Antidepressant use and risk of myocardial infarction. A longitudinal investigation of sex-specific associations in the HUNT study.

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Abstract

Objective. Antidepressants are thought to affect risk of cardiovascular disease (CVD), though the nature of the association is unclear. Men and women have unique cardiovascular risk factors, and sex differences in depression as well as the efficacy of antidepressants are important to consider. We examined whether antidepressant use was associated with risk of having a myocardial infarction (MI), and whether this association was sex-specific.

Methods. Data from the HUNT study were used, gathered from a population in Norway ($N = 31\,765$), collected from 1995 to 2008. These data were combined with the Norwegian Cause of Death Registry and the Norwegian Prescription Database. We performed logistic regression models to examine the association of antidepressant use on risk of having a fatal or non-fatal MI, adjusting for depression, anxiety, diabetes, systolic blood pressure, cholesterol, waist-hip ratio, smoking, age, and sex.

Results. The results indicated that antidepressant use was associated with a reduced risk of having MI at a later date (OR = 0.49 [0.38, 0.64]). Although this association was somewhat stronger for women (OR = 0.46 [0.31, 0.68]) compared to men (OR = 0.53 [0.37, 0.75]), analysis did not identify a sex-specific association of antidepressant use on MI. Follow-up analyses on different sub-types of antidepressants, showed that both SSRI and TCA were associated with reduced risk of MI.

Conclusions. In this population study, the use of antidepressants was associated with a reduced risk of MI. This association was stronger for women, though we detected no interaction between sex and antidepressant use in terms of reduced risk of MI. Although limitations apply regarding causality, especially concerning a dose-response relationship, the results suggest that antidepressant use might reduce the risk of MI among both men and women.

Keywords

Antidepressants, myocardial infarction, depression, psychocardiology

Acronyms

CVD = cardiovascular disease

DÅR = Norwegian Cause of Death Registry

HUNT = The Trøndelag Health Study (The HUNT Study)

MI = myocardial infarction

OR = odds ratio

NorPD = Norwegian Prescription Database

REK = Regional Committee for Medical and Health Research Ethics

SSRI = selective serotonin reuptake inhibitor

TCA = tricyclic antidepressants

WHR = waist hip ratio

Introduction

Depressive disorders are among the most common mental illnesses and represents a major public health issue worldwide (1). As the rate of depression is increasing, so is the use of antidepressants (2, 3). While treatment of depression is crucial in its own terms, it is also an independent risk factor of cardiovascular diseases (CVDs) like coronary heart disease and myocardial infarction (MI) (4, 5), and this further amplifies the importance of safe and effective management of depression. As antidepressants are used for treatment of a variety of illnesses other than depression, including COVID-19 (6), the safety of antidepressant use is of considerable public interest. Antidepressant medication has been linked to several mild and more severe side-effects, including increased mortality (7, 8), type 2 diabetes and serum inflammatory markers (9) and CVD outcomes like major adverse cardiac events (10), heart rhythm disorders (11) changes in the right ventricular volume (12), risk of abnormal bleeding (13, 14) and haemorrhagic stroke (15). There are also beneficial side-effects of antidepressants, like the inhibition of platelet aggregation (14) and anti-inflammatory effects (16). However, the association between antidepressant use and CVD remains controversial and in need of further investigation (17).

In general, selective serotonin reuptake inhibitors (SSRI) are more commonly found to have beneficial or non-detrimental cardiovascular effects, while the older-generation tricyclic antidepressants (TCA) have detrimental effects (18-21). CVD encompasses heart related disorders including MI and vascular related disorders like stroke, and different associations between specific CVD outcome and sub-groups of antidepressants have been observed (7, 22). A meta-analysis found that antidepressant use increased risk of all-cause mortality, including CVD, in the general population, while no change in mortality risk was observed among cardiovascular patients (23). When comparing the relationship between antidepressant therapy and risk of cardiovascular events

in patients with and without CVD, a cardioprotective effect was found only in the non-CVD-group (24), indicating that antidepressants may be harmful in the general population, but not for those with prior CVD. Although the majority of the studies has investigated the association between antidepressant use and CVD as a composite outcome, this approach has limitations as it can mask outcome-specific associations (25). To sum up, the associations between antidepressant use and CVD are evidently population-specific and depend on the type of antidepressant medication (TCA vs. SSRI) and type of outcome (mortality vs. morbidity, MI vs. stroke), and the type of population of the study (incident vs. recurrent CVD).

