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ORIGINAL ARTICLE

Risk of antidepressant initiation among users of cardiovascular agents and metformin.

Findings from the Trøndelag Health Study (HUNT) and Norwegian Prescription Database (NorPD), Norway

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Abstract

Cardiovascular disease and diabetes are risk factors for depression, yet the relationship between the drug treatments for these diseases and the risk of antidepressant initiation remains unclear. This study aimed to examine possible associations between the use of angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEI), acetylsalicylic acid (ASA), beta-blockers (BB), calcium channel blockers (CCB), diuretics, or metformin and risk of antidepressant initiation. The Trøndelag Health Study (HUNT3), Norway, was linked to the Norwegian Prescription Database (NorPD). Participants with no prescriptions of cardiovascular agents, metformin, or antidepressants for at least 6 months before HUNT3 (baseline) were eligible and followed for 10 years. The exposure was the use of cardiovascular agents or metformin, defined as mono- or polytherapy from baseline to end of follow-up. The outcome was the initiation of antidepressant use, indicated by the first drug dispensation during the study period and expressed as hazard ratios (HRs) with 95% confidence intervals (CI). Among 20 227 adults aged 40–70 years at baseline, we observed different associations between cardiovascular agents or metformin and the risk of antidepressant initiation. ARBs or CCB monotherapy was associated with a lower risk of initiating antidepressant use (HR 0.70; 95%CI 0.56–0.88 and HR 0.81; 95%CI 0.61–1.06, respectively) compared to no use of any drugs included in the study (reference). Reduced risk of antidepressant initiation was among ASA or statin polytherapy users, whereas there was a small increased risk among participants on ASA monotherapy. In contrast, there was no statistical evidence of associations between ACEI, BB, diuretics, or metformin and increased or decreased risk of antidepressant initiation. Our mixed

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ASA, acetylsalicylic acid; ATC, Anatomical Therapeutic Chemical classification; BB, beta-blockers; BMI, body mass index; CCB, calcium channel blockers; CI, confidence intervals; CVD, cardiovascular diseases; DM, diabetes mellitus; EHR, electronic health records; HADS, Hospital Anxiety and Depression Scale; HPA, hypothalamic–pituitary–adrenal axis; HRs, hazard ratios; HUNT, Trøndelag Health Study; NorPD, Norwegian Prescription Database; PH, proportional hazards; RAS, renin-angiotensin system; RCTs, randomized controlled trials.

findings indicate the possibility that some cardiovascular agents may be associated with a reduced risk of initiating antidepressant use while others may not. However, bias due to the limitations of the study design is possible.

KEYWORDS
antidepressants, cardiovascular agents, depression, metformin, neurosciences, pharmacoepidemiology, psychiatric disorders, psychiatry

1 | INTRODUCTION

Depression is a common mental condition and is the leading cause of disability worldwide.[1] Depression prevalence varies considerably across countries[2–4] and studies consistently report a higher prevalence of depression symptoms and disorders among those with cardiovascular diseases (CVDs) and diabetes mellitus (DM) than the general population.[2,5–9] Second-generation antidepressive agents targeting neurotransmitter systems are available; however, they can lead to adverse drug reactions or events,[10–12] have delayed initiation of efficacy,[13] and often have a poor (less than 50%) clinical response.[14] The discovery of new and improved antidepressants has not been fruitful in the past decades.[15] In contrast, finding new antidepressants among already available drugs with well-defined safety profiles (i.e., drug repurposing)[16] that affect biological pathways implicated in depression has aroused great interest.[17–19] Moreover, the hypothalamic–pituitary–adrenal axis (HPA), renin-angiotensin system (RAS), immuno-inflammation, metabolic processes, and oxidative stress have been identified as shared pathophysiological mechanisms of CVDs, DM, and depression.[20,21] Cardiovascular[22–26] and antidiabetic agents[27–29] targeting these mechanistic relationships have been associated with a reduced risk of depression. Although, it is still unclear which drugs can improve or prevent depression.[25,30–34]

Evidence investigating the association between cardiovascular agents and metformin on depression risk among the general population and those with CVDs or DM has been mixed. Among the total Danish population (over 3.7 million), depression risk was reduced among users of angiotensin II receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers (CCB) and beta-blockers (BB), low-dose acetylsalicylic acid (ASA), and statins.[22,23] In contrast, among 1.8 million Scottish hypertensive patients, mono- or polytherapy with ACEI, ARBs, CCB, and BB was associated with an increased risk of new-onset or recurrent depression compared to no use of these drugs.[32] However, a meta-analysis and systematic review of clinical and population-based studies suggested that statins may improve depression.[25,26,35] In contrast, the benefits of ARBs, ACEI, ASA, and CCB on depression were not confirmed.[25,33] So far, the associations between diuretics and improved mood disorders, including depression, have been limited.[23,25,33] Furthermore, case–control study of type 2 DM patients found a lower risk of depression among patients using metformin (N = 110) compared to a non-treated control group,[29] whereas a meta-analysis of the small number of pilot randomized controlled trials (RCTs) yielded no evidence of this drug's clinical benefits for depression.[31]

Electronic health records (EHRs) (e.g., hospital data and prescription records) combined with health surveys are a novel source for identifying potential drug repurposing signals.[16] From this perspective, observational EHRs-based studies can provide valuable "real-world evidence" of associations between drug use and health outcomes.[36] In Norway, we can combine extensive data from the national prescription registry with health surveys. This study aimed to assess cardiovascular agents and metformin as potential risk or protective factors for the initiation of antidepressant therapy, used as a proxy for the possible diagnosis of depression. Among over 20 000 adults, we wanted to examine whether and to what extent initiating therapy of cardiovascular agents or metformin is associated with risk of antidepressant initiation during a ten-year follow-up period.

2 | METHODS

2.1 | Data sources

We used data from the Trøndelag Health Study (HUNT), Norway, linked to the Norwegian Prescription Database (NorPD). The HUNT Study is a population-based health study that comprises adult residents (≥20 years old) of Trøndelag County (of around 190 000 inhabitants) in Norway. Four surveys have been conducted so far: the HUNT1 (1984–86), the HUNT2 (1995–97), the HUNT3 (2006–08), and the HUNT4 (2017–19), with a response rate of 77 212 (89.4%), 65 237 (69.5%), 50 807 (54.1%), and 56 078 (54%), respectively. The HUNT population is considered representative of general Norwegian adults.[37] The questions in HUNT include items on health conditions, including self-reported psychological symptoms, lifestyle, and sociodemographic characteristics. Details about the study are described elsewhere.[38]

NorPD contains electronic records of all prescription drugs dispensed by pharmacies in Norway since 2004 (https://www.fhi.no/en/hn/health-registries/norpd/). Drugs are classified according to the World Health Organization Anatomical Therapeutic Chemical classification (ATC) system.[39] This study included information from NorPD on the participant (i.e., sex and birth year), dispensed prescriptions (i.e., monthly and yearly dispensing) and drugs (ATC code).

