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Doctoral thesis

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Norsk Sammendrag (Norwegian Summary)

Hyppige helsetap globalt skyldes hjerte- og karsykdommer (Cardiovasular diseases, CVDs), diabetes, depresjon og angst. Disse sykdommer overlapper ofte og kan føre til økt sykelighet og dødelighet, samt økte samfunnskostnader. Individer med CVDs eller diabetes har en høyere risiko for å utvikle depresjon og angst. Dette kan skyldes både usunne livsstilsfaktorer og biologiske mekanismer som er felles for disse sykdommene. Nylige studier antyder at visse legemidler ved hjerte- og karsykdommer og diabetes kan også ha positive effekter på depresjon. Noen av disse legemidlene ved CVDs er angiotensinkonverterende enzymhemmere (ACE-I), angiotensin II-reseptorantagonister (ARBs), acetylsalisylsyre (ASA) og statiner samt metformin (antidiabetika). Hovedmålet med denne avhandlingen var å undersøke sammenhenger mellom depresjon- og angstsymptomer, og CVDs eller diabetes prevalens og legemiddelbehandling i en populasjon over tid. Avhandlingen består av tre vitenskapelige artikler (Artikler I-III) basert på en stor befolkningsundersøkelse, Helseundersøkelsen i Trøndelag (HUNT). Informasjon om legemiddelbruk blant HUNT deltakerne fra 2006 til 2019 ble hentet fra Reseptregisteret og er benyttet i Artikkel II og III.

Artikkel I undersøkte prevalensen av depresjon- og angstsymptomer i en populasjon med og uten CVDs eller diabetes fra 1995 til 2019. Resultatene antyder en mulig reduksjon i prevalensen av depresjon- og angstsymptomer hos både individer med og uten disse fysiske sykdommene. Depresjon- og angstsymptomer var imidlertid generelt høyere hos populasjonen med CVDs eller diabetes. Sammenhenger mellom CVDs eller diabetes og økt prevalens av depresjon- og angstsymptomer, viste generelt reduksjon over tid med unntak for depresjon og CVDs blant menn.

Artikkel II undersøkte sammenhenger mellom depresjonssymptomer og legemidler ved CVDs og metformin blant populasjon med CVDs eller diabetes i HUNT3 og HUNT4. Resultatene antyder at individer med CVDs som bruker ASA og statiner, sammenlignet med ikke-brukere, har en lavere prevalens av depresjonssymptomer. Dette gjelder for menn i hele studieperioden og kvinner i HUNT4.

Artikkel III undersøkte risikoen for oppstart av antidepressiv behandling blant HUNT3 deltakere som brukte ulike legemidler ved CVDs eller metformin over en 10 års periode. Studien viser at blant individer i alderen fra 40 til 70 år, var behandling med ARBs og CCB som monoterapi, samt ASA eller statin som kombinasjonsterapi, assosiert med en redusert risiko for oppstart av antidepressiv behandling.

Disse studiene viser at depresjon- og angstsymptomer er vanlige blant populasjon med CVDs eller diabetes, samt at prevalensen av depresjonssymptomer og risiko for oppstart av antidepressiv behandling varierer mellom ulike legemiddelgrupper. Ved behandling av CVDs eller diabetes bør det tas hensyn til depresjon- og angstsymptomer. Resultatene fra studiene gir ikke tilstrekkelig evidens om mulige positive effekter av legemidler ved CVDs på depresjonssymptomer blant individer med CVDs. Videre forskning bør identifisere og beskrive spesifikke befolkningsgrupper med CVDs eller diabetes, som kan ha nytte av legemiddelbehandling ved disse fysiske sykdommer i forebyggingen eller behandlingen av depresjon.

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In loving memory of my father Ivo,
whose presence will always be within me.

Contents

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List of papers

Three papers are included in this thesis and will be referred to as Paper I, Paper II and Paper III.

Paper I

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. https://doi.org/10.1186/s40359-021-00636-0

Paper II

Bojanić, I., Bjerkeset, O., Williams, L.J. *et al.* **Associations of Cardiovascular Agents and Metformin with Depression Symptoms:** A Cross-Sectional Analysis from the HUNT Study, Norway. *Drugs - Real World Outcomes* (2022). https://doi.org/10.1007/s40801-022-00321-7

Paper III

Bojanić I, Bjerkeset O, Williams L, Bjørngaard J. H, Sund R. E and Sletvold H. **Risk of antidepressant initiation drug among users of cardiovascular agents and metformin.** *Findings from the Trøndelag Health Study (HUNT) and Norwegian Prescription Database (NorPD), Norway*

Under review.

1. Introduction

Mental health conditions, cardiovascular diseases (CVDs) and diabetes mellitus (DM) are the major causes of disability and disease burden worldwide (1, 2). Depression and anxiety are common overlapping mental health conditions more prevalent among individuals with CVDs or DM than in the general population (3, 4), which lead to higher morbidity and mortality rates than each physical condition alone (5-7). Available antidepressant agents have limited efficacy (8) and adverse metabolic (9) and cardiovascular side effect profiles (10) that are unfavourable and even dangerous in CVDs and DM (11, 12). Emerging evidence points to the link between inflammation and mental health conditions (13), particularly depression (14, 15), and the potential benefits of anti-inflammatory agents in depression (16-18). Furthermore, cardiovascular and antidiabetic agents that reduce inflammation may, in addition to their primary therapeutic indication, prevent or improve depression (16, 19). Reduced depression risk and levels have been documented for several cardiovascular agents: renin-angiotensin system (RAS) agents (19-21), acetylsalicylic acid (ASA) (22, 23) and statins (24-26). Metformin, a first-line drug in type 2 DM treatment, was protective of depression (27-30) and improved depression (29, 31) in diabetic adults. Clinical and observational evidence on mental health benefits has been most robust for statins (24-26, 32, 33) and mainly mixed for RAS agents (19, 34, 35), ASA (36-38), and metformin (27, 39). However, methodological issues such as small samples and strict eligibility criteria of randomized controlled trials (RCTs) (40) limit the evidence on the effectiveness of these drugs in depression treatment. Alternatively, non-interventional ("real world") data (e.g., prescription records, health surveys and others) offer valuable and less explored sources for identifying new therapeutic approaches on the population level (41, 42). Thus, examining depression and anxiety symptoms in high-risk populations (e.g., CVDs and DM) on different drug treatments can be a valuable support to RCTs to identify and inform novel mental health prevention and treatment strategies. Furthermore, suggested differences in depression and anxiety risks and rates between cardiovascular and antidiabetic agents highlight the importance of acknowledging the use of these drugs among CVDs and DM patients (20, 22, 28, 43). The overall aim of this thesis was to investigate the relationships of depression and anxiety symptoms with CVDs and DM prevalence and drug treatments using population-based cohorts (HUNT participants) and the Norwegian Prescription Register (NorPD).

2. Background: Depression and anxiety in cardiovascular diseases (CVDs) and diabetes mellitus (DM)

Mental health conditions, such as depression and anxiety, affect individuals with physical diseases more often than the general population (44, 45), causing more pronounced health decrements than each disease alone (46, 47). This thesis focuses on self-reported depression and anxiety symptoms in CVDs and DM. To better understand this mental-physical comorbidity, a brief overview of CVDs, DM definitions and epidemiology is included. Thereafter, the main aspects related to depression and anxiety will be presented.

Cardiovascular diseases (CVDs) include heart or blood vessel disorders driven by atherosclerosis (plaque changes). Most risk factors for CVDs are modifiable: hyperlipidemia, hypertension, smoking, unhealthy diet, low physical activity and diabetes (48), while others include age, sex, genetics, socioeconomic status (e.g., education, income) and ethnicity (49). Improved surgical and medical treatments and access to health services have generally reduced the CVDs prevalence and mortality (50), yet rates vary across regions (51). CVDs mortality in Norway is below the average level in Western Europe and the lowest compared to other Nordic countries (52). CVDs have been estimated as the six leading causes of mortality in Norway in the past decades (53). Today, the fifth part of the entire population in Norway (21%) have CVDs or a high risk of developing the disease, and about 1.1 million use cardiovascular agents in treatment or prevention (52).

Diabetes mellitus (DM) is a complex metabolic disorder caused by defects in insulin secretion, insulin action, or both (54). Among several types of diabetes, type 1 DM (T1DM) and type 2 DM (T2DM) are the most common (55). Overweight and obesity, physical inactivity and an unhealthy diet are major risk factors for T2DM (56), whereas modifiable risk factors for T1DM are less known (57). T2DM accounts for between 90% and 95% of global diabetes prevalence, with the highest proportions in low- and middle-income countries (58). Norway and other Nordic countries have a relatively low incidence of diagnosed DM compared to other countries (59). Public health statistics estimate that 4.7% of the total Norwegian population (245 000 people) has been diagnosed with diabetes, of which 4% (216 000 people) with T2DM and 0.7% (28 000 people) with T1DM. Interpretation of these estimates needs caution as many people could be living with undiagnosed DM and disease detection varies across Norwegian data sources (60).

