (1.6)	34 (1.9)	216 (1.6)	
No	14,904 (98.4)	1785 (98.1)	13,156 (98.4)	
Cholesterol (mean)	5.4 (1.1)	5.2 (1.1)	5.5 (1.2)	< **0.0001**
Left ventricular ejection fraction				**0.009**
Normal	8948 (59.0)	1075 (60.3)	7873 (58.9)	
Reduced	4236 (28.0)	448 (25.2)	3788 (28.3)	
Not measured	1970 (13.0)	259 (14.5)	1711 (12.8)	
Medications prescribed at discharge (% prescribed)				
Anticoagulants	491 (3.2)	55 (3.1)	436 (3.3)	0.70
ARB	1222 (8.1)	164 (9.2)	1058 (7.9)	0.06
ACE inhibitors	10,455 (69.0)	1110 (62.3)	9345 (69.9)	< **0.0001**
Beta blockers	14,016 (92.49)	1601 (89.8)	12,415 (92.8)	< **0.0001**
Calcium antagonists	1180 (7.8)	168 (9.4)	1012 (7.6)	**0.006**
Digitalis	91 (0.60)	12 (0.7)	79 (0.6)	0.67
Diuretics	1595 (10.5)	198 (11.1)	1397 (10.5)	0.39
Nitrates	426 (2.8)	64 (3.6)	362 (2.7)	**0.03**
Other antiplatelet	13,939 (92.0)	1617 (90.7)	12,322 (92.2)	**0.04**

(continued on next page)

Table 1 *(continued)*

Variable	Total sample (n = 15,154)	Adherence		p-Value
		No n = 1782 (11.8%)	Yes n = 13,485 (88.1%)	
Other lipid lowering agents	60 (0.4)	8 (0.5)	52 (0.4)	0.70

Bold characters indicate $p < 0.05$.

[a] The sample consists of the observation period beginning approximately 6–10 weeks after the myocardial infarction and ending approximately one year later.

distress than those who did adhere. Those who were non-adherent to statins were more likely to be female, to have been born outside of Sweden, and more often retired or belonging to other employment categories. They were also more likely to be current smokers and less likely to be former smokers at the time of admission. Non-adherent patients were more frequently healthier: they were more likely to have normal BMI, lower mean cholesterol at time of infarction, and more often normal left ventricular ejection fraction. Frequencies were similar for the samples used for the other two OPs, for all covariates except for smoking status, hypertension, nitrates and other antiplatelet prescription at discharge. The covariates smoking and nitrates prescribed at discharge did not show any significant differences between the adherent and non-adherent groups during the full adherence OP, but hypertension was significantly different. Individuals from both adherent and non-adherent groups were equally prescribed other antiplatelets at discharge for the OP 2 and the complete OP, which was not seen in the sample from the OP 1. Because of our large sample sizes, small changes in frequencies between the samples can account for these discrepancies.

During Interview 2 patients were asked to name the cardiac medications they took regularly. Table 2 shows the correlation between this self-reported measure of statin use and actual adherence calculated using the prescription register. There was overall good correlation between the two measures (0.78), and in general, individuals who reported taking a statin did indeed adhere well to the regimen. A large number of participants reported no statin usage when in fact they were adherent, which could indicate a lack of knowledge about exactly which medications were prescribed to them. Only 6.5% of individuals who reported taking statins regularly were non-adherent according to the prescription register. When the analysis was repeated for males and females separately, the correlations were equally strong for both sexes. Notably, non-adherent females more frequently reported regular statin usage than males.

Table 2
Correlation of calculated adherence and self-reported medication usage.[a]

Self-reported usage	Calculated adherence n (%)		Tetrachoric correlation coefficient
Overall	Yes	No	
Yes	11,236 (93.5)	784 (6.5)	0.78
No	341 (37.0)	580 (63.0)	
Males			
Yes	8589 (93.7)	577 (6.3)	0.77
No	227 (38.1)	369 (61.9)	
Females			
Yes	2647 (92.8)	207 (7.2)	0.80
No	114 (35.1)	211 (64.9)	

[a] Subsample of 12,941 cases that completed Interview 2 and had complete information on self-reported usage.

