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ORIGINAL RESEARCH ARTICLE

Associations of Cardiovascular Agents and Metformin with Depression Symptoms: A Cross-Sectional Analysis from the HUNT Study, Norway

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Abstract

Background Cardiovascular agents, including angiotensin-converting enzyme inhibitors, angiotensin II receptor inhibitors, acetylsalicylic acid, statins, and metformin, have demonstrated benefits for depression. However, there is scant evaluation of these drugs' antidepressant properties in large population settings.

Objective This study aimed to examine cross-sectional associations between depression symptoms and the use of cardiovascular agents and metformin in populations with cardiovascular diseases or diabetes mellitus.

Methods Participants in the Trøndelag Health Study 2006–08 (HUNT3, $n = 40{,}516$) and 2017–19 (HUNT4, $n = 42{,}103$) were included and data on their drug use from 2006 to 2019 was retrieved from the Norwegian Prescription Database. The outcome was self-reported depression symptoms defined by the Hospital Anxiety and Depression Scale. Associations between cardiovascular agents or metformin use and self-reported depression were analyzed by multi-level logistic regression in sex-stratified samples.

Results Among men with cardiovascular diseases, use of acetylsalicylic acid was associated with reduced depression symptoms compared with acetylsalicylic acid non-users (reference) in HUNT3 and HUNT4 [risk ratio = 0.76; 95% confidence interval 0.59–0.94, risk ratio = 0.67; 95% CI 0.52–0.82, respectively]. Similarly, male statin users had a lower likelihood of reporting depression than statin non-users in HUNT3 (risk ratio = 0.70; 95% confidence interval 0.54–0.86) and HUNT4 (risk ratio = 0.67; 95% confidence interval 0.51–0.84). Associations between statins or acetylsalicylic acid use and reduced depression symptoms were detected in women with cardiovascular diseases in HUNT4. We found no statistical support for associations between other cardiovascular agents or metformin use and a reduced or increased depression symptom risk.

Conclusions Results suggest negative associations between acetylsalicylic acid or statin use and depression symptoms. However, longitudinal cohort studies and randomized controlled trials are required to confirm the antidepressant effects of these drugs.

1 Introduction

The prevalence of cardiovascular diseases (CVDs), diabetes mellitus (DM), and depression has been steadily rising and contributes heavily to the global burden of disease [1, 2], death, and disability [3]. Furthermore, individuals with CVDs or DM tend to be more prone to psychological conditions such as depression, both at symptomatic and diagnostic levels, than adults in general [4, 5]. Depression in those patients with CVDs or DM often leads to poorer treatment outcomes [6, 7], lower quality of life [8, 9], excess mortality [10], and increased healthcare costs [11, 12], compared with

Key Points

Acetylsalicylic acid or statin use was associated with a reduced risk of depression symptoms compared with non-use of these cardiovascular agents.

The use of other cardiovascular agents or metformin showed no statistical evidence for a relationship with depression symptom risk.

This study suggests the potential benefit of acetylsalicylic acid or statins for depression treatment. Further population-based studies with extended follow-up of the same subjects and studies with an experimental design are needed to firmly establish the antidepressant effects of cardiovascular and antidiabetic agents in people with cardiovascular diseases and diabetes mellitus.

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patients without depression. The importance of improved prevention and treatment of depression among patients with CVDs and DM is recognized and highlighted in clinical practice guidelines [13, 14].

Unfortunately, psychological conditions, including depression, often remain undetected and inadequately treated in populations with CVDs or DM [15, 16]. Sexual dysfunction, sedation, and weight gain are frequent side effects of antidepressant agents that often lead to poor adherence to these drugs [17]. Furthermore, some antidepressants can be associated with uncommon adverse drug reactions, such as QT interval prolongation, increased pulse, and hypertension [18, 19], which are problematic for people with pre-existing CVDs or DM [20, 21]. Therefore, there remains a need for novel depression treatments with an improved adverse-effect profile. Moreover, the growing burden of depression in populations with CVDs or DM makes it necessary to find an integrative approach to prevent and treat depression in these patient groups.

A growing body of literature suggests close but complex relationships between depression and physical diseases such as CVDs and DM [22, 23]. Some evidence points to shared pathophysiologies of depression, CVDs, and DM (such as hypothalamic-pituitary-adrenal axis, immuno-inflammatory, metabolic, and oxidative stress) that results in peripheral and central low-grade inflammation [22, 24]. Thus, inflammatory pathways may be an additional target in depression treatment [25–27]. Consequently, various anti-inflammatory, cardiovascular, and antidiabetic agents have been explored for putative antidepressant effects [24, 28–32]. To date, clinical and observational studies addressing relationships between pharmacotherapies for CVDs or DM and depression symptoms have been limited and inconsistent.

Several cardiovascular agents may be beneficial for depression. A review of the literature on drugs targeting the renin-angiotensin system (RAS) showed that angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) were associated with lower depression symptom levels or depression disorders, while other antihypertensive agents were not [27]. Moreover, RAS-acting agents have been associated with a reduced likelihood of hospitalization for mood disorders [33], decreased use of antidepressant agents [34], and improved mental health [35]. Other studies, however, reported neither increased nor reduced depression symptoms or disorders associated with RAS agent use [36, 37]. Investigation of associations between other cardiovascular agents, including calcium channel blockers (CCB) and beta-blockers (BB) with depression symptoms, have also yielded mixed results [36, 38]. Similarly, by reducing inflammation, treatment with inhibitors of cyclooxygenase, including acetylsalicylic acid (ASA) [28], or cholesterol-lowering drugs (statins) [31, 39], have potential antidepressant effects. The use of metformin, a first-line antidiabetic agent for type 2 DM treatment, has shown a promising improvement in depression in adults with DM [40–43]. However, evidence on the putative antidepressant effect of metformin remains limited and inconclusive [44].

Observational research suggests that cardiovascular agents and metformin might benefit depression, yet existing findings are conflicting. Furthermore, whether and to what degree these drugs can exert antidepressant effects in community settings remains unclear. Studies investigating the relationships of various cardiovascular and antidiabetic agents within large population-based samples with concurrent depression symptoms over time are still lacking. Therefore, this study aimed to examine the association between various cardiovascular and antidiabetic agents and depression symptom risk among adults participating in the large population-based health study, the Trøndelag Health Study (HUNT). Dispensed drug prescriptions of HUNT participants from the Norwegian Prescription Database (NorPD), a register of all dispensed prescriptions in Norway, allowed us to investigate the use of several drug classes with an 11-year interval adjusted for relevant confounders.