2.1 Depression and anxiety: definitions, pathophysiology, measurement, treatment, and epidemiology

Mental health conditions (also called mental illnesses or disorders) include various disorders that affect individuals thinking, feeling, mood and behaviour, and depression and anxiety are the most common (61). On the individual level, both mental health conditions are significant contributors to poor life quality (62), sick leave and early retirement (63), and a higher risk of other chronic diseases, including CVDs (64) and DM (65) suicidality (66), and early death (67). Depression and anxiety are leading causes of non-fatal health loss (measured by years lived with disability (YLDs)) and health burden worldwide (68). In Norway, depression and anxiety are ranked as the 10-top causes of age-standardized YLDs from 1990 to 2019 (53).

2.1.1 Definitions

The term «depression» often describes a mood disorder characterized by sadness or lowered mood, loss of interest or pleasure (i.e., anhedonia) and psychomotor retardation (69). In contrast, anxiety commonly refers to a more exaggerated state of worrying, the feeling of tension, and fear of possible harmful incidents (70). However, symptoms of depression and anxiety often coexist (71) and include common pharmacological treatment (72, 73), indicating that dysfunction of the same neurotransmitter pathways underlies both conditions (74). Moreover, the overlap of depression and anxiety increases with the severity of the symptoms, making a clear clinical distinction between these two conditions difficult (75).

2.1.2 Pathophysiology

Due to disease complexity and heterogeneity, biological causes of depression and anxiety are still not fully elucidated (76). The monoamine hypothesis offered a simplified yet most used neurobiological explanation of depression and anxiety (74), which remained a basic theoretical framework for developing antidepressant agents (77). This hypothesis postulates that deficiency in monoamine levels, including serotonin (5-HT), dopamine (DA) or noradrenaline (NA), at functionally essential receptor sites in the brain, is responsible for depression (74). The therapeutic delay between the initiation of antidepressant therapy and the observed improvement in depression and anxiety symptoms limits the monoamine hypothesis (78). Moreover, the limited success of antidepressants that act on neurotransmitters has indicated that

mechanisms of depression and anxiety are wider than neurotransmission (79). Clinical and preclinical evidence suggests stress response, hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and cortisol secretion as important mechanisms underlying depression and anxiety (80). Additional mechanisms involved in the overall pathophysiological condition or specific symptoms of depression and anxiety include immuno-inflammation and oxidative stress in the central nervous system (81), gene effects (82, 83) and changes in brain structures (76).

2.1.3 Measurement

Anxiety and depression are expressed through various symptoms (i.e., psychological, somatic, functional and social) (69, 70), which are generally measured eighter by diagnostic interviews (objectively, by a trained clinical expert) or self-rating instruments (subjectively, by self-report). To meet the criteria for anxiety or depression disorders, the symptoms must have persisted over a more extended period, at least two weeks for depression (84) and one to six months for anxiety disorders (84). Clinical diagnostic interviews, which cover a great variety of depression and anxiety symptoms, are a gold standard for diagnosing depression or anxiety, as defined by the current Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) (84, 85). The severity of depression and anxiety disorders (mild, moderate or serve) is often determined by symptom levels, persistence and functional impairment caused by these symptoms (86).

Self-rating instruments for depression and anxiety are not accepted diagnostic tools by DSM and ICD, yet they are proven screening and evaluation instruments for clinical purposes (87-89). Moreover, in epidemiological studies, self-rating scales are cost-effective and frequently used for assessing anxiety and depression symptoms. Commonly used screening scales for depression and anxiety in health studies are Beck Depression Inventory (BDI) (90), the Centre for Epidemiological Studies Depression Scale (CES-D) (91), the General Health Questionnaire (GHQ) (92), Hospital and Anxiety Depression Scale (HADS) (93) and the Patient Health Questionnaire (PHQ)9 (94). Self-rating scales focus on various psychological, somatic and social symptoms of anxiety and depression (95), and a few meet the diagnostic criteria of the DSM or ICD

system (96). Although increasing severity and duration of self-reported symptoms are often related to increasing the probability of meeting diagnostic criteria for depression and anxiety disorders, self-reported depression and anxiety do not necessarily reflect the clinical diagnosis of these diseases (97). Thus, addressing differences in the scope and coverage of the depression and anxiety instruments is essential when comparing the results of the studies (98).

Prescription data may help detect people suffering from possible depression and anxiety disorders in population-based cohorts when diagnosis information is unavailable (99). In the two first studies (Papers I and II) of this thesis, symptoms of depression and anxiety were assessed by the HADS self-reported scale. The third study (Paper III) used prescription data of antidepressant agents as an indicator for antidepressant therapy and possible diagnosis of depression.

2.1.4 Treatment

Antidepressants are the mainstay of pharmacological treatment among adults with moderate to severe depression or mild depression that persists alone or in combination with psychotherapy (72). Due to a lack of evidence-based efficacy and poor risk-benefit ratio, short-term mild depression is not an indication for antidepressant therapy (100, 101). Anxiety disorders (e.g., general anxiety disorders and other forms of anxiety) are also indications for antidepressant therapy (73).

Biological mechanisms for almost all currently marketed antidepressants include an increase in monoamine neurotransmitter (e.g., serotonin, noradrenaline and dopamine) levels. According to their primary mechanisms of action, antidepressants can be broadly grouped into the following categories:
1) monoamine neurotransmitter reuptake inhibitors (RIs), 2) monoamine oxidase inhibitors (MAOIs) and 3) alpha2-adrenoreceptor antagonists and serotonin receptor blockers (102). RIs include selective tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), serotonin reuptake inhibitors (SSRI), serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenaline and dopamine reuptake inhibitors (NDRIs) and noradrenaline reuptake inhibitors (NRIs). RIs express their effects by inhibiting the transporter

responsible for the reuptake of one or more monoamines (102). MAOIs act by inhibiting monoamine oxidase (MAO) activity, the enzyme that catalyzes the breakdown of the monoamine neurotransmitters (103). Mirtazapine is a noradrenergic and specific serotonergic antidepressant that acts as a potent alpha2-adrenoreceptor antagonist and 5-HT2A receptor blocker and reduces the activity of the receptor-negative feedback pathways leading to an increase in noradrenaline and serotonin transmission (104).

SSRIs are the current first-line drug treatment option for depression (72, 101) due to improved tolerability and safety profile, broader effectiveness (depression and anxiety), and reduced risk of overdose than TCAs (102). Despite evidence for higher efficacy than SSRIs (105), SNRIs are not typical first-line depression treatment (106), mainly due to adverse events (107) and increased suicide risks (108). However, the best drug choice depends on disease manifestation, drug-related adverse reaction profile, interaction potential, pharmacological properties, and patient comorbidities and preferences (106). Antidepressant agents can be a suitable and «best» depression treatment option for some patients, whereas they are ineffective (8) and even dangerous for others (109). Effective treatment and management of depression thus remain a challenge in psychiatric practice (110).

2.1.5 Epidemiology

Evidence indicates that depression and anxiety disorders and symptoms affect many of the world's population; however, estimated prevalence rates vary across world regions and countries (111-113). The European Study of the Epidemiology of Mental Disorders (ESEMeD) from six countries (Belgium, France, Germany, Italy, the Netherland, and Spain) estimated the 12-month and lifetime prevalence of mental disorders at 4.2% and 12.8% for depression and 6.4% and 13.6% for anxiety in 2001 to 2003 (112). For the same period, a national survey on the adult American population (National Comorbidity Survey-Replication, NCS-R) estimated the 12-month and lifetime prevalence of depression at 9.5% and 20.8% and any anxiety disorders at 18.1% and 28.8 % (113). Recent WHO estimates of the 12-month prevalence of mental disorders in the European Region ranged from 4.3% to 4.5% for depression and 3.8% to 4.0% for anxiety, with slightly higher rates in Eastern than Western countries (111). Among the Nordic countries, the

prevalence of depression disorders showed marginal differences (from 4.7% to 5.6%), whereas the total rates of anxiety disorders were lowest in Finland (3.2%) and the highest in Norway (7.4%). Both disorders were more frequent in women than men and older age groups (55-75 years) in all regions (111).

Norwegian public health data indicate that over a year, about one in ten (10%) and one in fifteen (15%) people will experience depression and anxiety disorders, respectively (114). However, a large Norwegian population-based study showed that from 1995 to 2019, both depressive and anxiety symptoms increased in younger adults (13–19 years) but decreased and then remained mainly unchanged in elderly adults (≥60 years), respectively (115). Data from Netherland (116), Germany (117) and Sweden (118) indicated the same age-specific trend in the prevalence of mental disorders and self-reported anxiety, respectively. Despite regional variations in estimates, there is general agreement between studies that depression and anxiety are highly prevalent worldwide and more common in women than men (119, 120). However, there is an ongoing debate about the growing global trend of these disorders (121, 122). Several studies examining trends in the prevalence of mental disorders among the populations worldwide found no evidence of any increase (116, 121, 123).

According to Norwegian Public Health statistics, self-reported psychological symptom prevalence declined from 1998 to 2005 but increased in 2012 (https://www.norgeshelsa.no/norgeshelsa/). The Danish population-based study reported a sharp rise (2% to 4.9%) in the prevalence of depression disorders from 2000 to 2006 (124), a trend observed among Finnish women from 2000 to 2011 (125). The increase in the population living with depression and anxiety over the past decades in the world (68) and in Nordic countries (124, 125) may result from population growth and ageing rather than the rising global epidemic of mental disorders (122). Compared to other European countries, the use of antidepressants in Nordic countries is suggested to be high, corresponding to the depression and anxiety prevalence data (126).