2.2 | Study population

This study included HUNT3 participants whose drug prescription records were collected from NorPD through a unique personal number. Based on available NorPD data from January 1st 2006, to the date of participation in HUNT3 (from 3 October 2006 to 25 June 2008), we identified and excluded individuals who received a prescription of one or more cardiovascular agents (i.e., ACEI, ARBs, ASA, BB, CCB, diuretics, or statins), metformin, or antidepressants. The date of drug dispensation was defined by month and year. Individuals with no dispensed prescriptions of drugs included in this study during 6 months before their participation date in HUNT3 (baseline) were eligible, from which we excluded participants aged <40 or > 70 years at baseline (n = 12 580). Participants aged 40–70 years were assumed to be most likely (i.e., at risk) to experience the exposure and outcome and were therefore included in the analysis. Due to a high number of competing risk factors (i.e., other comorbidities, polypharmacy, and death) that may interfere with the outcome (initiation of antidepressants), participants over 70 years of age were not analyzed. The remaining 20 227 individuals were included in the study population. Figure 1 shows the flow chart of the study participant selection process. The study population was followed for 10 years from enrolment in the HUNT3 study or up to their first dispensed antidepressant prescription, whichever occurred first.

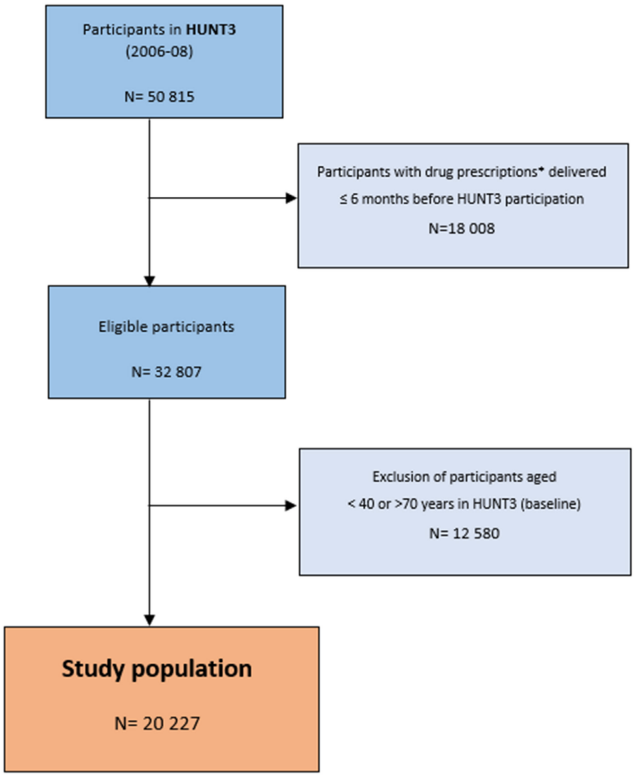

FIGURE 1 Flow chart showing selection process of study population. *Prescriptions of cardiovascular, antidiabetic, and antidepressant agents.

2.3 | Exposure

The exposure was defined as the use of one (monotherapy) or more (polytherapy) cardiovascular agents or metformin, based on the available data on the first dispensed prescription (defined by month and year). Dispensed prescriptions have been previously confirmed as a reliable measurement of drug use.[40] Selection of drug classes for the analysis was based on their associations with depression suggested by the literature[22–27,29] and the number of users in our data that provided sufficient statistical power. Diuretics as a drug subgroup (ATC C03) were included as a negative control because these drugs have not been associated with mood disorders.[23,25] The following cardiovascular agents and metformin, defined according to ATC codes, were analyzed: ACEI (C09A), ARBs (CO9C), ASA (B01A C06), BB (C07), CCB (C08), diuretics (C03), statins, that is, HMG-CoA-reductase inhibitors (C10A A), and metformin (A10B A02). The exposure status of study participants was defined by their first drug dispensation after the start of follow-up: (1) *monotherapy*- for participants who received a single drug class by their first dispensation (2) *polytherapy*- for participants who received more than one drug class by their first dispensation and (3) *no-drug use* (*reference*)- for participants with no dispensed prescriptions for metformin or any cardiovascular agents included in this study.

2.4 | Outcome

The outcome was the initiation of antidepressant therapy during the study period. The NorPD database provides diagnostic information from the ICD-10 or ICPC-2 for prescriptions only after 2008. Therefore, only antidepressant prescriptions were used as the outcome and proxy for possible depression (and/or anxiety) at the diagnostic level in this study. We used the first dispensation of an antidepressant agent to identify antidepressant therapy initiation. All antidepressants as a drug subgroup (ATC code NO6) were included in the analysis. Among them, the following antidepressant agents with ATC codes were the ones with highest number of users among the study population: non-selective monoamine reuptake inhibitors (N06A A), selective serotonin reuptake inhibitors (N06A B), monoamine oxidase A inhibitors (N06A G02), and other antidepressants (N06A X).

2.5 | Other covariates

Sociodemographic characteristics included: sex and age (mean and age groups 40–54 and 55–70 years). Lifestyle measurements included questions on current smoking (yes/no), physical activity per week (inactive versus active), and monthly alcohol consumption (no or low versus moderate to frequent). Physical activity was defined as light if it did not involve sweating or breathlessness. The participants were categorized as active (one time per week of hard/light physical activity) or inactive (no physical activity or less than one time per week). Alcohol consumption never or ≤ one time per week was

defined as no or low drinking, while drinking from two to three times or ≥ four times per week was defined as moderate to frequent drinking. Chronic diseases (yes/no) were determined with the question: "Do you suffer from a long-lasting (at least one year) illness or injury of a physical or psychological nature that impairs your functioning in your daily life?". The Hospital Anxiety and Depression Scale (HADS) was used to assess psychological symptoms of anxiety (HADS-A subscale) and depression (HADS-D) during the past week and describe symptom change (HADS-T) from HUNT2 to HUNT3. Questions on HADS have a 4-point Likert scale response option from 0 (no symptoms) to 3 (highest symptom level). We used total scores (HADS-T) by summing up valid HADS-A and HADS-D, defined as a response on five or more items. The missing response among participants who filled in 5 or 6 items was replaced with the sum of completed items multiplied by 7/5 or 6/5, respectively. 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.[41,42] Clinical measurements included height (m) and weight (kg) used to determine body mass index (BMI; kg/m^2).