2 Methods

2.1 Study Population

The HUNT is a large population-based health study of community-dwelling adults living in Trøndelag County, Norway, that comprises four cross-sectional surveys: the HUNT1 survey (1984–6), the HUNT2 survey (1995–7), the HUNT3 survey (2006–8), and the HUNT4 survey (2017–19). All adult inhabitants (aged ≥ 20 years) were invited to participate in all surveys, and the number of participants (response rate) was 77,212 (89.4%) in HUNT1, 65,237 (69.5%) in HUNT2, 50,807 (54.1%) in HUNT3, and 56,078 (54%) in HUNT4. The number of eligible adults in the county for the study has changed over time, and the presented number of participants with participation rates (in %) is for the data collection point. The population in HUNT is considered representative of general Norwegian adults and is ethnically homogenous with low migration [45]. All HUNT participants gave their written consent for research on their data. More information on the HUNT database is described elsewhere (https:/www.ntnu.edu/hunt/databankhttps:/www.ntnu.edu/hunt/databank). We used data from HUNT3 and HUNT4 surveys to derive a study population whose dispensed drug prescriptions were collected from NorPD. Of the total, 40,516 participants in HUNT3 and 42,103 in HUNT4 who answered the main questionnaires (Q1 and Q2) and yielded valid data on self-reported psychological symptoms (i.e., anxiety and depression) were eligible to study. Among them, over 23,000

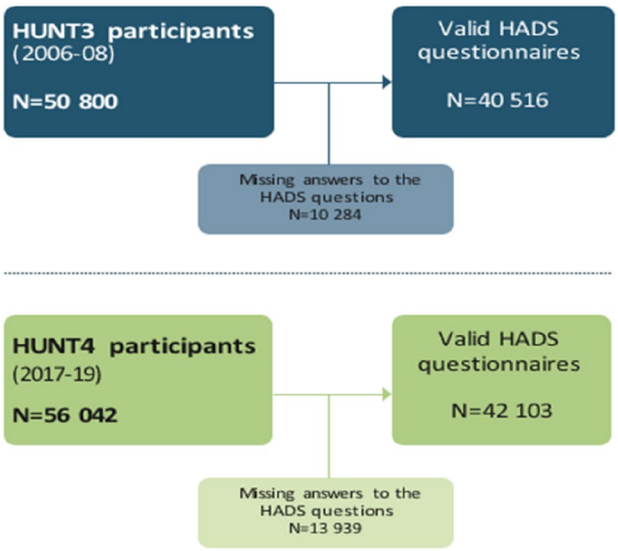

Fig. 1 Flow chart showing the selection criteria for study participants based on valid Hospital Anxiety and Depression Scale (HADS) questionnaires for selecting the study participants. Participants with five or more answers on the HADS-Depression subscale (HADS-D) and HADS-Anxiety subscale (HADS-A) questionnaires were included

participants participated in both studies. Samples analyzed included only participants who self-reported CVDs or DM status. Cardiovascular disease status was measured via questions on a history of myocardial infarction, angina, stroke, or heart failure (yes/no). History of type 1 DM, type 2 DM, and other DM types were defined as DM (yes/no). Participants who answered at least one question were classified as having CVDs or DM or not. Figure 1 shows the flow chart of the study participant selection process. HUNT participants gave their written consent for research on their data. This study was approved by the Regional Committees for Medical Research and Health Research Ethics in Norway (reference 2019/30292/REK Nord) and the Norwegian Centre for Research Data (reference 30292/NSD).

2.2 Data Material

This study used data on health conditions, including self-reported psychological symptoms, lifestyle, and sociodemographic characteristics from HUNT3 and HUNT4 surveys combined with the NorPD. The NorPD is a national database that contains information about all drugs dispensed by prescription at pharmacies to all inhabitants in Norway (about 4.8 million) since 2004 (https://www.fhi.no/en/hn/health-registries/norpd/). In Norway, all citizens, independent of socioeconomic status, have unrestricted access to health services, including partial or complete reimbursement of purchased drugs. The NorPD data material for this study included information on the participant (i.e., project ID and sex), dispensed prescriptions (i.e., monthly and yearly dispensing), and drug (i.e., Anatomic Therapeutic Chemical [ATC] code). Data collected from the HUNT questionnaires were linked to information on dispensed prescriptions of cardiovascular and antidiabetic agents drawn from the NorPD from January 2006 through December 2019 through a personal identification number.

2.3 Outcome Variable: Depression Symptoms

The main outcome variable in this study was self-reported depression symptoms. The clinical expression of depression differs from anxiety; however, both conditions show a considerable symptom overlap, and their concurrent assessment is recommended [46]. The Hospital Anxiety and Depression Scale (HADS) is a brief self-report questionnaire for depression and anxiety symptoms. The HADS consists of 14 items, seven for anxiety (HADS-A subscale) and seven for depression (HADS-D subscale), each scored on a Likert scale from 0 (no symptoms) to 3 (symptoms maximally present) [46]. At least five completed items on both HADS subscales (i.e., valid HADS questionnaires) were required for inclusion in this study. The score of participants who filled in five or six items was based on the sum of completed items multiplied by 7/5 or 7/6, respectively. There was a cut-off threshold of 8 (for normal to mild symptoms) on the HADS-D subscale; thus, depression and anxiety symptoms in our samples were not mutually exclusive. The rationale behind this approach is that symptoms of depression and anxiety often overlap [46], and mixed symptoms are common in populations with other somatic symptoms [47]. This cut-off value provides optimal sensitivity and specificity (about 0.80) and correlates well with clinical depression based on Diagnostic and Statistical Manual of Mental Disorders, Third Edition and International Classification of Diseases, Eighth Revision/Ninth RevisionI diagnostic criteria [48]. The HADS-D subscale is a reliable instrument for detecting symptoms of depression (with or without anxiety) and describing symptom severity among both general and clinical populations [49, 50]. Reliability was examined by ordinal and traditional Cronbach's alpha and performed well on both HADS-A and HADS-D subscales (ordinal alpha was 0.92 and 0.88; Cronbach's alpha was 0.87 and 0.81, respectively) [51].