Although women are at reduced risk of CVD events compared to men (26), they also have unique risk factors of coronary heart disease because of pregnancy related conditions, as well as other conditions like polycystic ovary syndrome and early menopause (27). Sex hormones also affect neurotransmitters important for antidepressant effects (28, 29). Further, there are sex-related differences in the prevalence and risk of traditional risk factors (30) and in medication prescription and efficiency, as well as sex-specific risk factors (31, 32). The association between depression and CVD has also been found to differ among men and women: the effects of depression on risk of stroke are greater for men (33), symptoms of depression are significantly stronger risk factors for MI among women compared to men (34). Sex differences are evident in pharmacodynamics, pharmacokinetics and side effects of medications (25, 35, 36), and women are more at risk of fatal ventricular tachycardia, which can be induced by antidepressants (37). The sex-specific effects of antidepressants are still inconclusive due to conflicting findings (38) and the tendency of sole inclusion of male subjects in studies on depression and antidepressants (29, 39). Sex differences in the association of depression symptoms and antidepressant use with incident MI and CVD in general, warrant further investigation (25).

Summary and research question

This review of the literature identifies several knowledge gaps concerning the potential benefits and risks associated with antidepressant use for CVD among men and women. Furthermore, there is a need to address sex-specific associations when examining CVD outcomes. In this current study we address the following research question: Is there an association between use of antidepressants and risk of MI, and is this association sex-specific?

Methods

Design

This study used data from the longitudinal population study The Trøndelag Health Study (HUNT). The general population in the former county of Nord-Trøndelag in Norway was invited to participate at several time points during the last forty years. Of these participants, those who used antidepressants were compared to those who did not use antidepressants. This study includes those aged 20 or older who participated at HUNT2 (1995-1997) and HUNT3 (2006-2008) surveys. The HUNT study has been covered in more detail elsewhere (40). Participants were aged 20 or older. The participants' data were matched with records from the Norwegian Prescription Database (NorPD) and the Norwegian Cause of Death Registry (DÅR). The NorPD recorded participants' use of prescription drugs, and the DÅR recorded participants who have died as well as the cause of death. The follow-up period was until 31st of December 2008, with an average time of 10.73 years between HUNT2 and HUNT3 surveys.

Participants

A total of 31 765 participants were included in this study, with a mean age of 50.36 (SD = 17.41) measured at the HUNT2 survey. Of these, 14 875 (46.83%) were male. See Figure 1 for a flow chart of participants and analyses. Of the 65 237 participants in the HUNT2 survey, 37 071 (56.83%) participated in the HUNT3 survey. A total of 93 898 people were invited to the HUNT2 survey, and 69.5 percent accepted. A total of 93 860 were invited to the HUNT3 survey, and 54.1 percent accepted. Non-participants in the HUNT3 survey were more likely to be younger, male, of lower socio-economic status, and suffering from certain diseases like diabetes mellitus, CVD, and psychiatric disorders (41).

(Insert Figure 1 about here)

Measures

***Myocardial infarction*.** At the HUNT2 and HUNT3 surveys, participants were asked whether they had previously had a MI, and if answered positively, how old they were at the time of the first MI. We used the DÅR records to identify those participants who had participated at HUNT2 but died of an MI in the time between HUNT2 and the end of HUNT3.

Antidepressant use. Participants were asked at the HUNT2 surveys whether they had used antidepressants during the last twelve months. Additionally, we used records from the NorPD to find those who had got prescriptions for antidepressants in the years between HUNT2 and HUNT3. The NorPD started in 2004, so it does not contain data for participants who used antidepressants exclusively before that time. It records anyone who got one or more prescriptions for an antidepressant according to the following ATC-codes: N06AA (TCA, tricyclic antidepressants), N06AB (SSRI, Selective serotonin reuptake inhibitors), N06AF (Monoamine oxidase inhibitors, non-selective), N06AG (Monoamine oxidase A inhibitors), N06AX (Other antidepressants). It also recorded the date the prescription was dispensed. From this, we generated a measure of whether participants had used antidepressants before HUNT3. Participants who used antidepressants exclusively between the period 1997 to 2004 were not included in this measure. The most common types of antidepressants prescribed were SSRIs; atypical and other antidepressants; and TCA. There were no users of non-selective monoamine oxidase inhibitors. Several participants used more than one type of antidepressant, and for some it was unknown which type of antidepressant they used. For more exact numbers, see Table 1.