Fig. 3 displays the results obtained from the propensity score analysis, as well as all other subsequent secondary analyses. In OP 1, emotional distress measured at Interview 1 was not significantly associated with decreased adherence (RR: 0.99, 95% CI: 0.98, 1.01, p-value: 0.44). Those who reported emotional distress at Interview 2 had a 5% lower chance of adhering to statin medication one year later than those who did not have emotional distress (RR: 0.95, 95% CI: 0.93, 0.98, p-value: 0.0004).There was a statistically significant, but small, decrease in adherence in the complete OP, with those reporting emotional distress at Interview 1 having 2% lower chance of adhering than those without (RR: 0.98, 95% CI: 0.96, 0.99, p-value: 0.03). Results were similar in the multiple imputation analysis (data not shown).

Secondary analyses showed that the most severe category of emotional distress ("I am extremely anxious or depressed") measured at Interview 1 was significantly associated with a decrease in adherence measured both one (RR: 0.95, 95% CI: 0.92, 0.99, p-value: 0.02) and two years (RR: 0.91, 95% CI: 0.86, 0.96, p-value: 0.001) following the MI when compared to the other two categories combined. The most severe category of emotional distress measured during Interview 2 was also significantly associated with a decreased risk of adherence one year after (RR: 0.96, 95% CI: 0.94, 0.98, p-value: 0.0002). Diagnosed depression and anxiety, however, were not associated with adherence at any time.

4. Discussion

The present study found that emotional distress reported approximately two months after the MI was not associated with statin adherence one year later. However, emotional distress two months after the MI was weakly associated with adherence two years later. Emotional distress reported one year after the MI was also a weak predictor of statin adherence one year later.

Studies on the association between depression and anxiety and statin adherence in patients with heart disease are limited. One study on coronary artery disease patients found that those who were clinically depressed were up to 13% less adherent than those who were not depressed [15]. Kronish and colleagues found that depression was a significant predictor of non-adherence after hospitalization, with a 15% increase in risk for those with comorbid depression [16]. Similarly, Benner and colleagues found a 19% increase in the odds of non-adherence compared to those who did not have depression [13]. One possible explanation for the discrepancy with our findings is age. In the two latter studies, the sample population was older than 65 years, with a large percentage being over 75 years old. This age group was not included in our study population, which may indicate that the link between depression/anxiety and statin adherence may be stronger in individuals older than 75 years. In fact, one other study using a sample in which < 20% of individuals were older than 75 years of age did not find a significant association between depression and statin use after they began their regimen [14]. Perhaps more importantly is the fact that we used a self-reported measure that is not intended as a diagnostic tool for clinical depression as was used in other studies, which may explain why the association in our study was small. However, when we performed a secondary analysis using clinically diagnosed depression and anxiety, results were consistent with no statistically significant associations. In their article, Benner and colleagues found that physician visits are associated with increased adherence [14]. It may be that in our study, those who have a clinical diagnosis are more likely to have more frequent contact with medical professionals than those who never received a diagnosis, and this contact may help improve their medication adherence. Additionally, individuals with a clinical diagnosis may be more likely to be on medication to treat the depression and anxiety symptoms that could lead them to not adhere to statins. It is important to note that individuals who received a diagnosis from primary care physicians are not identified through our inpatient and outpatient

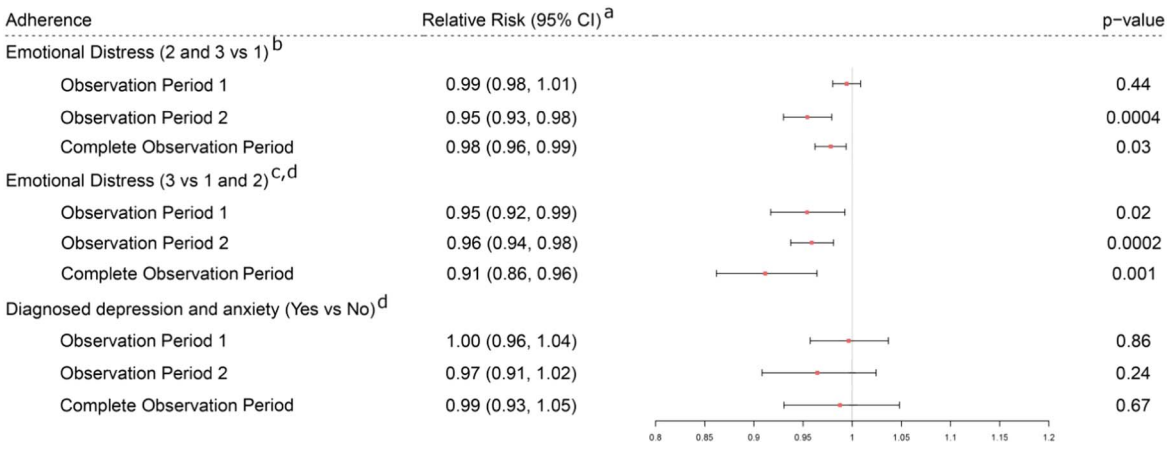

Fig. 3. Adjusted relative risk of emotional distress and diagnosed depression on being adherent to statin medication during three observation periods.

registers, indicating they may have more severe disease than those identified via other measures.