2.2 Depression and anxiety in CVDs and DM – shared biological links

CVDs and DM affect depression and anxiety incidence (and vice versa) via shared biology accompanied by common modifiable and behaviour risk factors (127-130). While underlying mechanisms between depression and CVDs are unclear, recent evidence support contributions from serotonergic and inflammatory pathways toward the comorbidity between these conditions (131). Innate immune dysfunction followed by chronic low-grade inflammation is also suggested as a bridging link between depression and DM (127). Other mechanisms by which inflammation promotes the development of depression, CVDs and DM, involve dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis (132, 133) and RAS (127, 134).

Serotonergic dysfunction is a mechanism involved in the pathophysiology of mental health conditions (74) that plays an important role in CVDs morbidity (135). Stress-induced inflammation resulting from HPA-axis and sympathetic neuro-system (SNS) activation leads to excess cortisol release and pro-inflammatory cytokine production, which are biological origins of depression (15). Cortisol increases blood pressure and causes blood vessel damage and plaque build-up, which are well-known early signs of future CVDs (136). Chronic hypercortisolemia and prolonged SNS activation promote insulin resistance and visceral obesity and lead to metabolic syndrome and T2DM (137). Accompanied by blood pressure regulation, RAS plays a significant role in inflammation mainly via action on angiotensin II receptor type 1 involved in stress regulation and consequently the secretion of several pro-inflammatory cytokines (138). RAS overactivation results in endothelial dysfunction and a pro-inflammatory activity that advances the progression of CVDs (139) and DM (137, 140) and the development of depression (138).

Stress and anxiety, both common symptoms of depression (80), can also increase inflammatory response (13) and, in turn, promote vascular and metabolic changes leading to CVDs (132) and DM (130), respectively. Although systematic inflammation was associated with depression and anxiety (13, 141), studies indicate a stronger association with depression, suggesting disorder-specificity. Higher concentrations of inflammatory markers are consistently suggested as risk factors for depression (142-146),

whereas evidence suggesting the same for anxiety remains unclear (147-149). A recent Mendelian randomization-based study suggested a potential causal link between an increase in systematic inflammation and depression but not anxiety (150, 151). Notably, an extensive population-based study of over 140 000 adults found strong associations of higher CRP levels and genetically-predicted higher IL-6 activity with symptoms of depression but not anxiety, indicating the possibility that inflammation is disorder-specific and causal related to depression (151). Due to the complexity of inflammatory pathways, it is still difficult to elucidate the true nature and direction of observed relationship between raised CRP and IL-6 levels and depression (146, 150, 151).

2.3 Epidemiology of depression and anxiety in CVDs and DM

2.3.1 Depression and anxiety in CVDs

Epidemiological evidence demonstrates a higher risk and prevalence of depression and anxiety in people with CVDs than in the general population (3, 152-156). WHO cross-sectional study from 17 countries reported a 2-fold higher risk for depression and anxiety disorders in CVDs than in the no-CVDs population, the pattern observed across cultures (3). The estimated depression and anxiety prevalence vary across CVDs sub-populations, instruments (clinical interviews vs self-rating scales) and time points after the event. About 7-15% of patients with acute myocardial infarction reported mild to moderate depression symptoms, whereas nearly 20% met the diagnostic criteria for major depression (152). Depression disorders were found in at least 1 in 5 patients with heart failure (HF) (range 10% for asymptomatic to 40% for serve HF), whereas prevalence rates were much higher among patients screened with questionnaires (33.6%) (155). A recent meta-analysis of observational studies of stroke survivors reported a pooled depression prevalence of 33%, with a significant reduction 1-5 years and more after the event (154), and anxiety from 18-25%, with minor changes 1-6 months or more after stroke (153). Clinically diagnosed depression is a powerful predictor of CVDs prognosis and treatment outcome (157) and survival (5, 6) or other complications followed by CVDs (158). Anxiety is common in CVDs (44, 153, 159, 160) and often occurs early after the acute event, predicting the later development of depression (161). Alone or with depression, anxiety in CVDs is associated with an increased risk of mortality (162) and new cardiac events (163, 164). However,

the causal nature of the observed prospective associations of CVDs with depression and anxiety are still largely unknown (159, 165).

Several traditional cardiovascular risk factors (48) also represent risk factors for depression and anxiety (129) indicating that shared biological mechanisms and confounding influence the relationships between CVDs and mental health conditions. The most common risk factors shared with CVDs and depression and anxiety include smoking (166), physical inactivity (167, 168), alcohol consumption (169, 170) and body mass index (BMI) (171).

2.3.2 Depression and anxiety in DM

Depression and anxiety are more common in people with DM than in non-diabetic adults (4, 172-175). A recent meta-analysis of observational studies suggested that nearly one in four (28%, 95%CI 27-29) individuals with T2DM worldwide suffer from depression, with prevalence rates higher for self-reported than clinically diagnosed depression and age group <65 years old (174). Furthermore, depression prevalence is estimated to be three times higher in people with T1DM and nearly two times higher in those with T2DM than in non-diabetic populations (175). Anxiety symptoms and anxiety disorders are detected in 40% and 14% of T1DM and T2DM patients (176), which are rates substantially higher than in the general population (177). There is a general agreement that depression and anxiety prevalence is higher in diabetic than non-diabetic populations, yet estimates vary across countries (4, 174, 178). A recent meta-analysis showed that, relative to global estimates, depression prevalence in the T2DM population was lower in Europe and Africa but higher in Australia and Asia (174). Furthermore, T1DM and T2DM differ in disease pathophysiology (179) and risk patterns related to psychopathology (130). However, it is unclear whether the prevalence of anxiety and depression differ significantly according to the type of DM (175, 176, 180). A few small sample studies reported higher rates of depression and anxiety in populations with T1DM than in T2DM (180, 181), whereas meta-analyses found no differences in the prevalence rates (175, 176).

There is a strong link between DM and mental health conditions, and several risk factors contribute to this relationship. BMI, consumption of hypercaloric diets, sedentary lifestyle, alcohol use and smoking are major contributors to T2DM (65) that also play a significant role in the pathophysiology of depression and anxiety (166, 169-171, 182).

2.4 Cardiovascular agents and metformin - drug repurposing candidates for depression

The discovery of new and improved antidepressants has not been fruitful in the past decades (183). Alternatively, the possibility of finding new targets for depression using drugs from other fields of medicine that affect biological pathways implicated in depression, so-called drug repurposing, has aroused great interest in psychiatry (184, 185). This process requires that the drug candidate for repurposing is safe and that its "off-label" use can be expanded safely with low costs (186). Given the comorbidity and shared pathogenic mechanisms of CVDs, DM and depression (127, 128), several cardiovascular and antidiabetic agents have been examined for their putative antidepressant action (19, 187-189). However, it is still unclear which one of the proposed candidates has therapeutic benefits for depression (39, 190, 191). Inflammatory nature (13) and overlapping symptoms of depression and anxiety (71) indicate possibilities for the potential benefits of these drugs on anxiety as well (192, 193). However, the role of inflammation in anxiety has been less established (147). Therefore, this thesis focuses on the relationship between depression, CVDs drugs and metformin.

The following chapter will review the evidence for relevant drug classes for CVDs treatment and the first-line T2DM treatment metformin. Table 1 shows a summary of selected observational studies assessing associations between the use of cardiovascular or antidiabetic agents and depression. For clarification, the term "drug" refers to a pharmaceutical drug (also called medication, medicine, pharmaceutical preparation, and others) as a chemical substance used to treat, prevent, cure, and promote well-being.

2.4.1 Statins

In past years, there has been an ongoing debate on the role of statins in depression treatment. Statins are best known as lipid-lowering agents beneficial to cardiovascular health (194). These drugs also have direct anti-inflammatory actions (195), which may benefit depression (187).

The higher efficacy of statins vs placebo in addition to SSRIs in improving depression symptoms in patients with depression at eight weeks of treatment has been demonstrated in clinical trials (24). Similarly, epidemiological evidence shows a reduced risk for hospitalization for depression (196) and post-stroke depression (197) for using statin adjuvant therapy to SSRI than SSRI alone. There is no documented difference in the safety profiles between statins (24, 198, 199), except for higher efficacy and onset of action of the lipophilic agents (24, 200). Statins' efficacy in preventing depression in healthy individuals is still unclear (201). However, robust clinical evidence demonstrates that their use is associated with lower depression symptom scores (199) and does not initiate depression symptoms in non-depressed individuals (24, 199).

Epidemiological studies have indicated that statins alone may be beneficial in preventing depression in the community and patient populations (23, 33, 202, 203). Reduced incidence of depression disorders during periods of statin treatment, irrespectively of antidepressive use was found in the Swedish cohort (33). In contrast, statin use was associated with decreased risk for early and lifetime depression only in patients with acute coronary syndrome (ACS) (23) or stroke (203), with no specific benefits on mood in a general population (204-206), findings supported by an updated meta-analysis (207). Furthermore, a sub-group meta-analysis suggested a lower risk of depression risks for statin users with coronary artery disease but not for the CVDs population in general and individuals with hypertension or heart failure on statin therapy (191). Statin use has also been associated with an increased 1-year incidence of depression in stroke survivors (208).