2.6 | Data analysis

We used Cox proportional hazards (PH) models to examine associations between cardiovascular agents and metformin and the risk for antidepressant therapy initiation. Estimates were presented as hazard ratios (HRs) with corresponding 95% confidence intervals (CI). The preliminary test of proportionality of hazard, using log–log curves[43] and Schoenfeld residuals,[44] suggested that the PH assumption may be violated. We addressed this issue by delaying the start of follow-up for three and six months and one year after baseline. Our models improved but yielded essentially the same results, indicating that possible non-proportionality in our data would not substantially influence the interpretation of our results. The follow-up time started in HUNT3 (baseline) for all study participants. To prevent introduction of immortal time bias to analysis, the follow-up time was restarted (split) at the first dispensation date (month/year) of cardiovascular agents or metformin (exposures). Participants defined as no-drug users (reference) at baseline were first followed to their first drug prescription; then their unexposed person time ended. Thereafter, they changed exposure status (to either mono- or polytherapy) and were followed to first antidepressant prescription or end of follow-up. Thus, the follow-up period included both pre- and post-exposure period during which participants could experience the outcome (i.e., they were not immortal).

Models were first adjusted for sex and age as a time-varying covariate (Model 1), thereby HADS-T and BMI at baseline as continuous variables (Model 2). The point estimates (Models 1) remained fairly robust after the adjustment (Models 2). Further adjustment for lifestyle and chronic diseases yielded minimal changes to the results, and these variables were not included in the main analysis (Models 1 and 2).

3 | RESULTS

The baseline characteristics of study participants according to the use of cardiovascular agents and metformin, monotherapy (mono), or polytherapy (poly) during the follow-up are shown in Table 1. The number of drug users (Table 1) is cumulative for the entire follow-up period. Users of various drug classes differed by sex, except for diuretics polytherapy, where there was an equal sex distribution. Men were more likely to be users of metformin and most cardiovascular agents, while BB, statin, and diuretic monotherapy users were more likely to be women. The mean age of the study participants ranged from 51–58 years, with most participants being non (current) smokers, physically active, and no or low alcohol consumers. Compared to reference, mono and polytherapy users of various drug classes showed marginal differences in self-reported chronic diseases, BMI (mean range 26.9–31.0 kg/m^2), and HADS-T score change from HUNT2 to HUNT3 (7.0 to 6.6). The initiation of antidepressant use was more common among the reference group than among participants using mono or polytherapy for all drug classes.

Of the total, 3194 participants (15.8%) received their first antidepressant prescription during the follow-up. Table 2 shows adjusted HRs with 95%CI (specified by Models 1 and 2) of antidepressant initiation according to cardiovascular agents and metformin mono or polytherapy during a 10-year follow-up. HRs adjusted for age (time-varying covariate), sex, HADS-T, and BMI (Models 2) with 95%CI of antidepressant initiation according to cardiovascular agents and metformin mono or polytherapy during a 10-year follow-up are shown in Figure 2.

Among the study population, ARBs or CCB monotherapy was associated with a 30% and 19% lower risk (HR) of antidepressant initiation compared to no use of any drugs in the study (HR 0.70; 95%CI 0.56–0.88 and HR 0.81; 95%CI 0.61–1.06, respectively). Furthermore, ASA or statins polytherapy was associated with reduced risk of antidepressant initiation compared to reference (HR 0.85; 95%CI 0.68–1.06 and HR 0.80; 95%CI 0.64–1.10). For those using ASA as monotherapy, there was a small evaluated risk (HR 1.27; 95% CI 1.02–1.57) of antidepressant initiation. Our results showed no signs of associations between ACEI, BB, diuretics, or metformin and increased or decreased risk of initiating antidepressant use.

4 | DISCUSSION

In a sample of over 20 000 community-dwelling adults, we observed mixed results regarding various classes of cardiovascular agents or metformin as a potential risk or protective factor for the initiation of antidepressant use. ARBs monotherapy and, to a lesser extent, CCB monotherapy, ASA or statin polytherapy were associated with reduced risk of the initiation of antidepressant use, while a small but elevated risk was found among ASA monotherapy users. Neither diuretics nor metformin showed any apparent association with the increased or decreased risk of initiating antidepressant use.

TABLE 1 Baseline characteristics of study participants according to the use of cardiovascular agents or metformin during a 10-year follow-up. The number of drug users (mono/polytherapy) is cumulative for the entire follow-up period.

	N total	Reference	ACEI		ARBs		ASA		BB	
Variables *n* (%)	**20227**	**11758**	**Mono *N* = 397**	**Poly *N* = 267**	**Mono *N* = 1181**	**Poly *N* = 217**	**Mono *N* = 655**	**Poly *N* = 1054**	**Mono *N* = 667**	**Poly *N* = 579**
Sex										
Women	10544	6462 (55.0)	172 (43.3)	82 (30.7)	524 (44.4)	87 (40.0)	316 (48.2)	357 (33.9)	361 (54.1)	162 (28.0)
Men	9683	5296 (45.0)	225 (56.7)	185 (69.3)	657 (55.6)	130 (60.0)	339 (51.8)	697 (66.1)	306 (45.9)	417 (72.0)
Age (years)										
Mean (SD)[a]		51.2 (7.7)	54.7 (7.9)	57.1 (7.8)	53.8 (8.0)	55.6 (7.6)	57.3 (7.9)	57.5 (7.2)	54.8 (8.2)	57.5 (7.3)
40–54	12115	8093 (68.8)	199 (50.1)	103 (38.6)	655 (55.5)	95 (43.8)	249 (38.0)	363 (34.4)	337 (50.5)	201 (34.7)
55–70	8112	3665 (31.2)	198 (49.1)	164 (61.4)	526 (44.5)	122 (56.2)	406 (62.0)	691 (65.6)	330 (49.5)	378 (65.3)
Chronic diseases										
No	6205	3669 (31.2)	120 (30.2)	81 (30.4)	372 (31.5)	75 (34.6)	199 (30.4)	312 (29.6)	195 (29.3)	170 (29.4)
Yes	5310	3103 (26.4)	97 (24.4)	69 (25.8)	302 (25.6)	63 (29.0)	187 (28.5)	304 (28.8)	175 (26.2)	156 (26.9)
Missing	8712	4986 (42.4)	180 (45.4)	117 (43.8)	507 (42.9)	79 (36.4)	269 (41.1)	438 (41.6)	297 (44.5)	253 (43.7)
Current smoking										
No	14557	8592 (73.1)	289 (72.8)	189 (70.8)	833 (70.5)	165 (76.0)	478 (73.0)	761 (72.2)	475 (71.2)	412 (71.2)
Yes	5219	2918 (24.8)	101 (25.4)	74 (27.2)	326 (27.6)	47 (21.6)	163 (24.9)	270 (25.6)	175 (26.3)	154 (26.6)
Missing	451	248 (2.1)	7 (1.8)	4 (2.0)	22 (1.9)	5 (2.4)	14 (2.1)	23 (2.2)	17 (2.5)	13 (2.2)
Physical activity										
Inactive[b]	809	391 (3.3)	11 (2.8)	12 (4.5)	48 (4.1)	9 (4.1)	31 (4.7)	61 (5.8)	36 (5.4)	33 (5.7)
Active[c]	19351	11330 (96.4)	385 (97.0)	254 (95.1)	1126 (95.3)	208 (95.9)	622 (95.0)	990 (93.9)	628 (94.2)	543 (93.8)
Missing	67	37 (0.3)	1 (0.2)	1 (0.4)	7 (0.6)	0	2 (0.3)	3 (0.3)	3 (0.4)	3 (0.5)
Alcohol consumption										
No or low[d]	10839	6263 (53.3)	217 (54.6)	144 (54.0)	623 (52.8)	116 (53.6)	355 (54.2)	572 (54.3)	338 (50.7)	326 (56.3)
Moderate to frequent[e]	9069	5313 (45.2)	171 (43.1)	120 (44.9)	544 (46.1)	99 (45.5)	292 (44.6)	465 (44.1)	318 (47.7)	241 (41.6)
Missing	319	182 (1.5)	9 (2.3)	3 (1.1)	14 (1.1)	2 (0.9)	8 (1.2)	17 (1.6)	11 (1.6)	12(2.1)
BMI										
Mean (SD)		26.2 (3.7)	28.3 (4.1)	28.1 (4.0)	28.3 (4.0)	28.1 (4.0)	26.7 (3.8)	27.2 (3.6)	26.9 (3.8)	27.6 (3.8)
Missing	90	47 (0.4)	3 (0.8)	1 (0.4)	7 (0.6)	1 (0.5)	3 (0.5)	7 (0.7)	4 (0.6)	3 (0.2)
HADS-T (HUNT2)										
Valid[f]	16308	9295 (79.1)	318 (80.1)	198 (74.2)	900 (76.1)	162 (74.7)	559 (85.3)	819 (77.7)	538 (80.8)	457 (78.9)
Mean (SD)		6.9 (5.1)	7.0 (4.7)	7.14 (5.2)	7.2 (5.1)	6.6 (4.5)	7.3 (5.0)	7.4 (5.4)	7.5 (5.2)	7.3 (5.2)
Missing	3919	2463 (15.8)	79 (19.9)	69 (25.8)	281 (23.8)	55 (25.3)	96 (14.7)	235 (22.3)	129 (19.2)	122 (21.1)