To our knowledge this is the first study to investigate the association between anxiety symptoms, in conjunction with symptoms of depression, and statin adherence. It has been argued that anxiety and depression should be investigated together in the cardiac literature, as a disposition towards negative affectivity, common to both anxiety and depression, may be more important than the constructs of individual conditions [31]. One other study concludes that investigating the impact of comorbid anxiety and depression on cardiac medication adherence may be of more value than either alone [6]. Similar to our study, the authors find that comorbid anxious and depressive symptoms had a weak negative association with general cardiovascular medication adherence [6]. One reason may be that different types of anxiety have different effects on medication adherence: state anxiety is associated with decreased adherence, whereas trait anxiety is associated with increased adherence [32]. The EQ-5D measure cannot differentiate between the two types of anxiety; therefore, this could explain weakened results.

There are several mechanisms via which depression and anxiety could affect medication adherence. The most obvious are the symptoms of depression. Feelings of hopelessness, low motivational levels and lack of energy and focus may lead to difficulties in following doctor recommendations, and thus a discontinuation their regimen [4]. Cognitive symptoms of depression, such as forgetfulness, distraction, inability to plan and develop new coping strategies, may also affect a person's ability to adhere to medications. Cognitive ability has also shown to be associated with lower statin adherence [33]. The way an individual responds to the anxiety/depression item on the EQ-5D may be a result of stressors and events going on in one's life, which can then lead to a de-prioritization of consistent statin usage. One study has found that the greater number of role transitions, such as new job, move, or health problem, and the more interpersonal conflict one reports, the more he or she is likely to not adhere to aspirin independent of current depressive symptoms [8].

4.1. Limitations

We are using adherence calculated from proportion of days covered using a prescription register. Although this measure accurately captures how often pills are dispensed to an individual, it does not reflect whether one actually takes it or not once in possession of these pills. We have investigated this measure with self-reported behavior, and found that over 93% of those who were considered adherent with the MPR measure also reported regularly taking their medication. Additionally, we were not able to adjust for socioeconomic data, which can affect both depression and medication adherence. However, our sample is from a Swedish register, a country which has comprehensive health care coverage, making it less likely that economic factors (such as low income or lack of health insurance) could prevent individuals from acquiring their medication.

Another limitation is that we did not have data on emotional distress for older individuals (> 75 years). One study on older patients found that they were less likely to adhere to statin medications [13]. This could be due to the fact that older adults have a greater number of comorbidities, which may influence the complexity of their medication regimen as well as their ability to remember complex regimens. Therefore, our study may be missing a potentially high risk group, which may have attenuated our results. Another limitation is though the EQ-5D has been validated in many cardiovascular subpopulations, [21] no validity studies have been done on post-MI patients. The EQ-5D does not diagnose clinical disease, and though it has been found to be associated with comorbid anxiety and depression, it was associated to a much lesser extent with anxiety alone [25]. This measure may thus not be as adequate at identifying individuals with anxiety in the absence of any depressive symptoms. However, as previously mentioned, it may be of greater interest to investigate comorbid anxiety and depression symptoms [6]. Our secondary analyses show that individuals who had a clinical diagnosis of depression and/or anxiety, as shown in their medical records, were not less likely than those without a clinical diagnosis to adhere to medication. Those who do have a diagnosis might already be in contact with health professionals, making them no less likely to adhere as studies have shown that this contact alone can improve adherence [14]. Our results are likely affected since our population that reported emotional distress includes both those who do have undiagnosed clinical depression and anxiety and those who do not.