Robust clinical evidence suggests statins as a beneficial and safe add-on therapy for depression (17, 24, 187), yet small samples and heterogeneity across studies limit the generalizability of the findings (201, 207). Observational studies have mainly demonstrated the preventive effects of statins on depression (22, 33, 203). However, the results have been mixed (204-206, 208), indicating that potential beneficial associations of statins partly depend on the study population characteristics or design.

2.4.2 Acetylsalicylic acid

Acetylsalicylic acid (ASA), also known as aspirin, inhibits cyclooxygenase (COX-1 and COX-2) activity and prostaglandins synthesis, molecules involved in inflammation (209). Due to its potent anti-inflammatory properties, ASA may effectively prevent or reduce depression (189).

Several clinical trials have demonstrated that the administration of ASA improves the effect of antidepressant treatment in patients with depression (16, 210-212). However, evidence has been inconsistent, suggesting no therapeutic benefits (37, 213, 214) or even adverse effects of ASA adjuvant therapy for depression (215) and no preventive effect on depression in healthy older adults used alone in low-dose (37).

Epidemiological studies suggested potential associations between ASA use and the development of depression in different populations (22, 23, 216). Danish data showed reduced seven-year depression incidence in population-based adults on low-dose ASA therapy (22), in contrast to the Swedish cohort, where ASA use was associated with reduced risk for early and late depression in ACS patients but not in ACS-free individuals (23). However, some epidemiological data failed to demonstrate that ASA use might be protective against depression in the young cohort (217), general adults (38, 204), and stroke patients (203). Furthermore, meta-analytic evidence suggested ASA use as a possible risk factor for depression, particularly with increasing age (36, 218).

Although low-dose ASA may improve the effectiveness of conventional antidepressant treatment (219), there is no clinical-based support for its use in the primary and secondary prevention of depression (189). Observational evidence for low-dose ASA therapy in preventing depression in general (220) and in the CVDs population (191) is promising but still inconclusive (221). Given the role of inflammation in outcomes of depression treatment (222), the benefits of ASA in the secondary prevention of depression require further investigation (223).

2.4.3 Renin-angiotensin system agents

In addition to blood pressure regulation (139), the renin-angiotensin system (RAS) is known modulatory pathway of central nervous system inflammation (138). ACEI and ARBs are effective antihypertensive agents with RAS targets (224) that can, by reducing neuroinflammation, exert potential benefits for inflammatory brain diseases such as depression (19).

To date, no RCTs have assessed the efficacy of RAS agents in treating and preventing depression (19, 225), except for some clinical data that showed that hypertension treatment with ACEI or ARBs in otherwise healthy adults is associated with improved mental health domains of quality of life (226).

Extensive population-based register studies indicate that RAS agents offer more advantages for mental health than other antihypertensive agents (22, 227-229). However, in Chinese patients initiating antihypertensive treatment, incidence and risk for depression were the lowest for users of ARBs than other agents but significantly higher in ACEI than ARBs users (229). Whereas in population-based Danish adults, a lower risk of depression was observed only for the use of two of six ACEI or ARBs (20). In contrast, no statistically significant association between ACEI or ARB use and reduced depression incidents and depression symptom prevalence was found in the Scottish population (230), and Australian and American older adults (231), respectively.

There is promising observational evidence that ACEI and ARBs can exert antidepressive effects by RAS targets (22, 227-229). However, findings are still unclear (190), with some indications that these drugs may even be risk factors for depression (232). Limitations of observational data (233) may explain this controversy regarding RAS agent use and depression (230, 231, 234, 235). Further clinical trials are necessary to verify the effectiveness of RAS agents in depression treatment and depression.

2.4.4 Calcium-channel blockers, beta-blockers and diuretics

Calcium-channel blockers (CCB) have been explored in psychopharmacology (236) due to the role of calcium homeostasis dysregulation in the pathophysiology of depression (237, 238), with clinical trials suggesting their efficacy as an adjuvant to depression treatment (239, 240). Beta-blockers (BB) have been previously associated with an increased risk of depression (241); however, a recent meta-analysis of RCTs contradicts these results (242). More robust evidence shows no significant associations between diuretics and improved depression (190, 191).

Observational studies addressing depression in the population on CCB, BB or diuretic treatment reported conflicting findings (20, 227, 229, 230, 235). An extensive Danish population-based study found lower 10-year depression incidence among users of CCB and BB but not diuretics (20). On the contrary, a higher incidence of new-onset depression was found in Scottish antihypertensive patients treated with CCB, BB or diuretics (230), results supported by a meta-analysis (191).

Existing clinical and observational data appear to provide no significant association of BB with altered depression risk, whereas the role of CCB and diuretics in depression remains unclear (190). Despite the limited clinical evidence base, CCB remain candidates for repurposing in psychiatry because of their biological plausibility (236, 237) and demonstrated benefits on mood disorders in extensive cohort studies (20, 227).

2.4.5 Metformin

Metformin is the first-line hypoglycaemic agent for T2DM (243), which is known to have several non-glycaemic beneficial effects (244). Emerging evidence suggests the role of metformin in ameliorating depression in T2DM due to the drug's anti-inflammatory and neuroprotective properties (31, 39, 245-247). Clinical trials of metformin in subjects with T2DM or prediabetes demonstrated both benefits (31) and lack of effect on mood (247, 248) with metformin administration compared to placebo. In a multi-centre RCT of non-diabetic outpatients with diagnosed depression, SSRI combined with metformin yielded a higher decline, response, and remission rate of depression symptoms than SSRI alone (249).

Metformin, alone or as a combination therapy, has been associated with reduced risk and incidence of depression in the population with diabetes (28, 30). However, in the Taiwanese cohort of T2DM subjects, lower risk and incidence of depression were found in users of metformin and sulfonylureas, but not each antidiabetic agent alone (250). In contrast, all antidiabetic drug classes, except for dipeptidyl peptidase-4 (DPP-4) inhibitors, showed no significant associations with reduced risk of depression in T2DM patients from Japan (251).

Despite solid biological support for the potential antidepressive effects of metformin (188, 252, 253), clinical (27, 39), and observational studies (250, 251) are still unable to conclude metformin's independent benefits on depression in diabetic populations. Further evaluation of potential therapeutic and preventive benefits of metformin treatment for depression in clinical and “real-world” settings is warranted.

Table 1. List and summary of selected observational studies regarding associations between the use of cardiovascular or antidiabetic agents and depression or anxiety

Author (year) Country (ref [a])	Study design	Drug class	Study population (N)	Exposure measurement	Outcome measurement	Main results
Redlich et al. (2014) Sweden (202)	Prospective cohort	Statins	Population-based adults (4 607 990)	Prescription records	Depression disorders (ICD-9/10 or ATC-code N06A)	Statin use vs no-use was associated with a lower risk of depression (OR 0.92, 95%CI 0.89-0.96) during 2-year follow-up, and risk reduction increased with higher age. Simvastatin had a protective effect, whereas atorvastatin was associated with an increased risk of depression.
Kang et al. (2015) Taiwan (208)	Retrospective cohort	Statins	Stroke patients (11 218)	Health Insurance Database	Depression disorders (ICD-9)	Stroke patients using statins had a higher risk (HR 1.59, 95%CI 1.30-1.95) for depression than stroke patients with no-statin prescription at 1-year follow-up after first-time hospitalization for stroke.
Agustini et al. (2019) Australia & USA (206)	Cross-sectional	Statins	Community-dwelling adults (19 114)	Self-reported	Self-reported depression (CES-D ≥ 8)	Statin use showed no statistically significant association with the risk of depression symptoms.
Köhler-Forsberg et al. (2019) Denmark (205)	Prospective cohort	Statins	Population-based statin users (193 977) no-statin users (193 977)	Prescription records	Depression disorders (ICD-9/10 or ATC-code N06A)	Statin use was associated with an increased risk of antidepressant use and depression diagnosis during 20-years follow-up but not after adjusting for antidepressant use.
Molero et al. (2020) Sweden (33)	Prospective cohort	Statins	Population-based statin users (1 149 384)	Prescription records	Depression and anxiety disorders (ICD-10)	Statin use was associated with a reduced risk for depression (HR 0.91, 95%CI 0.87–0.94) but not anxiety disorders.
Veronesse et al. (2018) USA (38)	Prospective cohort	ASA	Community-dwelling adults (4 070)	Self-reported	Self-reported depression (CES-D ≥ 16)	ASA use showed no statistically significant association with risk for development of depression symptoms at 8 year follow-up.
Glaus et al. (2015) Switzerland (204)	Prospective cohort	Statins ASA	Community-dwelling adults (1631)	Self-reported	Depression disorders (DSM-IV)	ASA or statin use at baseline did not reduce the incidence of depression at a 5.2-year follow-up, regardless of sex or age.
Wium-Andersen et al. (2017) Denmark (203)	Prospective cohort	Statins ASA NSAIDs	Stroke patients (147 487) no-stroke individuals (160 235)	Prescription records	Depression disorders (ICD-9/10 or ATC-code N06A)	All anti-inflammatory drugs decreased the risk for early-onset depression (<1 year) after stroke, primarily used in combination. ASA or NSAIDs increased the risk (HR 1.24, 95%CI 1.20-1.28 or HR 1.31 95%CI 1.27-1.35) for late-onset depression (≥1 year after stroke), whereas statin showed a tendency toward a decreased risk (HR 0.92, 95%CI 0.89-0.95) in stroke patients.
Wium-Andersen et al. (2017) Denmark (23)	Prospective cohort	Statins ASA NSAIDs	ACS patients (91 842) no-ACS individuals (91 860)	Prescription records	Depression disorders (ICD-9/10 or ATC-code N06A)	ASA and statin use was associated with decreased risk of early depression (HR 0.89, 95%CI 0.85-0.93 and HR 0.90, 95%CI 0.86-0.94, respectively) in ACS but not in the no-ACS population. In both populations, NSAID use was associated with an increased risk of late (≥1 year after ACS or study entry) but not early depression.
Kessing et al. (2019) Denmark (22)	Prospective cohort	Statins ASA ACEI ARBs	Population-based adults (1 576 253)	Health register data	Depression disorders (ICD-9/10 or ATC-code N06A)	Continued vs initial use of low-dose ASA (HR 0.75 95%CI 0.74-0.76), statins (HR 0.65 95%CI 0.64-0.66), ACEI or ARBs (HR 0.73, 95%CI 0.72-0.74) was associated with decreased incident depression or antidepressant prescription at 10 years of follow-up.
Boal et al. (2016) Scotland (228)	Prospective cohort	ACEI ARBs BB CCB Diuretics	Hypertension patients (144 066)	Prescription records	Depression disorders (ICD-10)	ACEI or ARBs monotherapy showed the lowest risk for hospital admission for depression during 5-year follow-up. BB (HR 2.11, 95%CI 1.12-3.98) and CCB (HR 2.28, 95%CI 1.13–4.58) showed higher risk than reference.