(Continues)

TABLE 1 (Continued)

	N total	Reference	ACEI		ARBs		ASA		BB	
Variables *n* (%)	**20227**	**11758**	**Mono *N* = 397**	**Poly *N* = 267**	**Mono *N* = 1181**	**Poly *N* = 217**	**Mono *N* = 655**	**Poly *N* = 1054**	**Mono *N* = 667**	**Poly *N* = 579**
HADS-T (HUNT3)										
Valid[f]	16542	9577 (81.5)	320 (80.6)	207 (77.5)	952 (80.6)	169 (77.9)	556 (84.9)	834 (79.1)	550 (82.5)	453 (78.2)
Mean (SD)		6.63 (5.1)	6.1 (4.4)	6.6 (5.0)	6.6 (4.7)	6.2 (4.7)	6.8 (4.9)	6.7 (5.1)	6.9 (4.8)	6.8 (5.1)
Missing	3685	2181 (13.4)	77 (19.4)	60 (22.5)	229 (19.4)	48 (22.1)	99 (15.1)	220 (20.9)	117 (17.5)	126 (21.8)
Initiation of antidepressant use[g]										
Yes	3194	2275 (19.3)	36 (9.1)	34 (12.7)	101 (8.6)	22 (10.1)	109 (16.6)	106 (10.1)	88 (13.2)	58 (10.0)
No	17033	9483 (80.7)	361 (90.9)	233 (87.3)	1080 (91.4)	195 (89.9)	546 (83.4)	948 (89.9)	579 (86.8)	521 (90.0)
	N total	**Reference**	**CCB**		**Diuretics**		**Statins**		**Metformin**	
Variables *n* (%)	**20227**	**11758**	**Mono *N* = 694**	**Poly *N* = 204**	**Mono *N* = 790**	**Poly *N* = 158**	**Mono *N* = 1132**	**Poly *N* = 1057**	**Mono *N* = 237**	**Poly *N* = 68**
Sex										
Women	10544	6462 (55.0)	331 (47.7)	86 (42.2)	481 (60.9)	79 (50.0)	689 (60.9)	371 (35.1)	83 (37.6)	22 (32.4)
Men	9683	5296 (45.0)	363 (52.3)	118 (57.8)	309 (39.1)	79 (50.0)	443 (39.1)	686 (64.9)	154 (62.4)	46 (67.6)
Age (years)										
Mean (SD)[a]		51.2 (7.7)	55.4 (7.7)	55.5 (8.0)	56.0 (8.0)	58.1 (7.7)	55.0 (7.3)	57.1 (7.4)	55.0 (7.7)	53.4 (8.4)
40–54	12115	8093 (68.8)	312 (45.0)	91 (44.6)	358 (45.3)	45 (28.5)	548 (48.4)	384 (33.3)	114 (48.1)	38 (55.9)
55–70	8112	3665 (31.2)	382 (55.0)	113 (55.4)	432 (54.7)	113 (71.5)	584 (51.6)	673 (66.7)	123 (51.9)	30 (44.1)
Chronic diseases										
No	6205	3669 (31.2)	202 (29.1)	57 (27.9)	236 (29.9)	45 (28.5)	314 (27.7)	324 (30.7)	79 (33.3)	16 (23.5)
Yes	5310	3103 (26.4)	182 (26.2)	64 (31.4)	209 (26.5)	44 (27.8)	306 (27.0)	307 (29.0)	60 (25.3)	18 (26.5)
Missing	8712	4986 (42.4)	310 (44.7)	83 (40.7)	345 (43.6)	69 (43.7)	512 (45.3)	426 (40.3)	98 (41.4)	34 (50.0)
Current smoking										
No	14557	8592 (73.1)	483 (69.6)	153 (75.0)	560 (70.9)	113 (71.5)	816 (71.9)	769 (72.8)	169 (71.3)	47 (69.1)
Yes	5219	2918 (24.8)	198 (28.5)	47 (23.0)	211 (26.7)	40 (25.3)	292 (25.8)	266 (25.2)	60 (25.3)	17 (25.0)
Missing	451	248 (2.1)	13 (1.9)	4 (2.0)	19 (2.4)	5 (3.2)	24 (2.3)	22 (2.0)	8 (3.4)	4 (5.9)
Physical activity										
Inactive[b]	809	391 (3.3)	29 (4.2)	5 (2.5)	34 (4.3)	2 (1.3)	36 (3.2)	64 (6.1)	3 (1.3)	3 (4.4)
Active[c]	19351	11330 (96.4)	660 (95.1)	198 (97.1)	755 (95.6)	156 (98.7)	1093 (96.6)	990 (93.7)	231 (97.5)	65 (95.6)
Missing	67	37 (0.3)	5 (0.7)	1 (0.4)	1 (0.1)	0 (0.0)	3 (0.2)	3 (0.2)	3 (1.2)	0 (0.0)
Alcohol consumption										
No or low[d]	10839	6263 (53.3)	389 (56.1)	114 (55.9)	400 (50.6)	83 (52.5)	627 (55.4)	571 (54.0)	128 (54.0)	33 (48.5)
Moderate to frequent[e]	9069	5313 (45.2)	295 (42.5)	86 (42.1)	376 (47.6)	74 (46.8)	486 (42.9)	470 (44.5)	106 (44.7)	35 (51.5)