2.4 Exposure Variable: Drug Use

Filled prescriptions of cardiovascular and antidiabetic agents were used as proxies for these drugs' consumption, which were confirmed as a reliable measurement of drug use [52]. Drugs were defined according to the World Health Organization (WHO) ATC classification system [53]. The study included the prescription of drugs with the following ATC codes: B01A C06 (ASA), C03 (Diuretics), C07

(BB), C08 (CCB), C09A (ACE-I), CO9C (ARBs), C10A A (HMG-CoA-reductase inhibitors or statins), A10B A02 (Metformin), A10B B (Sulfonylureas), A10B F (Glucosidase inhibitors), A10B G (Thiazolidinediones), A10B H (Dipeptidyl peptidase 4 (DPP-4) inhibitors), A10B J (Glucagon-like peptide-1 (GLP-1) analogues), and A10B K (Sodium-glucose co-transporter 2 (SGLT2) inhibitors). Cardiovascular agents, including ACE-I, ARBs, ASA, BB, CCB, statins, and diuretics, were analyzed among participants with CVDs, whereas metformin was analyzed among participants with DM. The choice of cardiovascular and antidiabetic agents to analyze was also based on the available number of users in our data material, which was sufficient to provide power for the statistical analysis. The number of participants using other antidiabetic agents than metformin was too small to provide precise prevalence estimates (95% confidence interval [CI]) and optimal statistical models. Therefore, these agents were excluded from the prevalence analysis and the multilevel logistic analysis. Associations of each ATC drug class (exposure) with anxiety and depression symptoms (outcome) were analyzed independently. In Norway, prescriptions have a validity period of 1 year from the date of issue. However, drugs used for treating chronic illnesses usually are typically dispensed at pharmacies in quantities corresponding to approximately 3 months' use. In this study, individuals with one or more drug prescriptions dispensed during the 9 months before participation in HUNT3 or HUNT4 were defined as drug users in HUNT3 and HUNT4, respectively.

2.5 Other Covariates

Sociodemographic characteristics of the study sample included: sex (classified as women and men), age (mean and age groups < 55, 55–64, and ≥ 65 years), and cohabitation status (living with someone vs living alone). Lifestyle measurements included "current smoking" (yes/no), physical activity (inactive vs active), and monthly alcohol consumption (no or low drinking vs moderate to frequent). Consuming alcohol never or one or less times per week was defined as no or low drinking, while drinking from two to three times or four or more times per week was defined as moderate to frequent drinking. In HUNT, leisure-time physical activity was measured by questions about light (i.e., no sweating or heavy breathing) and hard (i.e., sweating and heavy breathing) physical activity per week. We defined the respondents with no physical activity or less than one time per week as not physically active, while those with more than one time per week of hard/light physical activity were physically active. Chronic diseases (yes/no) were measured with the question: "Do you suffer from a long-lasting (at least 1 year) illness or injury of a physical or psychological nature that impairs your functioning in your daily life?". Clinical measurements included body mass index, categorized as underweight or normal (< 25 kg/m^2) or overweight or obese (≥ 25 kg/m^2) according to the World Health Organization defined cut-off for overweight and obesity classification [54]. Antidepressant use included prescriptions of drugs with the following ATC codes: N06A A (Non-selective monoamine reuptake inhibitors), N06A B (Selective serotonin reuptake inhibitors (SSRI), N06A G02 (Monoamine oxidase A [MAOA] inhibitors), and N06A X (Other antidepressants).

2.6 Statistical Analysis

The prevalence of self-reported depression symptoms was evaluated using cross-sectional data from HUNT3 and HUNT4 performed approximately 11 years apart. Descriptive statistics regarding baseline characteristics included frequencies and percentages. The study population's characteristics were stratified by sex. Categorical variables were compared using a χ^2 test between groups of participants at the 0.05 significance level. Depression symptoms prevalence rates shown in Fig. 2 were age standardized (using the age categories < 55, 55–64, and ≥ 65 years) by direct standardization using the age distribution of participants attending the screening in HUNT3 as the standard population. Each drug class and the risk of depression symptoms were analyzed by multilevel logistic models, using a cut-off of 8 on the HADS-D subscale. Anxiety status based on the HADS-A subscale was not specified in the model, and our analytic samples included individuals with pure depression and those with depression and anxiety symptoms. The rationale behind such an approach was that somatic health problems such as CVDs or DM showed stronger associations with mixed anxiety and depression symptoms than each symptom alone [55]. Of note, the authors of the HADS scale recommended that HADS-D and HADS-A subscales should be used separately [56]. Multilevel models were specified to account for repeated measurements on the same participants (i.e., non-independent observations), given that over 23,000 participated in both surveys. The used models take into account that the outcomes within the same individual are likely to be more similar than for two randomly selected individuals, whereas they do not explicitly address changes in the exposure (e.g., treatment discontinuation, change of drug, and others). By using model predictions, we calculated relative risk ratios (RRs) and absolute risk differences (RDs) for having depression symptoms for individuals with any dispensed drug prescription versus no drug prescriptions (reference category) 9 months before HUNT as the reference. Associations of drug use and self-reported depression were reported with 95% CIs. A multivariable analysis of cardiovascular agents was restricted to participants with CVDs, whereas an analysis of metformin was restricted to participants with DM. The rationality for this approach was to improve comparability

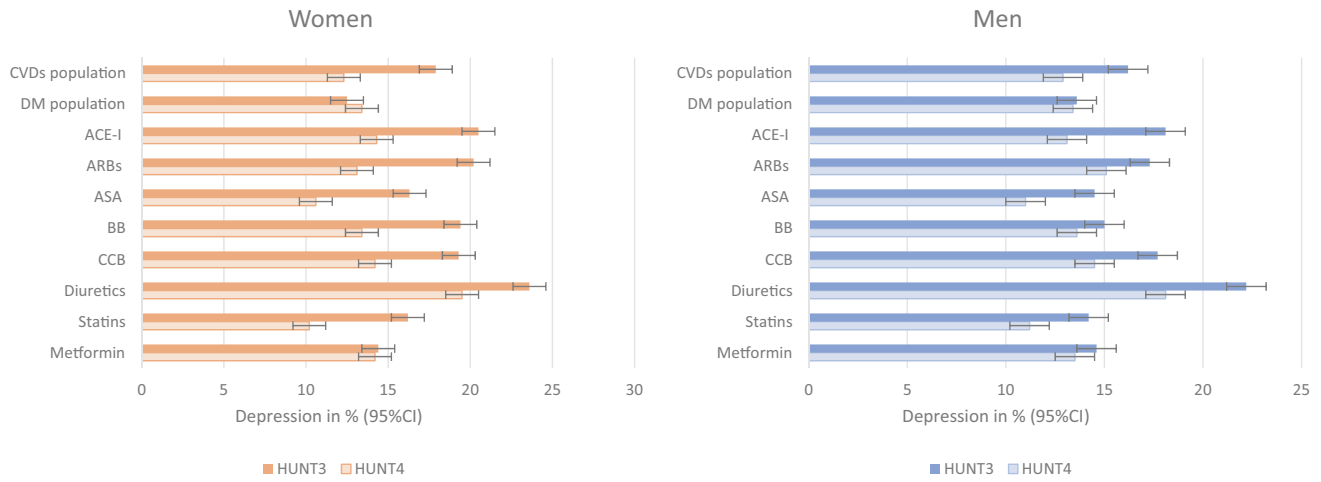

Fig. 2 Depression symptom prevalence (Hospital Anxiety Depression-subscale Depression [HADS-D] ≥ 8) among participants with cardiovascular diseases (CVDs; myocardial infarction/angina/stroke/heart failure) or diabetes mellitus (DM) stratified by sex, presented in total, and by prescriptions of cardiovascular agents and metformin, 9 months before HUNT3 or HUNT4 participation. Age standardized using the age distribution of participants attending a screening in HUNT3 as the standard population. *ACE-I* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *ASA* acetylsalicylic acid, *BB* beta-blockers, *CCB* calcium channel blocker, *CI* confidence interval, *HUNT* The Trøndelag Health Study