***Depression and anxiety*.** Symptoms of depression and anxiety were measured at HUNT2 using the Hospital Anxiety and Depression Scale (HADS) (42) includes 14 items with a 4-point scale indicating how the respondent has felt over a 2-week period prior to measurement. It was developed to measure the non-somatic symptoms of anxiety and depression and has demonstrated good

validity (43). In this study, a Norwegian translation of HADS developed for the HUNT study was used. Anxiety and depression were operationalised as continuous measures, and HADS has presented good psychometric properties in the general population in this age group (44).

In the analyses, we adjusted for the effect of several variables, measured at HUNT2.

Waist-hip ratio (WHR): The circumferences of the waist and hip were measured using a steel-band while participants were standing and rounded to the nearest centimetre. The waist was measured at the height of the umbilicus, and the hip at the thickest part.

Diabetes: Participants indicated whether they had diabetes mellitus. Self-report of diabetes in HUNT has been validated against general practitioner data (45).

***Blood pressure*:** Systolic blood pressure was measured by specifically trained nurses using a non-invasive blood pressure monitor based on oscillometry, with a cuff adjusted for arm circumference. Blood pressure was measured three times, and a mean was calculated from the second and third observations to ensure reliable measurements.

***Cholesterol*:** Total serum cholesterol was measured applying an enzymatic colorimetric cholesterol esterase method (40).

Smoking: Participants were asked how many years they had smoked tobacco daily.

(Insert Table 1 around here)

Statistical analyses

We used block-wise, hierarchical logistic regression to investigate the association of antidepressant use with the risk of having a non-fatal or fatal MI. Initially, we investigate a model with only antidepressant use and depression symptoms, adjusting for sex and age. Then we ran a second model, adding anxiety and other covariates representing the main risk factors (46): Diabetes, blood pressure, cholesterol, WHR, number of years participants smoked, age, and sex. Afterwards, we

investigated potentially divergent sex effects by running separate models for men and women. Additionally, we included an interaction term between antidepressant use and sex in the models, by creating a product of antidepressant use (0 = no use, 1 = use) and sex (0 = woman, 1 = man). All analyses were run in R v. 3.6.3. For the analyses, participants who had their first antidepressant prescription *after* having an MI were considered as not having used antidepressants. This was because having an MI is known to increase the likelihood of being depressed (47) and thus increasing the risk of using antidepressants. Similarly, those who died of an MI after the 31st of December 2008 (the last year of the HUNT3 survey), were not considered as having had an MI. This was because the last record of participants having survived an MI would have been know at HUNT3, and this ensured that the death dates would not run longer than the alive dates. Participants who reported MI or angina prior at HUNT2 were excluded from the analyses, in addition to participants with missing data on one or more of the predictors or outcome variables. Additional analyses were performed to examine the associations of different types of antidepressants: TCA, SSRI and other antidepressants. There were not enough registered users of monoamine oxidase inhibitors to allow for analyses of this group. In these analyses, some participants used more than one type of antidepressant and were thus included in more than one analysis. To examine a possible healthy user effect, antidepressant users were compared to non-users on all variables included in the study using t-tests and Pearson's chi-square tests. For continuous variables, heteroskedasticity was tested using Levene's test, and where present, Welch's correction was used for the t-test. Since continuous scales were used for anxiety and depression symptoms, the odds ratio (OR) represents the relative change in odds associated with a one-unit change in the HADS scale of these variables. At the request of reviewers, we also included an analysis of binary depression (no depression vs. depression) and antidepressant use on the risk of MI. In this analysis, we used the recommended cut-off score of 8 for possible cases of depression (42). "No depression and no antidepressant use" was set as the reference group.

Ethical considerations

Participation in the HUNT study was voluntary, and participants signed statements that they agreed their data could be used for research and connected to other national databases. NorPD and DÅR were responsible for matching the participants from HUNT to the data on their records, and we did not have access to the key used to do this matching. The protocols for the HUNT2 and HUNT3 surveys were approved by the Regional Committee for Medical and Health Research Ethics (REK) prior to this specific study (REK reference numbers 152/95/AH/JGE and 4.2006.250 respectively). A specific request for approval was made for the linkage to the mortality register (DÅR) and the NorPD (REK reference number 2018/619/REK).