Cao et al. (2019) China (229)	Retrospective cohort	ACEI ARBs BB CCB Diuretics	Hypertension patients (181 709)	Medical insurance data	Depression disorders (ATC-code)	Compared with ARB group, the risk for depression was highest for BB (HR 1.37, 95%CI 1.32–1.43) and lowest for CCB (HR 1.16, 95%CI 1.12–1.21). The lowest depression incidence was found for ARBs users among all antihypertensives. ACEI takers had a significantly higher depression risk than ARBs users.
Colbourne et al. (2021) USA (227)	Prospective cohort	ACEI ARBs BB, CCB Diuretics	Patients (58.6 million)	Electronic health records	Depression and anxiety disorders (ICD-10)	CCBs were associated with a lower incidence of depression (RR 0.88, 95%CI.86-0.90) and anxiety (RR 0.89 95%CI 0.87-0.91) disorders than BB and a higher incidence than ARBs (RR 1.26, 95%CI 1.23-1.29 and RR 1.19, 95%CI 1.17-1.22) for both first and recurrent diagnoses during 2 years.
Kessing et al. (2020) Denmark (20)	Prospective cohort	ACEI ARBs CCB BB Diuretics	Population-based adults (3 747 190)	Health register data	Depression disorders (ICD-9/10 or ATC-code N06A)	Continued vs initial use of ACEI, ARBs, CCB, BB was associated with significantly decreased rates of depression, whereas diuretic use was not at 10 years of follow-up.
Shaw et al. (2020) Scotland (230)	Prospective cohort	ACEI ARBs BB CCB Diuretics	Hypertension patients without previous mood disorders (538 730) Hypertension patients with previous mood disorders (262 278)	Prescription records	Depression disorders (ICD-9/10 or ATC-code N06A)	In patients without and with mood disorder history, all antihypertensive drugs were associated with an increased risk of new-onset and recurrent depression, respectively, with the risk lowest for ACEI or ARBs (HR 1.17, 95%CI 1.04-1.31) and highest for BB (HR 2.68, 95%CI 2.45-2.92).
Van Sloten et al. (2022) UK (234)	Prospective cohort	ACEI ARBs Diuretics	New users of ACEIs or ARBs (12 938) new users of diuretics (12 938)	Prescription records	Depression disorders (ICD-9/10 or ATC-code N06A)	Compared to diuretics, ACEIs or ARBs use was not associated with a lower risk of depression, regardless of lipophilicity, treatment duration or DDD.
Agustini et al. (2020) Australia & USA (235)	Cross-sectional	ACEI ARBs BB CCB Diuretics	Community-dwelling adults with hypertension (14 195)	Self-reported	Self-reported depression (CES-D ≥ 8)	Compared to other antihypertensives, the use of BB was associated with an increased risk of depression symptoms (OR 1.37, 95% CI 1.17–1.60). ACEI, ARBs and CCB use were not significantly associated with depression symptoms.
Akimoto et al. (2019) Japan (251)	Retrospective cohort	OHA	T2DM patients (40 214)	Patient medical records	Depression disorders (ICD-10)	No antidiabetic agent was statistically associated with reduced depression risk except for DDP-4 (OR 0.31, 95% CI 0.24-0.42).
Chen et al. (2019) China (30)	Case-control	Metformin OHA	Community-dwelling adults with T2DM (550) depression cases (110) & controls (440)	Self-reported	Self-reported depression (GDS-15 ≥5)	T2DM adults taking metformin had a lower risk of depression than those not using antidiabetic agents (OR 0.57, 95%CI 0.32–0.99).
Kessing et al. (2020) Denmark (28)	Prospective cohort	Metformin OHA Insulin	Population-based adults (≈ 5.4 million)	Prescription records	Depression disorders (ICD-9/10 or ATC-code N06A)	Continued use of metformin (alone or as a combination) was associated with decreased risk (HR 0.85, 95%CI 0.77-0.93) for depression or antidepressant prescription during the 10-year follow-up. No other antidiabetic agent or insulin showed significant associations with increased risk for depression.
Wahlqvist et al. (2012) Taiwan (250)	Prospective cohort	Metformin SU	Population-based adults (762 753)	Health Insurance data	Affective disorders, including depression (ICD-9)	Relative to a reference group, metformin combined with SU treatment was associated with decreased risk for incidence of affective disorders (HR 0.40, 95%CI 0.32-0.50) over 10 years, whereas each agent was not.
Wium-Andersen et al. (2022) Denmark (254)	Prospective cohort (nested case-control)	OHA Insulin	T2DM patients (116.699) no-DM individuals (116.008)	Prescription records	Depression disorders (ICD-9/10 or ATC-code N06A)	Metformin (low doses), DPP4 inhibitors, GLP1 analogues, and SGLT2 inhibitors were associated with decreased depression risk in T2DM patients compared to non-users; the risk lowest for SGLT2 inhibitors (OR 0.55, 95%CI 0.44-0.70) and highest for metformin (OR 0.92, 95%CI 0.88-0.97). Higher doses of insulin and SU were associated with higher depression risk.

Abbreviations: * **ref** = reference number; ACS: Acute coronary syndrome; T2DM: Type 2 diabetes mellitus (DM); ACEI: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; ASA: Acetylsalicylic acid; BB: Beta-blockers; CCB: Calcium-channel blockers; NSAIDs: Non-steroidal anti-inflammatory drugs; OHA: Oral hypoglycemic agents = sulfonylureas (SU), SU glinides combined, glitazones, dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon-like peptide 1 (GLP1) analogues, sodium-glucose transport protein 2 (SGLT2) inhibitors and acarbose.
ATC: Anatomical Therapeutic Chemical code; ATC N06 = Non-selective monoamine reuptake inhibitors, SSRI, MAO-A inhibitors, and other antidepressants; DDD: Defined daily dose.
DSM: Diagnostic and Statistical Manual of Mental Disorders; GDS-15: Geriatric Depression Scale; ICD: International Classification of Diseases. OR: Odds ratio; HR: Hazard ratio; CI: Confidence interval.

3. Aim and objectives of the thesis

In Norway, we have the possibility of combining an extensive amount of data from health studies with national and local registries. This thesis is purely descriptive using a national prescription registry combined with a population-based health study. The aim is to increase our knowledge of the relationships of depression and anxiety symptoms with CVDs and DM prevalence and drug treatments. More precisely, the objectives of this thesis are:

1) To estimate prevalence and differences in prevalence of depression and anxiety symptoms among the population with CVDs or DM over time, compared to adults without these physical conditions (Paper I).

2) To investigate cross-sectional associations between the use of cardiovascular agents or metformin and depression symptoms among adults with CVDs or DM over an 11-year interval (Paper II).

3) To examine the risk of antidepressant drug initiation among users of cardiovascular agents or metformin in a population-based cohort with a 10-year follow-up (Paper III).