between exposed (i.e., drug users) and non-exposed (i.e., no drug users = reference) participants and to control for potential confounding by these physical conditions. All statistical models were stratified by sex. The crude models considered only age adjustment (age and age squared).

Further analysis included adjustment for smoking status, chronic diseases, and antidepressant use. To minimalize the potential influence of pre-existing depression, we excluded participants using antidepressants yielding very similar results. The inclusion of other lifestyle variables and body mass index in models did not change our results. Thus, the reported final models included smoking status and chronic diseases as potential confounders, whereas participants with antidepressant use were excluded. The statistical software Stata® (Version 17) was used in the analysis. All models performed in this study are shown in the supporting information (Table 1 of the Electronic Supplementary Material).

3 Results

3.1 Study Population Characteristics

In total, 40,516 participants from HUNT3 and 42,103 from HUNT4 were enrolled in the study. Table 1 shows the sociodemographic, lifestyle and health characteristics, drug use, and depression symptoms among participants in HUNT3 and HUNT4 surveys, stratified by sex. The age distribution was relatively similar across three age groups in both periods and sexes, with most participants in the age group < 5 5 years. The prevalence of CVDs was approximately 13.0% in men and 6.0% in women during the study. Likewise, the proportion of DM participants was higher among men (5.4% in HUNT3 and 7.5% in HUNT4) than women (4.0% in HUNT3 and 5.1% in HUNT4). Depression symptom prevalence rates were slightly higher in men than women. The prevalence of cardiovascular agent use ranged between drug classes and sexes, for example, 2.8% of women used ACE-I in HUNT3, while 5.2% of men used ACE-I in HUNT4, and the prevalence of statin use was 12.5% among women in HUNT3 and 21.1% among men in HUNT4. Overall, the prevalence of cardiovascular agents and metformin use was higher in men than women, except for diuretics. In contrast, twice as many women than men used antidepressants. Most participants lived with someone, were non-smokers, physically active, reported no to low alcohol consumption and no chronic diseases, and were overweight to obese.

Figure 2 shows the depression symptoms prevalence among participants with CVDs or DM in total and for users of various cardiovascular agents and metformin. Among CVD groups, overall depression symptom prevalence was 17.9% in women and 16.2% in men in HUNT3, and 12.5% in both sexes in HUNT4. The depression prevalence rates among participants using cardiovascular agents varied considerably, from 23.6% among women using diuretics to 10.6% and 10.2% in users of ASA and statins in HUNT3, respectively. Depression prevalence ranged from 12.4 to 13.4% in women with DM and was 13.5% in men with DM in HUNT3 and HUNT4, respectively. Among them, about 14% of metformin users reported depression in the same period in both sexes.

Table 1 Sociodemographic, lifestyle and health characteristics, drug use, and depression symptoms among participants in HUNT3 and HUNT4 surveys, stratified by sex

Total *n* (%)	HUNT3 (2006–8) *N* = 40,516		HUNT4 (2017–19) *N* = 42,103	
	Women *n* = 22,688 (56.0)	Men *n* = 17,828 (44.0)	Women *n* = 24,098 (57.2)	Men *n* = 18,005 (42.8)
Age (years)				
Mean (SD)	53.6 (16.0)	55.3 (15.0)	54.9 (17.2)	57.3 (16.4)
< 55	11,825 (52.1)	8318 (46.7)	11,560 (48.0)	7382 (41.00)
55–64	5161 (22.8)	4623 (25.9)	4929 (20.5)	3904 (21.7)
≥ 65	5702 (25.1)	4887 (27.4)	7609 (31.5)	6719 (37.3)
Cohabitation				
Living with someone	17,928 (79.0)	14,832 (83.2)	18,183 (75.5)	14,602 (81.1)
Living alone	4760 (21.0)	2996 (16.8)	5915 (24.5)	3403 (18.9)
Current smoking				
No	16,673 (73.5)	13,597 (76.3)	21,349 (88.6)	16,449 (91.4)
Yes	5392 (23.8)	3800 (21.3)	2500 (10.4)	1440 (8.00)
Missing	623 (2.7)	431 (2.4)	249 (1.0)	116 (0.6)
Physical activity				
Inactive[a]	865 (3.8)	1061 (6.0)	815 (3.4)	800 (4.5)
Active[b]	21,424 (94.4)	16,513 (92.6)	22,744 (94.4)	16,882 (93.8)
Missing	399 (1.8)	254 (1.4)	539 (2.2)	323 (1.7)
Alcohol consumption				
No or low[c]	15,180 (66.9)	9616 (53.9)	19,853 (82.4)	13,074 (72.6)
Moderate to frequent[d]	6827 (30.1)	7894 (44.3)	3783 (15.7)	4672 (26.0)
Missing	681 (3.00)	318 (1.8)	462 (1.9)	259 (1.4)
Depression[e]				
No	20,680 (91.2)	15,930 (89.4)	21,874 (90.8)	16,109 (89.5)
Yes	2008 (8.8)	1898 (10.6)	2224 (9.2)	1896 (10.5)
CVDs				
No	21,252 (93.7)	15,575 (87.4)	21,544 (89.4)	15,070 (83.7)
Yes	1431 (6.3)	2250 (12.6)	1533 (6.4)	2366 (13.1)
Missing	5 (0.0)	3 (0.0)	1 021 (4.2)	569 (3.2)
DM				
No	21,776 (96.0)	16,856 (94.6)	22,436 (93.1)	16,366 (90.9)
Yes	904 (4.0)	968 (5.4)	1217 (5.1)	1352 (7.5)
Missing	8 (0.0)	4 (0.0)	445 (1.8)	287 (1.6)
Chronic diseases				
No	12,688 (56.7)	10,234 (57.4)	13,066 (54.2)	10,223 (56.8)
Yes	9324 (41.1)	7292 (40.9)	10,596 (44.0)	7589 (42.2)
Missing	496 (2.2)	302 (1.7)	436 (1.8)	193 (1.0)
BMI[f] (kg/m^2)				
Underweight to normal	8651 (38.1)	4363 (24.5)	9266 (38.4)	4721 (26.2)
Overweight to obese	13,956 (61.5)	13,409 (75.2)	14,644 (60.8)	13,148 (73.0)
Missing	81 (0.4)	56 (0.3)	188 (0.8)	136 (0.8)
Drug use[g]				
ACE-I				
No	22,056 (97.2)	17,039 (95.6)	23,332 (96.8)	17,076 (94.8)
Yes	632 (2.8)	789 (4.4)	766 (3.2)	929 (5.2)
ARBs				
No	21,519 (94.9)	16,904 (94.8)	22,300 (92.5)	16,318 (90.6)
Yes	1169 (5.1)	924 (5.2)	1798 (7.5)	1687 (9.4)
ASA				