Results

Descriptive statistics are shown in Table 2. Among the participants, 4055 (12.77%) used antidepressants. More women than men used antidepressants (16.65% vs. 8.36%, $\chi^2 = 1242.31$, $p < .001$). Of the total sample, 1047 had a fatal ($n = 404$) or non-fatal ($n = 649$) MI (6 participants had both), and men were overrepresented in both outcomes.

(Insert Table 2 around here)

The results of the logistic regression analyses are shown in Table 3. The odds ratio of antidepressant use on MI was 0.52, 95% CI [0.40, 0.67], indicating that antidepressant use was associated with significantly reduced odds of having an MI. Depression symptoms increased the risk of MI in the initial model (OR = 1.02 [1.00, 1.05]). Adding covariates to the model did not ameliorate the association of antidepressant use substantially, as it remained at 0.49 [0.38, 0.64]. Depression symptoms had a marginal association with MI (OR = 1.03 [1.00, 1.06]) and anxiety symptoms did not have a significant association with the odds of having an MI in the fully adjusted model including other risk factors and antidepressant use. The traditional risk factors of diabetes, waist-hip ratio, cholesterol, smoking, blood pressure all had significant associations with MI. Men were more likely to have an MI, OR = 1.77 [1.46, 2.15]. The fully adjusted model including known risk factors had a significantly better fit than the partially adjusted model including only antidepressant use and depression symptoms, $\chi^2 = 418.16$, $p < .001$, and R^2_{McFadden} increased from 0.19 to 0.23.

(Insert Table 3 around here)

When running separate analyses for men and women, the initial associations of antidepressant use were 0.46 [0.31, 0.68] and 0.57 [0.40, 0.80] for women and men respectively. After adjusting for

additional variables this association was strengthened further to 0.53 (0.37, 0.75) for men, while it remained stable for women. The models had somewhat larger $R^2_{McFadden}$ values for women than for men (0.30 vs. 0.19 for Model 2). We ran analyses testing a potential interaction between antidepressant use and sex. The interaction term was not significant, OR = 1.16, 95% CI [0.69, 1.94], indicating the absence of a sex-specific effect of antidepressant use on MI.

Follow-up analyses were performed with three different categories of antidepressants (see Table 4). Fully adjusted logistic regression models were run on the total sample, women and men, for each of the following three categories: TCA, SSRI and other antidepressants. Both TCA and SSRI were linked to a significant reduction in risk of MI across all three groups. There were no significant associations of other antidepressants with MI risk.

(Insert Table 4 around here)

The results from the bivariate analysis of differences between antidepressant users and non-users are presented in Table 5. The largest differences were observed in anxiety and depression symptoms where the antidepressant users scored higher (d = -.67 and -.47 respectively, representing a moderate to large effect size (48)). Non-users had higher systolic blood pressure, while antidepressant users had higher waist-hip ratio, higher cholesterol level, had smoked for longer and were more likely to be women ($\varphi = 0.12$). The effect size for the variables other than anxiety and depression symptoms were small, the highest observed for smoking (d = -.22).

(Insert Table 5 around here)

Comparing the OR of having an MI in different groups using “no depression/no antidepressant use” as the reference group showed that those with a depression score above 7 and not using antidepressants had the highest odds, while those non-depressed using antidepressants had the lowest odds (Table 6).

(Insert Table 6 around here)

Discussion

In this study, antidepressant use was associated with reduced risk of incident MI. This association was stable after adjusting for anxiety symptoms, depression symptoms, and traditional risk factors. The odds of having an MI were lower for those taking antidepressants versus those who did not. Men had an increased risk of having MI, but the negative association between antidepressant use and MI was stronger for women. Despite this, we found no evidence of an interaction between antidepressant use and sex. Consistent with other studies (49-51), more women than men used antidepressants. The results could imply that antidepressants have a cardioprotective effect, consistent with other studies that have found that antidepressants are not linked to increased risk of CVD (52, 53) or reduces the risk (24, 54, 55). From our results it is not evident whether the antidepressants have a direct attenuating effect on the risk of MI, or if they indirectly reduce the risk of MI by treating depression. As other studies suggesting that antidepressant use might be harmful in a non-CVD population (24), the result from this study contradicts this assumption. As antidepressants might be used for treatment for other than depression (6), it is plausible that antidepressant use has a general preventive effect, not only for depressed individuals. However, this warrants further investigation in large scale studies, as there are significant side-effects of antidepressant use.