TABLE 1 (Continued)

	N total	Reference	CCB		Diuretics		Statins		Metformin	
Variables *n* (%)	**20227**	**11758**	**Mono *N* = 694**	**Poly *N* = 204**	**Mono *N* = 790**	**Poly *N* = 158**	**Mono *N* = 1132**	**Poly *N* = 1057**	**Mono *N* = 237**	**Poly *N* = 68**
Missing	319	182 (1.5)	10 (1.4)	4 (2.0)	14 (1.8)	1 (0.7)	19 (1.7)	16 (1.5)	3 (1.3)	0 (0.0)
BMI										
Mean (SD)		26.2 (3.7)	27.8 (3.7)	27.9 (4.0)	28.4 (4.3)	28.7 (4.6)	27.5 (3.7)	26.6 (3.6)	30.4 (4.7)	31.0 (4.4)
Missing	90	47 (0.4)	2 (0.3)	0	5 (0.6)	2 (1.3)	4 (0.3)	7 (0.7)	1 (0.4)	0 (0.0)
HADS-T (HUNT2)										
Valid[f]	16308	9295 (79.1)	530 (76.4)	153 (75.0)	646 (81.7)	127 (80.4)	993 (87.7)	861 (81.5)	190 (80.2)	48 (70.6)
Mean (SD)		6.9 (5.1)	7.3 (5.2)	6.1 (4.8)	7.3 (5.4)	7.0 (4.6)	7.3 (5.0)	7.4 (5.2)	7.1 (5.2)	8.6 (5.7)
Missing	3919	2463 (15.8)	164 (23.6)	51 (25.0)	144 (18.3)	31 (19.6)	139 (12.3)	196 (18.5)	47 (19.8)	20 (29.4)
HADS-T (HUNT3)										
Valid[f]	16542	9577 (81.5)	529 (76.2)	150 (73.5)	643 (81.4)	131 (82.9)	939 (82.9)	866 (81.9)	192 (81.0)	47 (69.1)
Mean (SD)		6.63 (5.1)	6.8 (4.8)	5.7 (4.6)	7.1 (5.3)	7.0 (4.8)	6.7 (5.1)	6.8 (5.2)	6.6 (4.8)	7.0 (5.6)
Missing	3685	2181 (13.4)	165 (23.8)	54 (26.5)	147 (18.6)	27 (17.1)	193 (17.1)	191 (18.1)	45 (19.0)	21 (30.9)
Initiation of antidepressant use[f]										
Yes	3194	2275 (19.3)	73 (10.5)	25 (12.3)	125 (15.8)	19 (12.0)	148 (13.1)	104 (8.9)	26 (11.0)	8 (11.8)
No	17033	9483 (80.7)	621 (89.5)	179 (87.7)	665 (84.2)	139 (88.0)	984 (86.9)	953 (91.1)	211 (89.0)	60 (88.2)

Abbreviations: ACE-I, Angiotensin-converting enzyme inhibitors; ARBs, Angiotensin II receptor blockers; ASA, Acetylsalicylic acid; BB, Beta-blockers; CCB, Calcium channel blockers; HUNT, The Trøndelag Health Study.

Reference = participants with no dispensed prescriptions for metformin or any cardiovascular agents included in this study.

[a]SD, standard deviation.

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

[c]Active = less than once or more light/hard physical activity per week; Alcohol consumption.

[d]No or low drinking = Never or ≤1 time/week.

[e]Moderate (2–3 times/week) to frequent (≥4 times/week); BMI = Body mass index (kg/m^2).

[f]HADS-T, Hospital Anxiety and Depression Scale-Total; Valid -HADS-T-defined by at least five answers on HADS-Anxiety (HADS-A) and HADS-Depression (HADS-D) Scales.

[g]Initiation of antidepressant use -defined by the first dispensation of antidepressant agents after HUNT3.

TABLE 2 Adjusted Hazard Ratios (HRs) with 95% confidence interval (CI) of antidepressant initiation according to cardiovascular agents and metformin mono- or polytherapy during a 10 year follow-up.

Drug class	Person years	Outcome/total study population	Model 1	Model 2
ACEI				
Mono	1876.5	36/397	0.70 (0.55–1.05)	0.84 (0.59–1.20)
Poly	1378.5	34/267	1.14 (0.81–1.61)	1.07 (0.73–1.58)
Reference	155928.1	2332/11758	1	1
ARBs				
Mono	5510.4	101/1181	0.73 (0.59–0.89)	0.70 (0.56–0.88)
Poly	1129.9	22/217	0.87 (0.57–1.32)	0.77 (0.46–1.28)
Reference			1	1
ASA				
Mono	3770.2	109/655	1.34 (1.10–1.64)	1.27 (1.02–1.57)
Poly	5713.5	106/1054	0.89 (0.73–1.09)	0.85 (0.68–1.06)
Reference			1	1
BB				
Mono	3691.3	88/667	1.00 (0.81–1.25)	0.95 (0.74–1.21)
Poly	3248.7	58/579	0.89 (0.68–1.16)	0.86 (0.64–1.15)
Reference			1	1
CCB				
Mono	3045.8	73/694	0.92 (0.72–1.16)	0.81 (0.61–1.06)
Poly	1036.2	25/204	1.04 (0.70–1.55)	1.16 (0.75–1.78)
Reference			1	1
Diuretics				
Mono	5758.8	125/790	1.07 (0.89–1.28)	0.98 (0.80–1.20)
Poly	1075.5	19/158	0.88 (0.56–1.39)	0.90 (0.56–1.45)
Reference			1	1
Statins				
Mono	6209.7	148/1132	0.99 (0.83–1.17)	0.95 (0.78–1.15)
Poly	5629.1	104/1057	0.86 (0.70–1.06)	0.80 (0.64–1.10)
Reference			1	1
Metformin				
Mono	1350.6	26/237	0.92 (0.63–1.36)	0.98 (0.66–1.46)
Poly	390.4	8/68	0.98 (0.49–1.97)	0.61 (0.23–1.63)
Reference			1	1

Model 1: Adjusted for age as time-varying covariate and sex.

Model 2: Model 1 plus adjusted for HADS-T and BMI (continuous).

Reference = participants with no dispensed prescriptions of metformin or any cardiovascular agents included in this study.

Outcome = the first antidepressant prescription during a 10-year follow-up.