4. Materials and methods

4.1 Data sources

4.1.1 The HUNT Study

The Trøndelag Health Study (HUNT) is a population-based health study of the adult population (aged ≥ 20 years) in Trøndelag county (former Nord-Trøndelag county, Figure 1). Four surveys have been conducted so far: HUNT1 (1984-86), HUNT2 (1995-97), HUNT3 (2006-08), and HUNT4 (2017-19), with response rates of 89.4%, 69.5%, 54.1%, and 54%, respectively. The population in HUNT is considered representative of general Norwegian adults and ethnically homogenous (predominantly White Caucasian) with low net migration (about 3%) (255-258). Most participants participated in more than one of the surveys, resulting in about 126 000 unique individuals in the HUNT database that can be followed through local and national health registries by personal identification (ID) number.

HUNT data are available for researchers with previous ethical approval (for more information, see https://www.ntnu.edu/hunt/about-hunt).

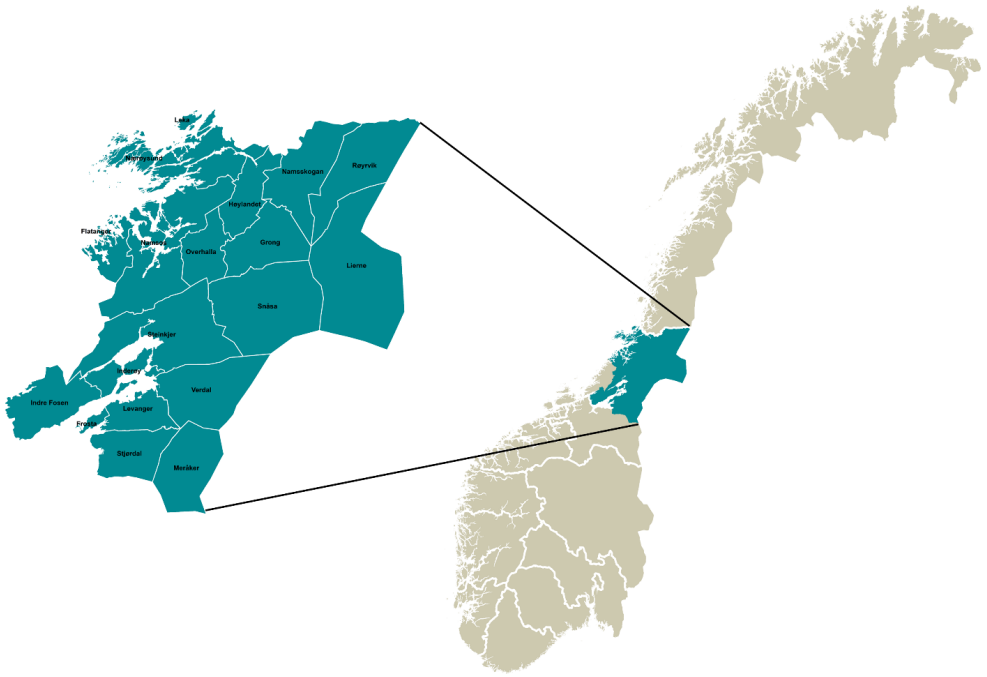

Figure 1. Map of Norway and the county of Nord-Trøndelag (created by Jon Olav Sliper)

HUNT2, HUNT3 and HUNT4 surveys, comprising about 93 860 community-dwelling adults, form the primary data material for this thesis. The HUNT study has been designed to cover a broad range of health-related topics through repeated surveys. These surveys included written questionnaires (Q1 and Q2), oral interviews about health-related topics, blood sampling analysis (e.g., glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, CRP and others) and standardized clinical examinations (e.g., height, weight, waist and hip circumferences, and blood pressure). Q1 was sent by mail invitation and handed in on attendance at a screening station, where interviews, clinical examinations, and blood sampling took place. Q2 was distributed at the screening station and returned by prestamped mail.

4.1.2 The Norwegian Prescription Database (NorPD)

The NorPD is a national health register of all drug prescriptions dispensed in the Norwegian pharmacies from 2004. Data include information about the prescriber (i.e. sex, birth year, profession/speciality), drug user (i.e. sex, birth year), dispensed prescriptions (i.e. dispensing month/year, the prescriptions number of packages and defined daily dosage (DDD), reimbursement codes) and drug (i.e. article number, brand name, package size, package unit, drug strength, Anatomical Therapeutic Chemical (ATC) code, DDD value, DDD unit and prices). Every prescription contains the user's unique ID number, making it possible to identify all prescriptions chronologically to each individual. NorPD lacks individual-level information on drugs dispensed to hospitals and nursing homes. Over-the-counter (OTC) drugs are not registered in NorPD unless dispensed by prescription. The area of application and prescribed dose is in a free-text format and is not available for research. Data on the indication for prescriptions are not included, but reimbursement codes (The International Classification of Diseases, 10th revision; ICD-10 or International Classification of Primary Care, 2th revision; ICPC-2) on the prescription may occasionally serve as a proxy for diagnosis. Details on the NorPD database are available at https://www.fhi.no/en/hn/health-registries/norpd/norwegian-prescription-database/.

4.1.3 Linkage of HUNT studies with National Prescription Database (NorPD)

This thesis's available NorPD data included prescriptions from 2006 to 2019 on the population in Nord-Trøndelag invited to HUNT surveys. After obtaining ethical approval, information from NorPD was merged with data files of the participants in the HUNT3 or HUNT4 studies (Papers II and III).

4.2 Study population

The HUNT participants who completed the main questionnaires (Q1 and Q2) constituted the underlying population (i.e., source population) from which the study populations for all three studies was drawn. The study population in the first study (Paper I) included participants in HUNT2, HUNT3 and/or HUNT4. Among them, 17 581 individuals were participants (i.e., answered Q1 and Q2) in all three HUNT surveys (HUNT2-4), 28 368 in HUNT2 and HUNT3, and 22 354 in HUNT2 and HUNT4. In the second and third study (Papers II and III), we linked NorPD data on dispensed prescriptions from January 2006 to December 2019 to HUNT3 and HUNT4 participants (i.e., the study population in Paper II) and HUNT3 participants (i.e., the study population in Paper III).

Paper I

We started with individuals who participated in at least one of the HUNT 2-4 surveys (HUNT2 N=65 228; HUNT3 N=50 800; HUNT4 N=56 042) and excluded those who provided no valid information on self-reported depression and anxiety symptoms (outcome), measured by HADS questionnaires (3 890, 10 284 and 13 939, respectively). Next, we excluded those who provided no information (i.e., missing all items) on CVDs or DM status (independent variable). Final analytical samples were analyzed independently by CVDs and DM status (yes/no). Analysis by CVDs status included 61 284, 40 508, and 40 443 participants from HUNT2, HUNT3 and HUNT4, respectively. Accordingly, analytical samples of 61 229 participants in HUNT2, 40 504 in HUNT3, and 41 371 in HUNT4 were analyzed by DM status. Analytical samples of participants with both physical conditions (CVDs and DM) were too small to achieve the necessary statistical power and precision of results

(i.e., 204, 164, and 182 among women and 262, 283, and 385 among men in HUNT2, HUNT3, and HUNT4, respectively) and thus were not analyzed as a separate group.

Paper II

Of all invited (93 860), 40 516 participants in HUNT3 and 42 103 in HUNT4 had valid HADS scores (outcome information) and thus fulfilled the inclusion criteria for the study population in this study. We excluded participants missing all items on CVDs status (8 and 1590) or DM status (11 and 732) in HUNT3 or HUNT4, respectively. Furthermore, information on dispensed drug prescriptions of the eligible study participants was collected from NorPD. The analytical samples for the analysis of cardiovascular agents (exposures) included only participants who reported CVDs in one or both HUNT surveys (2 574 women and 3 915 men). Accordingly, analysis of metformin (exposure) was carried out in a analytical sample of participants with DM in HUNT3 or HUNT4 (1 708 women and 1 898 men).

Paper III

This study population for this study comprised 50 815 participants in HUNT3 whose drug prescription records were collected from NorPD from 1th January 2006 to the date of study participation (from 3th October 2006 to 25th June 2008). Individuals who received a prescription of one or more cardiovascular agents (i.e., ACEI, ARBs, ASA, BB, CCB, diuretics or statins), metformin or antidepressants six months before their participation date in HUNT3 (baseline) were excluded. Lastly, we excluded participants aged <40 or >70 years at baseline (n=12 580) and ended up with the sample of 20 227 individuals for the analyses. 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 (other comorbidities, polypharmacy, and death) that may interfere with the outcome (initiation of antidepressants), participants over 70 years of age

were not analyzed. The study population was followed for 10 years from enrolment in the HUNT3 study or up to their first dispensed antidepressant prescription.

4.3 Study variables

4.3.1. Independent and exposure variables

Self-reported CVDs and DM status (Papers I and II)

Self-reported CVDs and DM status were independent variables in the analysis for Paper I, based on questions (yes/no) on the history of these diseases in HUNT2, HUNT3 and HUNT4. Questions on heart diseases (myocardial infarct or angina) or stroke were used to define CVDs status (yes/no) in Paper I. History of heart failure was a question in HUNT3 and HUNT4 and was therefore included in definition of CVDs status in Paper III. DM status (yes/no) in Papers I and II was defined by previous or current DM, including T1DM, T2DM or other types of DM. Reason for this is that type of DM was not part of the main questionnaires in HUNT4. One answer to the questions about the history of CVDs or DM was sufficient for defining the disease status in both studies.