We did not have information on diagnoses of depression, and we were therefore unable to adjust for the presence of a depression diagnosis in the participants. Since antidepressants are commonly prescribed to treat depression, and depression has been linked to increased risk of MI (5) it is thus a possible confounding indicator. At the HUNT2 survey, however, participants indicated the level of depression symptoms they were experiencing at the time. Depression was a weak (total sample) and not significant (male and female) predictor of MI when adjusting for known risk factors. This was unexpected given prior findings in the same population (56, 57) and in general on depression as a

risk factor for CVD and MI (4, 5, 58) This surprising finding can be explained by depression being measured earlier than both antidepressant use and MI, or that the other risk factors are given more predictive power in sex-specific analysis. We examined the differences among antidepressant users and non-users on the variables included in the main analyses. Antidepressant users were more depressed and anxious, had a longer history of daily smoking. For the other health variables, the differences were marginal, which did not indicate the presence of a healthy user bias.

Most of the participants in the study used SSRI type antidepressants, but a large portion of those using antidepressant reported combined use of different types. We did not analyse dosage and the number of prescriptions a patient received. As the literature indicated that different types of antidepressant medications differently affect risk of CVD outcome (29), and that TCAs are more cardiotoxic than e.g. SSRI (19) we did secondary analyses of the association between different types of antidepressant medication and MI. Contrary to our expectations, the analysis showed that both TCA and SSRI had significant negative associations with MI risk, though other antidepressant medication did not.

Strengths and limitations

Because the NorPD was established in 2004 and the HUNT3 survey ended in 2008, there was a limited time in which the relationship between antidepressants and MI could be discovered. Participants were asked at the HUNT2 Survey to indicate whether they had used antidepressants during the last twelve months. Otherwise, all data on antidepressant use came from between 2004 and the end of HUNT3 survey in 2008. Since the HUNT2 survey ended in 1997, there is a gap in the data between when depression and anxiety were assessed and when data on antidepressant use could be assessed, and this represents an important limitation in this study. We specifically excluded participants with prior CVD. However, other studies have found that antidepressants are less likely to impact the risk of cardiovascular events in post-CVD patients (23). Since we excluded

participants with previous cases of CVD, the results cannot be generalised to post-CVD patients. However, lack of specificity in outcome has hampered the general research, and focusing on a population free of CVD at baseline, running separate analysis for men and women, and addressing one specific outcome, i.e. MI, represent a strength of this study.

Other strengths of this study include robust analyses, a large sample, and inclusion of the traditional risk factors as covariates. As the participants were followed for several years, we could identify those who received antidepressants before they had an MI. The use of registry data also eliminates some of the problems with self-reported data. However, some data were self-reported, like smoking, diabetes and non-fatal MI. It should be noted that several of the self-reported variables in HUNT, including diabetes, have been validated against register data (45). We were unable to adjust for the presence of a diagnosis of depression, so we cannot conclude that antidepressant use reduces the risk of MI among clinically depression patients. However, when adjusting for symptom-level depression among initially CVD-free participants, antidepressant use was associated with a reduced risk of MI.

Conclusion

The results add to the growing list of studies that show antidepressants to be safe in terms of cardiovascular risk. Although limitations apply to CVDs other than MI and concerning dosage and duration of antidepressant use, our results indicate that men and women with no known history of CVD, are equally likely to benefit in terms of MI risk in receiving antidepressant medication, and that this applies for both SSRI and TCA.