Table 1 (continued)

Total *n* (%)	HUNT3 (2006–8) *N* = 40,516		HUNT4 (2017–19) *N* = 42,103	
	Women *n* = 22,688 (56.0)	Men *n* = 17,828 (44.0)	Women *n* = 24,098 (57.2)	Men *n* = 18,005 (42.8)
No	20,602 (90.8)	15,219 (85.4)	21,882 (90.8)	15,191 (84.4)
Yes	2086 (9.2)	2609 (14.6)	2216 (9.2)	2814 (15.6)
BB				
No	20,421 (90.0)	15,561 (87.3)	22,012 (91.3)	15,881 (88.2)
Yes	2267 (10.0)	2267 (12.7)	2086 (8.7)	2124 (11.8)
CCB				
No	21,318 (94.0)	16,498 (92.5)	22,218 (92.2)	15,974 (88.7)
Yes	1370 (6.0)	1330 (7.5)	1880 (7.8)	2031 (11.3)
Diuretics				
No	21,125 (93.1)	16,798 (94.2)	22,995 (95.4)	17,303 (96.1)
Yes	1563 (6.9)	1030 (5.8)	1103 (4.6)	702 (3.9)
Statins				
No	19,856 (87.5)	14,983 (84.0)	20,492 (85.0)	14,211 (78.9)
Yes	2832 (12.5)	2845 (16.0)	3606 (15.0)	3794 (21.1)
Metformin				
No	22,159 (97.7)	17,227 (96.6)	23,397 (97.1)	17,164 (95.3)
Yes	529 (2.3)	601 (3.4)	701 (2.9)	841 (4.7)
Other antidiabetic agents				
No	22,631 (99.8)	17,745 (99.5)	24,014 (99.7)	17,905 (99.4)
Yes	57 (0.02)	83 (0.5)	84 (0.3)	100 (0.6)
Antidepressants				
No	20,394 (89.9)	16,939 (95.0)	21,516 (89.3)	17,073 (94.8)
Yes	2294 (10.1)	889 (5.0)	2582 (10.7)	932 (5.2)

ACE-I angiotensin-converting enzyme inhibitors, *Antidepressants* non-selective monoamine reuptake inhibitors, *ARBs* angiotensin II receptor blockers, *ASA* acetylsalicylic acid, *BB* beta-blockers, *BMI* body mass index, *CCB* calcium channel blockers, *CVDs* cardiovascular diseases (myocardial infarct/angina/stroke/heart failure), *DM* diabetes mellitus, *HADS-D* Hospital Anxiety and Depression-subscale Depression, *HUNT* The Trøndelag Health Study, *Other antidiabetic agents* sulfonylureas, glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, sodium-glucose co-transporter 2 inhibitors, selective serotonin reuptake inhibitors, monoamine oxidase A inhibitors, and other antidepressants, *SD* standard deviation

[a]Inactive = never or no light/hard physical activity per week; light physical activity (no sweating or heavy breathing) vs hard physical activity

[b]Active = less than once or more light/hard physical activity per week

[c]No or low drinking = never or one or less times/week

[d]Moderate (two to three times/week) to frequent (four or more times/week)

[e]Depression symptoms defined by HADS-D ≥ 8

[f]BMI; underweight to normal: BMI < 25 kg/m^2; overweight to obese: BMI ≥ 25 kg/m^2

[g]Drug use defined as one or more dispensed drug prescriptions during 9 months before participations in HUNT3 or HUNT4 surveys

3.2 Associations Between Drug Use and Depression Symptoms

Multilevel logistic models (Table 2) that included participants with CVDs showed that the use of statins or ASA was associated with a lower depression symptom risk compared with non-users of these cardiovascular agents. The identified associations remained essentially unchanged after adjustment for potential confounders (i.e., age, smoking, and chronic diseases) and after excluding individuals using antidepressants. Men with CVDs using statins had a 30–33% lower likelihood of reporting depression than no users in HUNT3 and HUNT4, respectively (RR = 0.70; 95% CI 0.54–0.86, RD = − 0.05; 95% CI − 0.08 to − 0.01) and

Table 2 Associations between drug use (reference = non-users) and depression symptoms among participants with CVDs and/or DM in HUNT3 and HUNT4 studies. RR and RD with 95% CI