Use of cardiovascular agents and metformin (Papers II and III)

Dispensed prescriptions of cardiovascular and antidiabetic agents from January 2006 to December 2019 from NorPD served as a "proxy" for defining the use of these drugs (exposure variables) in Papers II and III. Dispensed prescriptions have been previously confirmed as a reliable measurement of drug use (259). The selection of drug classes for the analysis was based on their associations with depression suggested by literature (22, 28, 34, 207) 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 (28, 34). 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). Of all antidiabetic agents used in T2DM

treatment, only metformin had the number of users for sufficient statistical power. Analysis of other antidiabetic agents (i.e., sulfonylureas, glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, and sodium-glucose co-transporter 2 (SGLT2) inhibitors) included only descriptive statistics in Paper II.

In Paper II, we defined drug use as having at least one dispensed prescription nine months before participation in HUNT3 or HUNT4. In Norway, drugs used for treating chronic diseases are used daily and typically dispensed in quantities that cover approximately three months' use. In our data, the period from the first dispensation date (January 2006) to the first participation date in HUNT3 (October 2006) was nine months. Therefore, we chose a fixed-time period of nine months as the shortest period available to collect drug prescriptions before participation in HUNT3. An initial, exploratory analysis showed that most of the HUNT3 and HUNT4 participants identified in NorPD had from three to four drug dispensations during nine months. As cardiovascular and antidiabetic agents are used long-term and daily in CVDs and DM, we assumed that one filled (i.e., dispensed) prescription of these drugs during nine months would be sufficient to define individuals on these drug treatments.

In Paper III, we used the first dispensed prescription to define exposure as using one (monotherapy) or more (polytherapy) cardiovascular agents or metformin. The date of dispensation was month and year. 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.

4.3.2 Outcomes

Anxiety and depression symptoms; The HADS Scale (Papers I and II)

The Norwegian version of the HADS was available in Q1 in HUNT2 and Q2 in HUNT3 and HUNT4. This brief-self rating scale (14 items) covers the core psychological dimensions of anxiety and depression (260) and was designed for screening purposes in non-psychiatric medical patients with somatic diseases (261). HADS questions are designed to define and distinguish anxiety from depression and do not address anxiety and depression symptoms that overlap with somatic diseases (i.e., dizziness, headaches, insomnia, anergia, fatigue and others). The HADS total (HADS-T) includes seven items for anxiety (HADS-A subscale) and seven for depression (HADS-D subscale), each scoring from 0 (no symptom present) to 3 (highest symptom levels) on a 4-point Likert scale. The HADS is a valid and reliable instrument across various samples and settings (87), including the general population (262, 263), patients with CVDs (88), DM (89) and patients at clinics (264).

Participants with at least five of seven completed items on both subscales (i.e., valid HADS responses) were included in the analysis. We assumed similar responses to the questions not answered as those answered. Thus, the HADS scores with one or two missing items on each subscale were replaced sum of completed items multiplied by 7/6 and 7/5, respectively. Recommended cut of values for describing symptoms are: 8-10 (mild), 11-14 (moderate) and 15-21 (serve) (260). Due to a low number of individuals with HADS scores 11 and above in our sample, we chose a traditional cut-off value of eight to define clinically significant symptoms of anxiety and depression (mild to severe). A categorical approach to HADS is reliable for independently identifying anxiety and depression symptoms and rating symptom severity among populations with CVDs (88) and DM (89). Moreover, cut-off eight showed optimal sensitivity and specificity (about 0.80) and a good correlation with a clinical diagnosis of depression (DSM-III and ICD-8/9) (87).

The first study of this thesis (Paper I) investigated associations of depression and anxiety symptoms with the disease status (i.e., CVDs and DM). For this purpose, we used HADS subscales independently and categorized participants according to their scores, as having no symptoms of anxiety (HADS-A <8) or depression (HADS-D <8) and mild to serve symptoms of anxiety (HADS-A ≥8) or depression (HADS-D ≥8), respectively.

The second study (Paper II) focused mainly on depression symptoms as an outcome, and thus in our primary analysis, we applied only HADS-D scores to classify participants as those with no or few symptoms of depression (scores <8) and mild to severe depression (scores ≥8). In an additional analysis, both HADS scales were used to assess depression without anxiety (defined by HADS-D ≥8 & HADS-A ≤ 8) as an outcome, and the results were not essentially changed.

initiation of antidepressant use (Paper III)

The NorPD database provides diagnostic information from the ICD-10 or ICPC-2 for prescriptions only after 2008. Hence, we decided to use only antidepressant prescriptions as the outcome and proxy for possible depression (and/or anxiety) at the diagnostic level in Paper III. The outcome of this study was the initiation of antidepressant use, indicated by the first dispensation of antidepressant agents during the study period. All antidepressants as a drug subgroup (ATC code NO6) were included in the analysis. Among them, the following groups of antidepressants with ATC codes were the ones with the most users among the study population: non-selective monoamine reuptake inhibitors (RIs) (N06A A), selective serotonin reuptake inhibitors (SSRI) (N06A B), monoamine oxidase A (MAO-A) inhibitors (N06A G02), and other antidepressants (N06A X).

4.3.3. Other covariates

Other covariates in all studies (Papers I-III) were based on HUNT questionnaires and included: sociodemographic characteristics, lifestyle, and clinical measurements.

Sociodemographic characteristics 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). Direct measurements of socioeconomic status (e.g., education level, income) were not included in HUNT3 and HUNT4 databases.

Lifestyle measurements included: current smoking (yes/no), monthly alcohol consumption (no or low drinking versus moderate to frequent) and physical activity (inactive versus active). Based on smoking measurements from HUNT, participants who never smoked or have smoked previously occasionally were defined as no current smokers, whereas those who smoke daily or occasionally smoke as current smokers. Alcohol consumption was measured in the last 12 months and described numerically (i.e., times drinking per month) in HUNT2, whereas categorically in HUNT3 and HUNT4 (i.e., never; no at all in the last year; about once a month; once a week; 2-3 times a month and 2-3 times a week). In this thesis, we defined drinking never or ≤ one time per week was defined as no or low drinking, while two-three times or ≥ four times per week was moderate to frequent drinking. In HUNT, physical activity was measured by questions about weekly average hours of light (i.e., no sweating or heavy breathing) and hard (i.e., sweating and heavy breathing) physical in the last year. In all studies, 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 or light physical activity were physically active.

Body mass index (BMI), computed as weight (in kg) divided by height (in meters) in HUNT, was used as a general indicator of overweight and obesity but also as a possible risk factor for cardio-metabolic diseases, depression and anxiety (171). According to the WHO overweight and obesity classification, we classified participants as underweight to normal (BMI < 25 kg/m2) and overweight to obese (BMI ≥ 25 kg/m2).

4.4 Statistical analyses.

All statistical analysis was performed using the Stata statistical software, versions 16 and 17 (© Stat Corp LP). Statistical significance was set at $p < .05$, and two-sided tests were used where applicable.

4.4.1 Descriptive statistics (All Papers)

Descriptive statistics included baseline characteristics described in frequencies and percentages presented across sexes. Differences between group frequencies for categorical variables were compared using the Chi-square test (Paper II). Prevalence rates presented in the Figures (Papers I and II) were age-standardized (using the age categories <55, 55-64 and ≥ 65 years) by direct standardization method where the age distribution of participants attending the screening in HUNT3 served as a standard.

4.4.2 Cross-sectional analysis (Papers I and II)

Cross-sectional associations of depression and anxiety symptoms with disease status (CVDs and DM) (Paper I) and depression symptoms with cardiovascular agents and metformin (Paper II) were analyzed by multilevel logistic analysis. Multilevel models were sex-stratified and specified to account for repeated measurements on the same participations (non-independent observations). The measures of associations included absolute [Prevalence differences (PD)] and relative [Prevalence ratios (PR)] measures with corresponding 95% confidence intervals (95% CI). Reported estimates were calculated based on model predictions, where PR represents the ratio between the mean predicted probability and the PD difference in the mean predicted probability. PR and PD were calculated for specific age groups.

Paper I

Reported estimates (PR and PD) for symptoms of anxiety and depression among participants with and without CVDs or DM (reference) were calculated for ages 40, 60 and 80 years (estimates for age

60 years were presented in the results section in Paper I). Interaction terms were included between participation in HUNT survey(s) and the self -reported diseases status to allow the change in CVDs and DM status to vary across survey years. All models were adjusted for age and age squared.

An initial, exploratory analysis, included sociodemographic variables (i.e., cohabitation) and lifestyle measurements (i.e., smoking, alcohol consumption, physical activity, and BMI). Further adjustment for BMI included categorical (cut-off at 25 kg/m^2) and continuous approach. Models with BMI as a continuous variable included restricted cubic splines to test for possible non-linear associations between the continuous change of BMI and the outcome (anxiety and depression symptoms) at four prespecified percentiles of BMI distribution (i.e., 5th, 25th, 75th, and 95th) that correspond to different BMI values (i.e., 20.7 kg/m2, 24.1 kg/m2, 26.3 kg/m2, 28.9 kg/m2, and 34.9 kg/m2, respectively). Adjusting for covariates did not substantially alter the results, and, therefore, we decided to include only age-adjusted models in the final analysis.