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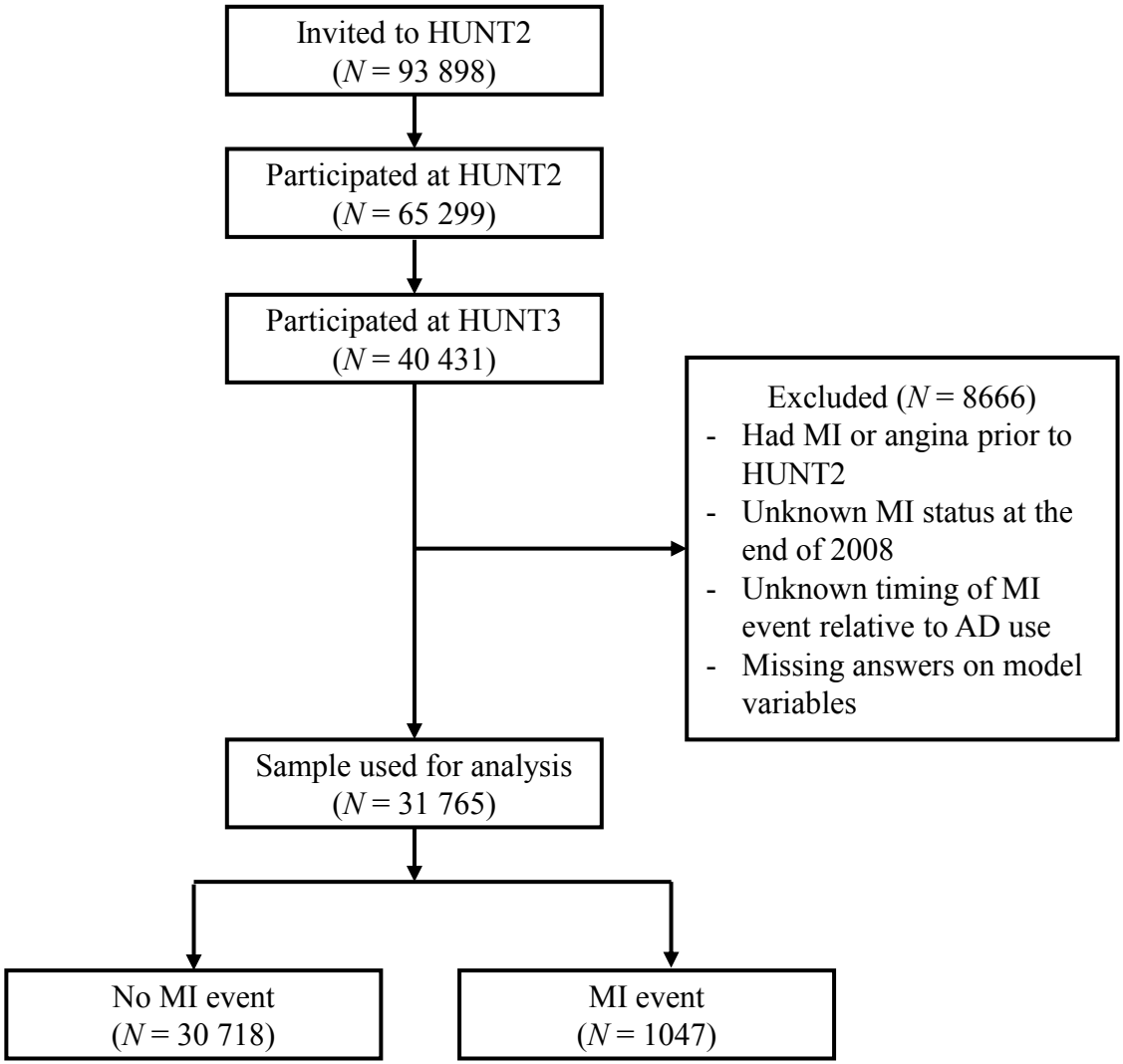

Figure 1. Flowchart of participation.
Note. MI = myocardial infarction. AD = antidepressant

Table 1. *Number of participants using various antidepressants*

	Women		Men	
	Using	Percent	Using	Percent
TCA	842	29.9%	324	26.1%
SSRI	1526	54.3%	627	50.4%
MAO-A	28	1.0%	8	0.6%
Other	751	26.7%	357	28.7%
Unknown	212	7.5%	140	11.3%
Any antidepressant	2812		1243	

Note. TCA: Tricyclic antidepressants. SSRI: Selective serotonin reuptake inhibitors. MAO-A: Monoamine oxidase A inhibitors. Other: Other antidepressants. For some participants it is unknown which antidepressant they used. Percent shows the percentage of all the antidepressant users that used this antidepressant. Note that the first four rows are not mutually exclusive, a participant may have used more than one type of antidepressant.