	HUNT3 (2006–8)		HUNT4 (2017–19)		HUNT3 (2006–8)		HUNT4 (2017–19)	
Drug class	RR[a] (95% CI)	RR[b] (95% CI)	RR[a] (95% CI)	RR[b] (95% CI)	RD[a] (95% CI)	RD[b] (95% CI)	RD[a] (95% CI)	RD[b] (95% CI)
ACE-I								
Women	1.17 (0.83–1.51)	1.38 (0.89–1.88)	1.16 (0.76–1.55)	1.38 (0.84–1.91)	0.03 (− 0.02 to 0.07)	0.05 (− 0.01 to 0.10)	0.02 (− 0.02 to 0.06)	0.03 (− 0.01 to 0.08)
Men	1.06 (0.80–1-32)	1.03 (0.75–1.31)	1.07 (0.80–1.35)	1.02 (0.73–1.31)	0.01 (− 0.03 to 0.04)	0.00 (− 0.03 to 0.04)	0.01 (− 0.02 to 0.04)	0.00 (− 0.03 to 0.04)
ARBs								
Women	1.10 (0.76–1.44)	1.19 (0.70–1.68)	1.04 (0.68–1.40)	1.30 (0.79–1.81)	0.01 (– 0.03 to 0.06)	0.02 (– 0.04 to 0.08)	0.00 (– 0.03 to 0.04)	0.03 (– 0.02 to 0.07)
Men	1.05 (0.75–1.36)	1.14 (-0.77 to 1.50)	1.05 (0.79–1.31)	1.12 (0.82–1.42)	0.01 (– 0.03 to 0.05)	0.02 (– 0.03 to 0.06)	0.01 (– 0.03 to 0.04)	0.01 (– 0.02 to 0.05)
ASA								
Women	0.85 (0.71–1.00)	0.85 (0.59-1.10)	0.81 (0.62–1.01)	0.70 (0.47–0.94)	– 0.02 (– 0.05 to 0.00)	– 0.02 (0.06–0.02)	– 0.02 (– 0.05 to 0.00)	– 0.03 (– 0.06 to – 0.00)
Men	0.74 (0.59–0.89)	0.76 (0.59-0.94)	0.66 (0.52–0.80)	0.67 (0.52–0.82)	– 0.04 (– 0.07 to – 0.01)	– 0.04 (– 0.07 to – 0.00)	– 0.06 (– 0.08 to – 0.03)	– 0.05 (– 0.08 to – 0.02)
BB								
Women	1.18 (0.91–1.46)	1.26 (0.88–1.64)	0.78 (0.57–1.00)	0.78 (0.52–1.03)	0.02 (– 0.01 to 0.06)	0.03 (– 0.01 to 0.07)	– 0.03 (– 0.05 to 0.00)	– 0.02 (– 0.05 to 0.01)
Men	0.83 (0.67–1.00)	0.78 (0.61–0.96)	0.99 (0.79–1.19)	0.93 (0.72–1.14)	– 0.03 (– 0.05 to 0.00)	– 0.03 (– 0.06 to – 0.00)	– 0.00 (– 0.03 to 0.02)	– 0.01 (– 0.03 to 0.02)
CCB								
Women	1.03 (0.85–1.21)	1.13 (0.76–1.50)	0.79 (0.56-1.03)	0.69 (0.41–0.98)	0.01 (– 0.02 to 0.03)	0.02 (-0.03 to 0.06)	– 0.03 (– 0.06 to 0.00)	– 0.03 (– 0.06 to – 0.00)
Men	1.09 (0.84–1.34)	1.03 (0.76–1.31)	1.09 (0.84-1.33)	1.12 (0.85–1.40)	0.01 (– 0.02 to 0.05)	0.00 (– 0.03 to 0.04)	0.01 (– 0.02 to 0.04)	0.01 (– 0.02 to 0.05)
Diuretics								
Women	1.35 (1.04–1.67)	1.31 (0.91-1.70)	1.32 (0.93–1.71)	1.28 (0.82–1.74)	0.05 (0.01–0.09)	0.04 (– 0.01 to 0.08)	0.03 (– 0.01 to 0.07)	0.03 (– 0.02 to 0.07)
Men	1.36 (1.05–1.67)	1.31 (0.97-1.64)	1.34 (1.00–1.67)	1.12 (0.79–1.45)	0.05 (0.01–0.09)	0.04 (– 0.00 to 0.08)	0.04 (0.00–0.08)	0.01 (– 0.02 to 0.05)
Statins								
Women	0.83 (0.64–1.02)	0.99 (– 0.69 to 1.29)	0.75 (0.54–0.95)	0.66 (0.44–0.87)	– 0.03 (– 0.06 to 0.01)	– 0.00 (– 0.04 to 0.04)	– 0.03 (– 0.06 to – 0.00)	– 0.04 (– 0.07 to – 0.01)
Men	0.73 (0.58–0.88)	0.70 (0.54–0.86)	0.67 (0.52–0.82)	0.67 (0.51–0.84)	– 0.04 (– 0.07 to – 0.01)	– 0.05 (– 0.08 to – 0.01)	– 0.05 (– 0.09 to – 0.02)	– 0.05 (– 0.09 to – 0.02)
Metformin								
Women	1.39 (0.89–1.88)	1.70 (0.87–2.53)	1.12 (0.79–1.45)	1.26 (0.79–1.73)	0.04 (– 0.00 to 0.08)	0.04 (0.00–0.08)	0.01 (0.02–0.05)	0.02 (– 0.01 to 0.06)
Men	1.18 (0.77–1.58)	1.33 (0.79–1.87)	0.85 (0.60–1.09)	0.95 (0.66–1.24)	0.02 (– 0.02 to 0.05)	0.03 (– 0.01 to 0.06)	– 0.02 (– 0.05 to 0.01)	– 0.01 (0.04–0.03)

ACE-I angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *ASA* acetylsalicylic acid, *BB* beta-blockers, *CCB* calcium channel blockers, *CI* confidence interval, *CVDs* cardiovascular diseases, *DM* diabetes mellitus, *HF* heart failure, *HUNT* Trøndelag Health Study, *MI* myocardial infarction, *RD* risk difference, *RR* risk ratio

[a]Adjusted for age and age squared, women, $n = 2574$, men, $n = 3915$ for all cardiovascular agents; women, $n = 1708$, men, $n = 1898$ for metformin

[b]Adjusted for age and age squared, smoking, impairment due to long-lasting diseases and participants with antidepressant use were excluded; women, $n = 2027$, men, $n = 3540$ for all cardiovascular agents; women, $n = 1382$, men, $n = 1723$ for metformin

RR and RD between individuals with drug prescriptions and without drug prescriptions (reference) 9 months before participation in HUNT surveys at age 55 years

Depression symptoms defined by Hospital Anxiety and Depression Scale-Depression subscale ≥ 8

RR = 0.67; 95% CI 0.51–0.84; RD = − 0.05; 95% CI − 0.09 to − 0.02). Within the same sample, the use of ASA was associated with, on average, a 24% and 33% lower depression symptom risk in HUNT3 and HUNT4, respectively. Furthermore, similar associations of statins or ASA with, on average, a 33–34% lower depression symptom risk were detected in HUNT4 among women (RR = 0.66; 95% CI 0.44–0.87, RD = − 0.04; 95% CI − 0.07 to − 0.01 and RR = 0.70; 95% CI 0.47–0.94, RD = − 0.03; 95% CI − 0.06 to − 0.00, respectively). In contrast, there was no statistical evidence suggesting associations between other cardiovascular agents (i.e., ACE-I, ARBs, and diuretics) and metformin with a reduced depression symptom risk. Our data showed associations between lower depression symptom risk and the use of CCB in women in HUNT4 and BB among men in HUNT3 with CVDs; however, these associations were attenuated in the analysis, including participants with pure depression symptoms (HADS-D ≥8 and HADS-A < 8) as the outcome. Overall, we found no statistical evidence for an increased risk of depression for any of the drug classes included in the analysis.