4.2. Strengths

Despite its limitations, this study has the benefit of utilizing several comprehensive, high quality national registers reporting real-world data for MI patients. This ensures that our results are generalizable to the Swedish population ages 74 and under with a first MI. Though not every patient chooses to participate in SEPHIA, approximately 80% of the eligible patients are included [18]. In fact, our adherence measures corroborate well with adherence levels previously reported on the entire Swedish population. When restricting the observation period to one year, one study found that 87.3% of individuals were adherent [19]. Utilizing quality registers also ensures that information was standardized across hospitals and accurately collected by medical professionals for all participants. In this study, we used measurements of anxiety and depression at two time points. This ensures that we can characterizes short-term emotional distress after the MI as well as in the

longer term (up to one year later). The use of a prescription register from a country with comprehensive health care coverage also ensures that all prescription data was appropriately collected, as there is no medication pickup that would go undocumented. Lastly, we had a large dataset with many variables, which made conducting propensity score analyses possible, and subsequently, allows us to make stronger causal inferences.

5. Conclusion

Although not a strong predictor, emotional distress was significantly associated with long-term lower statin adherence in patients with a recent MI. The clinical relevance of these findings remains to be investigated; more studies are needed to establish the importance of emotional distress on statin adherence. However, medical professionals interested in improving adherence to medication should be aware that this is a potential vulnerable population among those recovering from a myocardial infarction. Future studies should look at undiagnosed clinical depression and anxiety, both individually and in combination, and assess their impact on statin adherence.

Contributions

CL, JW, CH, and EO designed the study, interpreted the findings, revised the manuscript, and approved its final form. CL drafted the manuscript.

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Conflicts of interest

None

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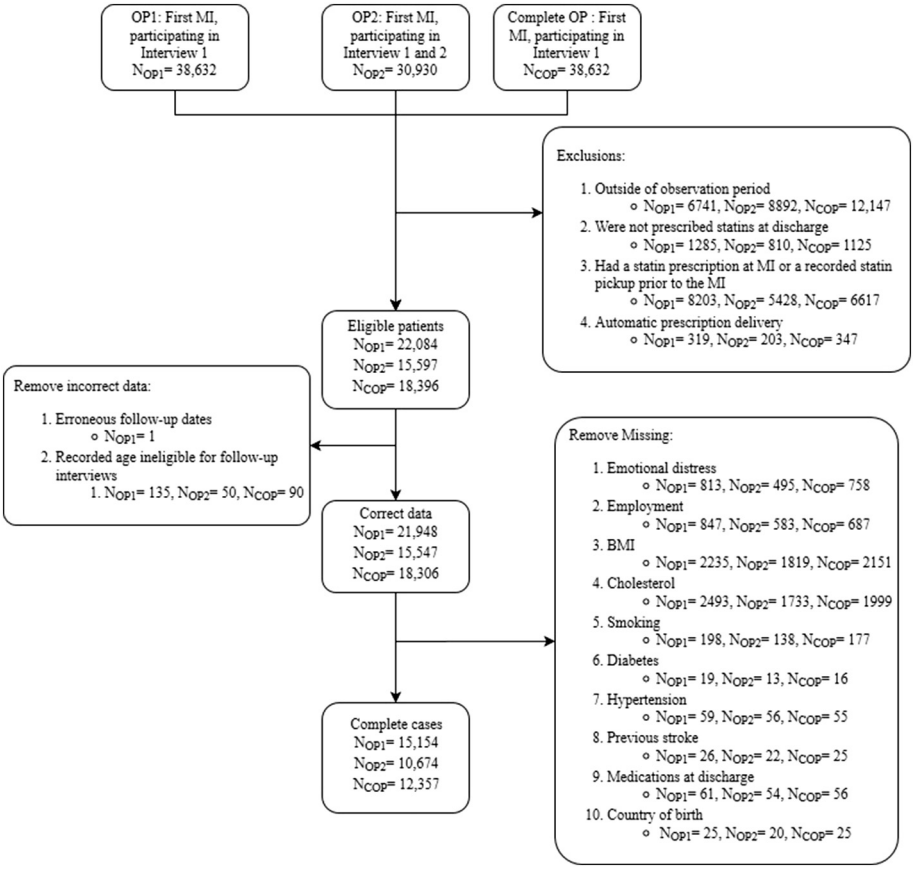
Appendix 1 Flowchart of exclusions and removal of missing data for the three observation periods. Exclusions and removals were done sequentially as numbered in the diagram. OP1: Observation period 1 (Interview 1 to Interview 2); OP2: Observation period 2 (one year after Interview 2); COP: Complete observation period for adherence (two years after Interview 1)



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