Table 2. *Descriptive statistics and differences according to MI status (N = 31 765).*

	Women			Men		
	No MI (*N* = 16 560)	Had MI (*N* = 330)	*p*	No MI (*N* = 14 158)	Had MI (*N* = 717)	*p*
Depression	3.03 (2.84)	3.83 (2.95)	< 0.001	3.33 (2.81)	3.87 (3.06)	< 0.001
Anxiety	4.41 (3.34)	3.99 (3.37)	0.026	3.88 (3.00)	3.47 (2.99)	< 0.001
Age	44.54 (12.91)	64.74 (12.72)	< 0.001	45.10 (12.50)	59.10 (12.64)	< 0.001
Smoking	9.78 (11.89)	17.51 (17.86)	< 0.001	11.38 (13.39)	24.11 (16.86)	< 0.001
Waist-Hip ratio	0.79 (0.06)	0.82 (0.06)	< 0.001	0.89 (0.05)	0.92 (0.05)	< 0.001
Cholesterol	5.72 (1.23)	6.92 (1.26)	< 0.001	5.76 (1.12)	6.49 (1.08)	< 0.001
SBP	129 (19)	155 (25)	< 0.001	136 (16)	149 (20)	< 0.001
Antidepressant use						
No	13779 (83.2%)	299 (90.6%)	< 0.001	12953 (91.5%)	679 (94.7%)	0.002
Yes	2781 (16.8%)	31 (9.4%)		1205 (8.5%)	38 (5.3%)	
Diabetes						
No	16384 (98.9%)	300 (90.9%)	< 0.001	13956 (98.6%)	677 (94.4%)	< 0.001
Yes	176 (1.1%)	30 (9.1%)		202 (1.4%)	40 (5.6%)	

Note. Continuous variables show mean (standard deviation), categorical variables show frequency (percentage). MI = myocardial infarction, SBP = systolic blood pressure. Units for the variables: Depression and anxiety: scores ranging from 0–21. Age and smoking: years. Cholesterol: mmol/L. SBP: mmHg.

Table 3. *Association of antidepressant use and risk of myocardial infarction*

	Whole sample (*N* = 31 765)				Women (*N* = 16 890)				Men (*N* = 14 875)			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
Predictors	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Antidepressant use	0.52***	(0.40, 0.67)	0.49***	(0.38, 0.64)	0.46***	(0.31, 0.68)	0.46***	(0.31, 0.68)	0.57**	(0.40, 0.80)	0.53***	(0.37, 0.75)
Depression	1.02*	(1.00, 1.05)	1.03*	(1.00, 1.06)	1.04	(1.00, 1.08)	1.05	(1.00, 1.10)	1.02	(0.99, 1.05)	1.02	(0.99, 1.05)
Anxiety			0.99	(0.96, 1.01)			0.97	(0.93, 1.02)			0.99	(0.96, 1.03)
Diabetes			2.94***	(2.19, 3.96)			3.93***	(2.48, 6.23)			2.45***	(1.66, 3.60)
SBP			1.01***	(1.01, 1.02)			1.02***	(1.01, 1.02)			1.01***	(1.01, 1.02)
Cholesterol			1.35***	(1.28, 1.43)			1.15**	(1.05, 1.27)			1.42***	(1.32, 1.53)
WHR			14.13***	(4.33, 46.09)			60.10***	(8.55, 422.31)			7.14**	(1.61, 31.71)
Smoking			1.02***	(1.02, 1.03)			1.03***	(1.02, 1.04)			1.03***	(1.02, 1.03)
Age	1.10***	(1.10, 1.11)	1.07***	(1.06, 1.08)	1.13***	(1.12, 1.14)	1.10***	(1.09, 1.12)	1.09***	(1.08, 1.10)	1.06***	(1.05, 1.07)
Gender	2.51***	(2.19, 2.88)	1.77***	(1.46, 2.15)								
R^2_{McFadden}	0.19		0.23		0.24		0.30		0.14		0.19	
LL	-3,728.41		-3519.33		-1,242.98		-1154.66		-2,467.47		-2333.47	
AIC	7,466.81		7060.65		2,493.95		2329.32		4,942.93		4686.94	

Note. **p* < .05; ***p* < .01; ****p* < .001. WHR = waist-hip ratio. SBP = systolic blood pressure. Antidepressant use = baseline is no antidepressant use. Diabetes = baseline is non-diabetic. Gender = baseline is female. MI = myocardial infarction. OR = odds ratio. CI = confidence interval. LL = log likelihood. AIC = Akaike information criterion. Model 1 includes antidepressant use, depression symptoms, age and sex. Model 2 includes all predictors. Units for the variables: Depression and anxiety: HADS scores ranging from 0–21. Age and smoking: years. Cholesterol: mmol/L. SBP: mmHg.