Our findings appear broadly aligned with observational,[22,23,34] preclinical, and clinical[18,45–47] studies suggesting a reduced risk of depression among ARB, CCB, and statin users while partially supporting epidemiological evidence of the associations between ASA and depression.[22,23,34] Consistent with our results, the Danish population-based studies showed a lower 10-year incidence of depression measured by clinical diagnosis or antidepressant prescription among continuous users (i.e., with ≥3 cumulative prescriptions) of ACEI, ARBs or CCB[23] or statins[22] compared with individuals with 1–2 prescriptions of these drugs. In contrast, our data did not confirm associations between BB and depression found among Danish adults.[23]

The large register-based study suggested that low-dose and high-dose ASA were associated with reduced and increased incidence of depression (based on clinical diagnosis or antidepressant prescription), respectively.[22] These results may, to some degree, align with our data, showing the associations between ASA polytherapy and reduced risk of antidepressant initiation. However, the definition of exposures, reference group, and study design used by Kessing et al.[22] differ from ours, which challenges a direct comparison of findings between the studies.

Furthermore, an investigation of prescription data of over 58 million Americans aged 18–90 years showed a lower incidence of

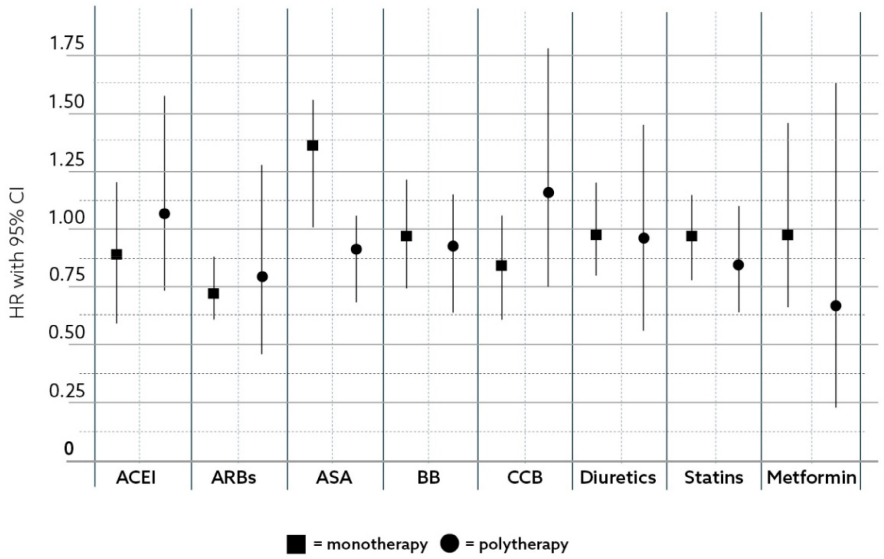

FIGURE 2 Adjusted Hazard Ratios (HRs) with 95% confidence intervals (CIs) for the initiation of antidepressant use according to cardiovascular agents and metformin mono- or polytherapy during a 10-ten year follow-up. Participants with no dispensed prescriptions for metformin or any cardiovascular agents included in this study as a reference.

2-year clinically diagnosed depression for individuals treated with ARBs than those with CCB (controls) but higher for those treated with BB than CCB.[34] A comparative analysis of ARBs and ACEI by Colbourne et al.[34] found that the risk of depression diagnosis was lower among ARBs users; the results support ours. There are studies suggesting CCB mechanism of action on nervous system activity through inflammation[48] and calcium signalling[49] and associations between CCB and improved outcomes among people with serious mental illnesses other than depression.[50] Despite the theoretical basis for the antidepressive effect of CCB, evidence that exposure to this drug may benefit depression is still minimal and inconsistent.[23,25,32,51] Considering the weak associations of the CCB monotherapy with reduced risk of antidepressant initiation, our results broadly align with these findings.

Relative to comparison groups and study design, associations of cardiovascular agents with risk of antidepressant initiation detected in our data are mixed compared with the existing literature.[22,23,34] For example, Kessing et al.[22,23] selected participants with only 1–2 drug prescriptions during follow-up as a reference to control potential confounding due to hypertension. In contrast, the reference group for each drug class analyzed in this study included participants with no prescriptions for any of the drug classes included in the study. Our findings suggest that cardiovascular agents and metformin are differently associated with risk of antidepressant initiation, with exposure to ARBs or CCB monotherapy and ASA or statin polytherapy being associated with reduced risk. These findings might be partly explained by various mechanisms of action (via the drug's anti-inflammatory or central nervous system action), possibly also by the study design and settings.

4.1 | Strengths and limitations

Strengths of this study include the large population-based sample, the ability to link a health survey to EHR and the examination of several drug classes over an extended follow-up time. Given the high burden of depression among people with CVDs and DM, our study also addresses a clinically relevant topic. However, several limitations need to be considered when interpreting these results. As other population-based studies, participation in HUNT surveys is likely to select the «healthier» part of the adult population, where individuals with severe chronic conditions, such as CVDs, DM, depression, and anxiety symptoms, and those in hospitals and nursing homes are likely underrepresented.[52,53] As a result, the frequency of risk factors for the development of CVDs, DM, and depression may be lower among individuals in this study than the random sample of adults aged 40–70 years. Hence, this selection bias may cause the true relationship between the exposure and outcome to be underestimated. Revision of clinical guidelines over the past years[54] has resulted in lower diagnostic and pharmacotherapy treatment thresholds for CVDs and DM,[55] resulting in a "generally healthier part of the population" diagnosed and treated for these diseases.[56] At least to some extent, such a change may have underestimated our findings.

This study selected participants with no dispensed prescriptions for cardiovascular agents, metformin, and antidepressants six months before baseline. Exploratory analysis in a previous study[57] and chronic drug treatments for CVDs and DM indicate that a six-month treatment-free period can be expected to have sufficient sensitivity to capture the individuals not using these drugs. By such design, participants diagnosed and treated for depression earlier in life or those on non-pharmacological depression treatments might still be included in the analysis. This limitation could be expected to influence results, possibly in the direction of underestimation. An adjustment for the HADS-T aimed to minimize the influence of the possible inclusion of participants with increased psychological symptoms at baseline in the analysis. However, this analysis did not account for change in HADS-T and BMI and other time-varying factors (e.g., psychological or physical conditions, disease severity, lifestyle) and competing risk factors (i.e., death) that could influence the findings. Due to a lack of mortality

data, participants included in exposure groups in this study would have contributed with person times during the whole follow-up even if they died. Given that higher mortality is expected among participants with CVDs or DM, an underestimation of the true associations is possible.