4 Discussion

This large population-based study of 58,000 individuals from two HUNT surveys showed that among participants with CVDs, the use of ASA and statins was associated with a reduced risk of depression symptoms compared with non-users of these drugs. Our data provided no statistical support that the use of other cardiovascular agents or metformin was associated with reduced or increased depression symptom risk among the population with CVDs or DM, respectively.

Overall, the findings from this study align with and further strengthen existing evidence suggesting that among people with CVDs, pharmacological treatment with statins or ASA [28, 57–59] might alleviate depression symptom burden. A meta-analysis of seven observational studies from five countries ($N = 9187$ participants) reported a 32% reduced likelihood of depression among statin users compared with non-statin users [57]. Similarly, and supportive of our findings, two population-based Scandinavian studies demonstrated negative associations of statin use with depression disorders and symptoms [28, 58]. A prospective cohort study of over 4.6 million Swedish adults found that any statin use vs no-statin use reduced the odds of depression by 8% [58]. Another large Danish study examining ~30% of the adult population found that statin use was associated with a decreased rate of incident depression at the 5-year follow-up [28]. The difference in study design (prospective) and depression instrument (clinical diagnosis) restricts direct comparison of studies by Redlich et al. [58] and Kessing et al. [28] with our findings. Still, both studies have some similarities to ours, such as population-based samples from Scandinavian countries and analysis accounted for CVDs. In line with our results, two observational studies from Denmark have also suggested that ASA use may benefit depression [28, 59]. A cohort study of 91,842 patients with the acute coronary syndrome (ACS) and a matched population with no ACS found that patients with ACS using ASA or statins had a decreased risk of depression compared with no-ACS drug users at 1 and up to 12 years follow-up [59]. Similarly, a study reported a decreased risk of incident depression among adult ASA users, with no-ASA users as a reference and adjusting for CVDs and depression as possible confounding factors [28]. Recent large randomized controlled trials of ASA in older adults did not support these epidemiological findings [60, 61], although a recent randomized controlled trial of rosuvastatin, in particular, and ASA (Aspirin®) in youth depression showed a possible signal in favor of statin but not aspirin use [31].

Generally, previous research supports associations between ASA or statin use and the reduced depression symptoms from our analysis. However, this study found that negative associations were consistent among male individuals, but only in HUNT4 among female ASA or statin users. This inconsistency may partly reflect the sex differences in study participants' characteristics detected in our data, which should be considered in the interpretation of the results. Post hoc analysis of sex effects is also vulnerable to a type 1 error. Our previous study that investigated trends in depression and anxiety symptom prevalence over more than 20 years in adults with CVDs and DM compared to the general population showed that CVDs were consistently associated with increased depression symptom risk in men but not women [62]. In this study, the prevalence of CVDs and depression symptoms, together with statin or ASA use, was higher among men than women. Of note, the use of antidepressants was nearly two times higher in women than men, which suggests that depression is more likely to be diagnosed and treated in women than men who are ≥ 50 years [63].

These results contrast with other observational studies that found no statistical evidence for a relationship between statin use and depression symptoms [64, 65]. However, the authors of these studies emphasized the possibility that participant characteristics, particularly the inclusion of individuals with fewer medical comorbidities, could influence the findings [64, 65]. Additionally, meta-analytic evidence based on observational data showed associations between ASA use and increased depression risk [30]. However, the meta-analysis included large-sample studies, participants aged ≥ 65 years, high-dose ASA users, diverse depression instruments (self-report vs clinical diagnosis), and study populations (CVDs vs no-CVDs).

Aside from ASA or statins, this study provided no statistical support for associations of other cardiovascular agents or metformin with reduced depression symptoms. Other observational studies challenge our results [33, 38, 40, 41, 43]. A large national health study from Denmark (n = 3,747,190) demonstrated a decreased depression incidence among adults with hypertension treated with RAS agents compared with other treatment groups [38]. Likewise, a Scottish study of 525,046 patients with hypertension suggested antidepressant effects of RAS agents vs other antihypertensive monotherapies at a 5-year follow-up [33]. The study found that the risk of hospital admission was 53% lower for ACE-I or ARB users than in the non-treated group, whereas two times higher for CCB and BB users than for patients treated with the RAS agents [33]. In a Taiwanese population-based cohort study of 800,000 subjects, Wahlqvist et al. showed a higher risk of depression in people with DM than in healthy controls, which was reduced by using metformin and the combination of metformin and a sulfonylurea [43].

Given the study design and outcome measurement, our results are consistent with recent population evidence of antihypertensive drug use and depression. A cross-sectional analysis of 14,195 population-based Australian and American older adults (median age ≥ 75 years) with hypertension free from other CVDs showed no associations between ACE-I or ARBs and self-reported depression [36]. Unlike the study of Agustini et al. [36], hypertension was not part of the criteria for CVDs in our study as self-reported data on the history of hypertension were not collected in HUNT. Angiotensin-converting enzyme inhibitors and ARBs are among the first-line antihypertensives in Norway, commonly used in the primary prevention of CVDs in combination with various non-medical lifestyle interventions (e.g., regular physical activity, healthy diet, smoking cessation, and others) [13], which may moderate relationships between drug use and depression symptoms. However, there is still a possibility that not using hypertension in definition of CVDs may have altered the analysis of ACE-I or ARBs and the outcome in our data.

Population-based studies have suggested that metformin treatment may improve depression [40, 41], and there are pilot studies suggesting a beneficial effect of metformin in depression [32]. Unlike previous studies but supportive of our results, a recent meta-analysis of randomized controlled trials found no evidence for the consistent benefit of metformin on depression symptoms [44]. There may be several reasons for the discrepancy between our results and previous observational studies. The prevalence of DM increased from HUNT3 to HUNT4 surveys, which may indicate underreported DM in HUNT3. However, the proportion of metformin use did not increase accordingly, despite metformin being the sole first-line agent in the treatment of type 2 DM. Furthermore, owing to DM being a progressive disorder, most affected adults proceed with combined antidiabetic treatment to manage blood glucose levels. Diabetes and depression also share common risk factors including obesity and physical inactivity such that the use of metformin might be a proxy of operative risk factors for depression. This might mask any potential benefit of metformin. Among participants with DM, prescriptions of other antidiabetic drugs were markedly lower than metformin, indicating either the first-line treatment status of metformin or that this population may represent a "healthier" group of the DM population, also supported by the mean age of the population in this study.