Table 4. *Odds ratio of the different antidepressant groups on MI risk.*

	Whole sample (N = 31 765)		Women (N = 16 890)		Men (N = 14 875)	
Antidepressant	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
TCA	0.28***	(0.15, 0.53)	0.37*	(0.16, 0.86)	0.21**	(0.08, 0.58)
SSRI	0.45***	(0.31, 0.65)	0.38***	(0.22, 0.65)	0.51**	(0.30, 0.84)
Other	0.64	(0.41, 1.00)	0.64	(0.33, 1.26)	0.63	(0.34, 1.16)

Note. *p < .05; **p < .01; ***p < .001. Each row represents a model with one specific antidepressant as the predictor, adjusted for all covariates: depression, anxiety, diabetes, systolic blood pressure, cholesterol, waist-hip ratio, years smoked, age and gender (the latter only in the first column). MI: Myocardial infarction. OR: Odds ratio. CI: Confidence interval. TCA: Tricyclic antidepressants. SSRI: Selective serotonin reuptake inhibitors. Other: Other antidepressants.

Table 5. *Comparison of users of antidepressants with non-users* (N = 31,765)

	Non-users (N = 27,710)	AD users (N = 4,055)	Group difference	Effect size
Depression	3.00 (2.67)	4.48 (3.55)	$t(4,744) = -25.44$, $p < .001$[a]	$d = -0.47$
Anxiety	3.84 (2.93)	6.21 (4.06)	$t(4,693) = -35.73$, $p < .001$[a]	$d = -0.67$
SBP	133.58 (18.43)	131.57 (18.66)	$t(31,763) = 6.49$, $p < .001$	$d = 0.11$
Cholesterol	5.75 (1.19)	5.87 (1.21)	$t(31,763) = -5.84$, $p < .001$	$d = -0.10$
WHR	0.84 (0.08)	0.83 (0.07)	$t(5,360) = 7.86$, $p < .001$[a]	$d = 0.13$
Smoking	10.53 (12.91)	13.44 (13.19)	$t(5,254) = -13.14$, $p < .001$[a]	$d = -0.22$
Age	45.17 (13.16)	46.36 (12.20)	$t(5,530) = -5.74$, $p < .001$[a]	$d = -0.09$
Diabetes				
No	27,337 (98.7%)	3,980 (98.2%)	$\chi^2(1) = 6.10$, $p = .014$	$\varphi = 0.01$
Yes	373 (1.3%)	75 (1.8%)		
Sex				
Women	14,078 (50.8%)	2,812 (69.3%)	$\chi^2(1) = 487.67$, $p < .001$	$\varphi = 0.12$
Men	13,632 (49.2%)	1,243 (30.7%)		
Had MI				
No	26,732 (96.5%)	3,986 (98.3%)	$\chi^2(1) = 36.51$, $p < .001$	$\varphi = 0.03$
Yes	978 (3.5%)	69 (1.7%)		

Note. AD = antidepressants. SBP = systolic blood pressure. WHR = waist-hip ratio. MI = myocardial infarction. Continuous variables show mean (standard deviation), categorical variables show frequency (percentage). Independent samples *t*-tests were used to test group differences on continuous variables. [a]Welch's approximation due to heteroskedasticity. Pearson's chi-square test was used to test group differences on categorical variables. Units for the variables: Depression and anxiety: HADS scores ranging from 0–21. Age and smoking: years. Cholesterol: mmol/L. SBP: mmHg.

Table 6. Associations of categorical depression and antidepressant use on risk of MI.

	N	(%)	OR	*p*
No depression, no AD	25,814	(81.27)	(reference)	
No depression, AD	3271	(10.30)	0.48	<.001
Depression, no AD	1896	(5.97)	1.21	.120
Depression, AD	784	(2.47)	0.64	.077

Note. Categorical depression was created by using the recommended HADS cut-off scores of 8. AD = antidepressant use. OR = odds ratio. MI = myocardial infarction. Model adjusted for anxiety, diabetes, systolic blood pressure, cholesterol, waist-hip ratio, years smoked, age and sex.