Furthermore, physical conditions such CVDs and DM are individual risk factors for depression, where drug treatments for these comorbidities (e.g., cardiovascular or antidiabetic agents) might be a proxy for increased and decreased depression risk, influencing our results in both directions. Another challenge was distinguishing participants into mono- or polytherapy groups. We used a simplified approach and classified the study participants according to their first prescription during the follow-up, which likely overestimated the number of monotherapy users and probably reported estimates for this exposure group. Moreover, this study design could not capture changes in exposure over time (i.e., from mono- to polytherapy and vice versa, changes between drug classes or drug discontinuation), which is likely to bias our results, potentially in both directions. Because of the multiple indications for antidepressants, relying solely on antidepressant prescriptions as a proxy for depression may have misclassified the outcome. Therefore, the findings for drugs included in this study cannot be transferred directly to the diagnosis of depression. Likewise, cardiovascular agents and metformin may also have multiple indications with varying underlying depression risks, potentially influencing our findings in both directions.

All abovementioned may, to some degree, affect our findings by over-or underestimating the risk of antidepressant initiation among users of drugs included in this study. Finally, diversity in study populations, health care systems, treatment guidelines, and validity and reliability in EHRs and health survey data complicate the comparison between studies and should be considered in the generalizability of our findings.

4.2 | Conclusions

This study found mixed evidence regarding antidepressant initiation among users of metformin and/or various classes of cardiovascular agents as mono- or polytherapy. ARBs monotherapy use, in particular, was associated with a reduced risk of initiating antidepressant use. Ultimately, whether and to what degree these drug classes de- or increase the risk for depression should be evaluated by observational studies using methodologically robust designs, for example, self-controlled designs[58] or active-comparator new-user design,[59] and such evidence can play an important role in candidate agent selection.

AUTHOR CONTRIBUTIONS

All authors contributed substantially to the conceptualization, design of the study, and writing of the manuscript. IB performed statistical analysis in collaboration with JHB and 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, JHB, and ERS critically revised the content. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors IB, OB, LJW, MB, JHB, ERS, and HS declare no conflict of interests regarding the content of this article.

DATA AVAILABILITY STATEMENT

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 so are not publicly available. However, data are available from the authors upon reasonable request and with permission from the HUNT, The Regional Ethical Committee, and Norwegian Data Protection Authority. The dataset used in this study is stored in 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 HUNT Research Centre. To protect participants' privacy, HUNT Research Centre aims to limit data storage outside the HUNT databank and cannot deposit data in open repositories. 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.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

All HUNT participants were informed about the study and gave their informed consent to participate. The consistent included the use of the data material in the future, and it was approved by the Regional Committees for Medical Research and Health Research Ethics. This study was approved by the Regional Committees for Medical Research and Health Research Ethics in Norway (reference2019/30292/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.

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REFERENCES

1. Mental illness among adults in Norway. *Public Health Report - Health Status in Norway [Online Document]*. Institute of Public Health, 2016 [updated 08 August 2016]. Available from: https://www.fhi.no/en/op/hin/mental-health/psykisk-helse-hos-voksne/.
2. Bojanić I, Sund ER, Sletvold H, Bjerkeset O. Prevalence trends of depression and anxiety symptoms in adults with cardiovascular diseases and diabetes 1995–2019: the HUNT studies. *Norway BMC Psychology*. 2021;9(1):1-16.
3. Yu B, Zhang X, Wang C, Sun M, Jin L, Liu X. Trends in depression among adults in the United States, NHANES 2005–2016. *J Affect Disord*. 2020;263:609-620.
4. Bretschneider J, Janitza S, Jacobi F, et al. Time trends in depression prevalence and health-related correlates: results from population-based surveys in Germany 1997–1999 vs. 2009–2012. *BMC Psychiatry*. 2018;18(1):394.
5. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. *J Affect Disord*. 2012;142:S8-S21.
6. Chobufo MD, Khan S, Agbor VN, et al. 10-year trend in the prevalence and predictors of depression among patients with heart failure in the USA from 2007–2016. *Int J Cardiol*. 2020;301:123-126.
7. Ghaemmohamadi MS, Behzadifar M, Ghashghaee A, et al. Prevalence of depression in cardiovascular patients in Iran: a systematic review and meta-analysis from 2000 to 2017. *J Affect Disord*. 2018;227:149-155.
8. Ormel J, Von Korff M, Burger H, et al. Mental disorders among persons with heart disease — results from world mental health surveys. *Gen Hosp Psychiatry*. 2007;29(4):325-334.
9. Lin EHB, Von Korff M, Alonso J, et al. Mental disorders among persons with diabetes--results from the world mental health surveys. *J Psychosom Res*. 2008;65(6):571-580. Mental disorders among persons with diabetes—Results from the World Mental Health Surveys.
10. Mago R, Tripathi N, Andrade C. Cardiovascular adverse effects of newer antidepressants. *Expert Rev Neurother*. 2014;14(5):539-551.
11. McIntyre RS, Park KY, Law CWY, et al. The association between conventional antidepressants and the metabolic syndrome. *CNS Drugs*. 2010;24(9):741-753.
12. Khawam EA, Laurencic G, Malone DA Jr. Side effects of antidepressants: an overview. *Cleve Clin J Med*. 2006;73(4):351-353. 356–61.
13. Kennedy SH. A review of antidepressant therapy in primary care: current practices and future directions. *The Primary Care Companion for CNS Disorders*. 2013;15(2):23071.
14. Sidor MM, MacQueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J Clin Psychiatry*. 2010;71(2):953.
15. Blackburn TP. Depressive disorders: treatment failures and poor prognosis over the last 50 years. *Pharmacol Res Perspect*. 2019;7(3):e00472.
16. Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discov*. 2019;18(1):41-58.
17. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 2016;16(1):22-34.
18. Vian J, Pereira C, Chavarria V, et al. The renin-angiotensin system: a possible new target for depression. *BMC Med*. 2017;15(1):144.
19. El Massry M, Alaeddine LM, Ali L, Saad C, Eid AA. Metformin: a growing journey from glycemic control to the treatment of Alzheimer's disease and depression. *Curr Med Chem*. 2021;28(12):2328-2345.
20. Penninx BWJH. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. *Neuroscience & Biobehavioral Reviews*. 2017;74:277-286.
21. Grigolon RB, Brietzke E, Mansur RB, et al. Association between diabetes and mood disorders and the potential use of anti-hyperglycemic agents as antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;95:109720.
22. Kessing LV, Rytgaard HC, Gerds TA, Berk M, Ekstrøm CT, Andersen PK. New drug candidates for depression - a nationwide population-based study. *Acta Psychiatr Scand*. 2019;139(1):68-77.
23. Kessing LV, Rytgaard HC, Ekstrøm CT, Torp-Pedersen C, Berk M, Gerds TA. Antihypertensive drugs and risk of depression: a nationwide population-based study. *Hypertension*. 2020;76(4):1263-1279.
24. De Giorgi R, De Crescenzo F, Rizzo Pesci N, et al. Statins for major depressive disorder: a systematic review and meta-analysis of randomized controlled trials. *PloS One*. 2021;16(3):e0249409.
25. Tao SH, Ren XQ, Zhang LJ, Liu MY. Association between common cardiovascular drugs and depression. *Chin Med J (Engl)*. 2021;134(22):2656-2665.
26. De Giorgi R, Rizzo Pesci N, Quinton A, De Crescenzo F, Cowen PJ, Harmer CJ. Statins in depression: an evidence-based overview of mechanisms and clinical studies. Frontiers. *Psychiatry*. 2021;12(1250):1-24.
27. Kessing LV, Rytgaard HC, Ekstrøm CT, Knop FK, Berk M, Gerds TA. Antidiabetes agents and incident depression: a Nationwide population-based study. *Diabetes Care*. 2020;43(12):3050-3060.
28. Woo YS, Lim HK, Wang SM, Bahk WM. Clinical evidence of antidepressant effects of insulin and anti-hyperglycemic agents and implications for the pathophysiology of depression-a literature review. *Int J Mol Sci*. 2020;21(18):6969.
29. Chen F, Wei G, Wang Y, et al. Risk factors for depression in elderly diabetic patients and the effect of metformin on the condition. *BMC Public Health*. 2019;19(1):1063.
30. Kim H-B, Kim J-S, Jung J-G. The association between aspirin use and depression: a systematic review and meta-analysis of observational studies. *Pharmacoepidemiol Drug Saf*. 2020;29(6):613-622.
31. Moulton CD, Hopkins CWP, Ismail K, Stahl D. Repositioning of diabetes treatments for depressive symptoms: a systematic review and meta-analysis of clinical trials. *Psychoneuroendocrinology*. 2018;94:91-103.
32. Shaw RJ, Mackay D, Pell JP, Padmanabhan S, Bailey DS, Smith DJ. The relationship between antihypertensive medications and mood disorders: analysis of linked healthcare data for 1.8 million patients. *Psychol Med*. 2021;51(7):1183-1191.