4.1 Strengths and Limitations

The major strength of this study is the large study samples drawn from the two extensive population-based surveys combined with registry-based drug dispensation that reduced selection and recall bias in drug exposure data. Combining the two large databases, HUNT and NorPD provided considerable statistical power, suitable for detecting drug use associations with depression symptoms that otherwise could not be easily detected. Our analyses used dispensed prescriptions as proxies for drug use, which are considered superior to information on drug use collected from medical records or self-reported questionnaires [52]. Although drug dispensation may not reflect the drug's actual consumption, it is regarded as a valid and reliable indicator of drug use [66]. The proportion with invalid or missing drug prescription registration in this study population was minimal. Possible confounding by indication was handled by restricting the multivariate analysis to the population with CVDs or DM, excluding participants using antidepressants and adjusting for potential risk factors such as other chronic diseases.

There is also some weakness in the use of these data sources. First, this study used self-reported depression symptoms as the outcome measurement, based on the HADS-D subscale. Although this instrument is confirmed to have high validity compared with the diagnostic interview [49], under-reporting or over-reporting of depression is still possible, compared to diagnostic categories of depression. In addition, CVDs and DM were self-reported, which introduced the possibility of reporting bias and misclassification of these diseases. However, given the differences in symptoms, diagnostic procedures and the time course of these two physical conditions, we assume reliability and validity are higher for CVDs than DM self-reporting. Second, patient-level data on drug use in hospitals and other institutions are not routinely collected, which may, to some degree, have affected our results. Third, NorPD lacks information about the diagnosis or severity of the conditions treated. Omitting the duration and severity of CVDs and DM as significant risk factors for depression from the

analysis may affect our results. The indication for use and the prescribed doses are included, but only in free text, which is not easily used for analysis. The reimbursement code may function as a proxy for diagnosis in some cases [67]. For example, since March 2008, prescribers in Norway have had to use either the Tenth Edition of the International Classification of Diseases codes or the International Classification of Primary Care codes as the reimbursement codes for prescriptions. Participants using antidepressant agents were excluded from the analysis to minimize the influence of a pre-existing depression diagnosis on the results. However, it is important to acknowledge that various indications for antidepressants and non-pharmacological treatments for depression (i.e., psychotherapy) may limit the use of antidepressants as the single proxy for the diagnosis of depression.

Furthermore, this study investigated drug use within drug classes. Pharmacological and anti-inflammatory effect differences vary between individual drugs within one drug class, which can affect their association with depression [38]. We also used a simplified approach to measure exposure that did not address the differences between study participants' sustained and intermittent drug use or treatment discontinuation. In addition, this study did not include combination therapy (i.e., concomitant drug use). The rationality of this decision was study design and many possibilities for drug combinations in our data that were challenging to define and interpret. Moreover, our data included only prescriptions for antidepressants and drugs for CVDs and DM, which did not allow us to investigate drugs for other conditions (i.e., polytherapy) used by study participants. Alternatively, we adjusted for other chronic diseases that may indicate the use of drugs other than cardiovascular or antidiabetic agents. However, all of the above limitations regarding exposure measurement complicate the clinical interpretation of our results.

Finally, given the cross-sectional study design, our results show an association without suggesting any causality between the use of ASA or statins and a reduced risk of depression. The use of preventive medications such as statins may be a proxy of health literacy and self-efficacy, and therefore of other adaptive health behaviors. Conversely, a drug such as metformin is a treatment for established DM that itself is driven by adverse lifestyle risks such as a poor diet and physical inactivity, which are independent risk factors for depression. Moreover, an inverse relationship in results may be possible, meaning that previous depression among the participants in our study may have affected their drug use.

5 Conclusions

In this large cross-sectional study of the Norwegian adult population, treatment with ASA or statins was associated with reduced depression symptoms among men with CVDs, while other classes of cardiovascular agents were not. Women with CVDs benefitted from using ASA or statins regarding depression symptoms in the HUNT4 survey; however, this relationship was not statistically evident in HUNT3. Over 11 years, the prevalence of depression symptoms decreased among the CVD group and increased among the DM group, while drug use increased for most drug classes. However, metformin usage was not related to depression symptom levels among men and women with DM. It is necessary to point out that the symptoms of depression in our study refer to depression with and without anxiety. However, the analysis of depression without anxiety (defined by HADS-D ≥ 8 and HADS-A < 8) showed essentially the same results. These findings extend our knowledge about the psychological aspects of CVDs and DM, which are physical conditions ranked in the World Health Organization's top ten global causes of death and disability [3]. Moreover, this study contributes to novel perspectives of CVDs and DM drug treatment that may be relevant to preventing or reducing depression symptoms among populations affected by these conditions. Whether long-term pharmacotherapy for CVDs or DM alone or in combination with antidepressant therapy can help prevent the development of depression symptoms among these patient groups needs further investigation using prospective and experimental study designs.

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Declarations

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Ethics approval This study was approved by the Regional Committees for Medical Research and Health Research Ethics in Norway (reference 2019/30292/REK Nord) and the Norwegian Centre for Research Data (reference 30292/NSD). All study methods were carried out following the institutional guidelines and according to the ethical standards in human research.

Consent to participate All HUNT participants were informed about the study and gave their informed consent to participate and this consent included the use of the data material in the future.

Consent for publication Not applicable.

Availability of data and material The data used in this study are available from the HUNT databank, but restrictions apply to the availability of these data. The data were used under license for the current study and thus are not publicly available. However, data are available from the authors upon reasonable request and with permission from HUNT, The Regional Ethical Committee, and Norwegian Data Protection Authority. The dataset used in this study are stored in the HUNT databank using a personal identification number given to all Norwegians at birth or immigration as a key identification. The HUNT Research Centre has permission from the Norwegian Data Inspectorate to store and handle these data. The HUNT data are available for scientists who wish to use them for research and non-commercial purposes without breaching participant confidentiality. The researcher will always receive an anonymous or "de-identified" dataset after receiving approval of a research protocol by the Regional Ethical Committee and the HUNT Research Centre. To protect participants' privacy, the HUNT Research Centre aims to limit data storage outside the HUNT databank and cannot deposit data in open repositories. The HUNT databank has precise information on all data exported to different projects and can reproduce these on request. There are no restrictions regarding data export to give approval of applications to HUNT Research. For more information about HUNT data, see https://www.ntnu.edu/hunt/data**.**

Code availability Not applicable.

Authors' contributions All authors contributed substantially to the conceptualization, design of the study, and writing of the manuscript. IB performed the statistical analysis in collaboration with ERS. All authors contributed to the interpretation of the results of the analysis. IB wrote the article's first draft, and HS, OB, LJW, MB, and ERS critically revised the content. All authors read and approved the final manuscript.

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