33. Li Y, Fan Y, Sun Y, Alolga RN, Xiao P, Ma G. Antihypertensive drug use and the risk of depression: a systematic review and network meta-analysis. *Front Pharmacol*. 2021;12:777987.
34. Colbourne L, Luciano S, Harrison PJ. Onset and recurrence of psychiatric disorders associated with anti-hypertensive drug classes. *Transl Psychiatry*. 2021;11(1):319.
35. Yatham MS, Yatham KS, Ravindran AV, Sullivan F. Do statins have an effect on depressive symptoms? A systematic review and meta-analysis. *J Affect Disord*. 2019;257:55-63.
36. Xu H, Li J, Jiang X, Chen Q. Electronic health Records for Drug Repurposing: current status, challenges, and future directions. *Clinical Pharmacology & Therapeutics*. 2020;107(4):712-714.
37. Åsvold BO, Langhammer A, Rehn TA, et al. Cohort profile update: the HUNT study, Norway. *medRxiv*. 2021;52(1):e80-e91.
38. HUNT Databank [Internet]. [cited 10 Oct 2020]. Available from: 2021 https://hunt-db.medisin.ntnu.no/hunt-db/
39. WHO Collaborating Centre for Drug Statistics Methodology [Internet]. 2021. Available from: https://www.who.int/medicines/regulation/medicines-safety/about/collab-centres-norwegian/en/.
40. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sørensen HT. The Nordic countries as a cohort for Pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol*. 2010;106(2):86-94.
41. Stafford L, Berk M, Jackson HJ. Validity of the hospital anxiety and depression scale and patient health Questionnaire-9 to screen for depression in patients with coronary artery disease. *Gen Hosp Psychiatry*. 2007;29(5):417-424.
42. Sultan S, Luminet O, Hartemann A. Cognitive and anxiety symptoms in screening for clinical depression in diabetes a systematic examination of diagnostic performances of the HADS and BDI-SF. *J Affect Disord*. 2010;123(1):332-336.
43. Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in cox regression. *Stat Med*. 1995;14(15):1707-1723.
44. Therneau TM, Grambsch PM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81(3):515-526.
45. Walker AJ, Kim Y, Borissiouk I, et al. Statins: neurobiological underpinnings and mechanisms in mood disorders. *Neuroscience & Biobehavioral Reviews*. 2021;128:693-708.
46. Brownstein DJ, Salagre E, Köhler C, et al. Blockade of the angiotensin system improves mental health domain of quality of life: a meta-analysis of randomized clinical trials. *Australian & New Zealand Journal of Psychiatry*. 2018;52(1):24-38.
47. Bergantin LB. The interactions between Alzheimer's disease and major depression: role of Ca(2+) channel blockers and Ca(2+)/cAMP Signalling. *Curr Drug Res Rev*. 2020;12(2):97-102.
48. Saddala MS, Lennikov A, Mukwaya A, et al. Discovery of novel L-type voltage-gated calcium channel blockers and application for the prevention of inflammation and angiogenesis. *J Neuroinflammation*. 2020;17(1):132.
49. Andrade A, Brennecke A, Mallat S, et al. Genetic associations between voltage-gated calcium channels and psychiatric disorders. *Int J Mol Sci*. 2019;20(14):3537.
50. Hayes JF, Lundin A, Wicks S, et al. Association of Hydroxylmethyl Glutaryl Coenzyme a Reductase Inhibitors, L-type Calcium Channel antagonists, and Biguanides with rates of psychiatric hospitalization and self-harm in individuals with serious mental illness. *JAMA Psychiat*. 2019;76(4):382-390.
51. Agustini B, Mohebbi M, Woods RL, et al. The association of antihypertensive use and depressive symptoms in a large older population with hypertension living in Australia and the United States: a cross-sectional study. *J Hum Hypertens*. 2020;34(11):787-794.
52. Åsvold BO, Langhammer A, Rehn TA, et al. Cohort Profile Update: The HUNT Study, Norway 2022 [cited dyac095]. Available from 10.1093/ije/dyac095
53. Langhammer A, Krokstad S, Romundstad P, Heggland J, Holmen J. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. *BMC Med Res Methodol*. 2012;12(1):1-14.
54. Povl Munk-Jørgensen ABAADKLELKT. Implementation of ICD-10 in the Nordic countries. *Nord J Psychiatry*. 1999;53(1):5-9.
55. Ellis RP, Hsu HE, Song C, et al. Diagnostic category prevalence in 3 classification systems across the transition to the international classification of diseases. *Tenth Revision, Clinical Modification JAMA Network Open*. 2020;3(4):e202280.
56. Decode Study Group obotEDESG. Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. DECODE study group on behalf of the European diabetes epidemiology study group. *BMJ (Clinical Research Ed)*. 1998;317(7155):371-375.
57. Bojanić I, Bjerkeset O, Williams LJ, Berk M, Sund ER, Sletvold H. Associations of cardiovascular agents and metformin with depression symptoms: a cross-sectional analysis from the HUNT study. *Norway Drugs - Real World Outcomes*. 2022;9(3):503-516.
58. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ*. 2016;354:i4515.
59. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol*. 2015;11(7):437-441.

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