Paper II

The prevalence of depression symptoms (based on HADS-D≥ 8) was analyzed independently for each cardiovascular agent and metformin, where analytical samples comprised individuals with "pure depression symptoms" (i.e., without anxiety symptoms) and those with depression and anxiety symptoms. The reason for such operationalization of depression was that physical conditions, such as CVDs and DM, showed stronger associations with mixed anxiety and depression symptoms than each symptom alone (265). Reported estimates (PR and PD) for depression symptoms for individuals with any drug prescription vs no drug prescriptions (reference) nine months before participation in HUNT were calculated for age 55 (mean age of the population in HUNT).

Multilevel models for cardiovascular agents were restricted to participants with CVDs, and models for metformin to those with DM. This approach aimed to improve, to some extent, the comparability

between exposed (i.e., drug users) and non-exposed (i.e., no-drug users=reference) participants. Participants in the HUNT surveys partly comprise the same individuals, thus creating dependency (or non-independence) among these observations. The multilevel regression models were applied to account for this feature of HUNT data and contribute to "more correct" estimates and statistical precision. These models analyze both surveys simultaneously, estimating the outcomes within the same individual that are likely to be more similar than outcomes for two individuals at random. However, the used models do not explicitly address for the treatment discontinuation - this would require a different model specification. The crude models were age adjusted (i.e., age and age squared). Further analysis included covariates smoking status, chronic diseases and antidepressants use. Adjustment for antidepressant use and exclusion of participants using antidepressants yielded similar results. After inclusion of other lifestyle variables and BMI in models results remained largely unchanged. Thus, the reported final models included smoking status and chronic diseases as relevant covariates, excluding participants with antidepressant prescriptions before HUNT3 or HUNT4.

4.4.3 Prospective analysis (Paper III)

We used Cox proportional hazards (PH) models to examine associations between cardiovascular agents and metformin and the risk of antidepressant use initiation. Diagnostic analysis (e.g., log-log curves (266) and Schoenfeld residuals (267) suggested a violation of the PH assumption. This issue was addressed by delaying the start of follow-up for three and six months and one year after baseline. The result was improved models but essential unchanged results indicating that possible non-proportionality in the data probably would not substantially influence the interpretation of study findings. 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. In that way, each participant could contribute to the analysis with person-times twice, once before and once after being exposed for the first time. 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) and thereby for HADS-T and BMI at the baseline as continuous variables (Model 2). Further inclusion of lifestyle variables and chronic diseases as adjustment variables yielded marginal changes to the results, and therefore these variables were not included in the final analysis (Models 1 and 2).

4.5 Ethical considerations

HUNT data were collected prior to this thesis, and participants gave their written consent for research on their data and were given the possibility to withdraw from participation at any time. The Regional Committees for Medical Research and Health Research Ethics in Norway regard the benefits of HUNT to outweigh any potential disadvantages for individual participants (255-257). All the studies of this thesis were approved by REK (reference 2019/30292/ REK Nord) and the Norwegian Centre for Research Data, NSD (reference 30292/NSD). The data used in this thesis were anonymous, used under the licence of the current studies and not publicly available. This PhD research project received permission to use HUNT and NorPD data upon application (until 31 July 2023) to answer the project's purpose.

5. Main results

5.1 Paper I:

Prevalence trends of depression and anxiety symptoms in adults with cardiovascular diseases and diabetes 1995-2019: *The HUNT studies, Norway*

The prevalence of anxiety and depression symptoms were lower in 2017-19 (HUNT4) than in previous study periods (HUNT2-3) and this applied for adults with and without CVDs and DM; however, women reported more anxiety symptoms than men. Moreover, higher levels of depression symptoms were observed among participants with CVDs than those free from these conditions across study periods (HUNT2-4). Although positive associations between psychological symptoms (depression and anxiety) and disease status (CVDs and DM) declined over time, men with CVDs were consistently more likely to report depression symptoms compared to men with no CVDs. Compared with men aged 60 years without CVDs, men with CVDs had, on average, a depression symptom prevalence that was 45% (PR[1]=1.45, 95CI% 1.33-1.54) and 26% higher (PR=1.26, 95%CI 1.12-1.39) in HUNT2 and HUNT4 respectively. In women aged 60 years with DM, the prevalence of depression symptoms was on average 36% higher in HUNT2 (PR=1.36, 95%CI 1.17-1.56) and 24% higher in HUNT4 (PR=1.24, 95%CI 1.06-1.42) than in women without DM at the same age. The study confirmed that psychological symptoms are common in the population with CVDs. The results also suggest that prevalence of depression and anxiety symptoms vary according to CVDs and DM status and sex.

[1] The measures of association used to present the main results in Paper I differ from those used in the published article for this study.

5.2 Paper II:

Associations of cardiovascular and antidiabetic drugs with depression symptoms: *A cross-sectional analysis of HUNT studies, Norway*

Men with CVDs using ASA had a depression symptom prevalence that was 24% and 33% lower than men with CVDs not using ASA in HUNT3 and HUNT4 (PR=0.76; 95%CI 0.59-0.94 and PR=0.67; 95%CI 0.52-0.82, respectively). Within the same sample, statin users had a depression symptom prevalence that was 30% and 33% lower than non-users in HUNT3 (PR[2]=0.70; 95%CI 0.54-0.86) and HUNT4 (PR=0.67; 95%CI 0.51-0.84), respectively. Similar associations between use of statins or ASA and decreased depression symptom prevalence were detected in women with CVDs in HUNT4 but not in HUNT3. The results gave no support that the prevalence of depression symptoms was higher or lower among users of metformin or other cardiovascular agents included in this study. Our results indicate possible relationship between the use of ASA or statins and reduced depression symptoms; however, the potential antidepressive effects of these cardiovascular agents need further investigation.

[2] The measures of association used to present the main results in Paper II differ from those used in the published article for this study.

5.3 Paper III:

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

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

Among 20 227 adults aged 40-70 years at baseline (HUNT3), there were different associations between the use of cardiovascular agents or metformin and the risk of antidepressant initiation. ARBs or CCB monotherapy was associated with a 30% and 19% lower risk of antidepressant initiation compared to reference (HR 0.70; 95%CI 0.56-0.88 and HR 0.81; 95%CI 0.61-1.06, respectively). Furthermore, there was a reduced risk of initiating antidepressant use among ASA or statins polytherapy users (HR 0.85; 95%CI 0.68-1.06 and HR 0.80; 95%CI 0.64-1.10), with a small increased risk for the ASA monotherapy group. The results yielded no statistical evidence of associations between ACEI, BB, diuretics or metformin use and increased or decreased risk of antidepressant initiation. The mixed findings may indicate that some cardiovascular agents may, while others not, be associated with a lower risk of initiating antidepressant therapy or bias due to the limitations of study design.

5.4 Summary of the main findings

Adults with CVDs, and to a lesser extent DM, had generally a higher prevalence of both depression and anxiety symptoms compared to adults without CVDs or DM. However, these results were more consistent for CVDs and depression among men. The depression symptom prevalence and risk of initiating antidepressant therapy varied by type of CVDs treatment. More specific findings were:

- The use of ASA or statins compared to no use of these drugs was associated with a reduced prevalence of depression symptoms in men with CVDs from HUNT3 (2006-08) to HUNT4 (2017-2019) and women with CVDs in HUNT4.

- Among adults aged 40-70 years at baseline (HUNT3), ARBs and CCB monotherapy and ASA or statin polytherapy were associated with a lower risk of antidepressant initiation compared to reference during a 10-year follow-up.

- Compared with non-users, there was no evidence that the prevalence of depression symptoms was lower or higher among metformin users, nor was there any sign of increased or decreased risk of antidepressant initiation.

6. Discussion

There is limited data from the whole population samples that informs about the changes in disease prevalence over time. The added value of this research includes providing new and up-to-date knowledge on prevalence of depression and anxiety symptoms, from 1995 to 2019, in community-dwelling adults among the general Norwegian population (Paper I). Furthermore, this thesis provides new knowledge on depression symptom prevalence according to cardiovascular agents and metformin usage at two-time points (Paper II), and the risk of antidepressant drug initiation among users of cardiovascular agents or metformin (Paper III), in a previously non-investigated population, and exploring several drug classes concomitantly.

To our knowledge, Paper I is the first study in the general Nordic population to describe the changes in prevalence of depression and anxiety symptoms in community-dwelling adults with and without CVDs or DM over the past two decades. Such descriptive prevalence studies are valuable to evaluate the status and trends of mental health and can aid in the development and strategies of population-based healthcare. Furthermore, these results are helpful in hypothesis generation and give direction for further research.

Papers II and III add to the growing literature on associations between depression symptoms and use of CVDs drugs and metformin by replicating the results of this research phenomenon using hierarchically different study designs and relevant outcomes. So far, the literature has been inconclusive, and the evidence in Papers II and III is still not strong enough to make definitive conclusions. These results highlight the need for further research to understand better whether, how, and to what extent CVDs drugs and metformin may impact mental health.

6.1 Comparison with the results from previous studies

The findings in Paper I might indicated a slight decline in overall depression and anxiety symptom prevalence among study participants (majority aged ≥65 years), which broadly aligns with prevalence data from other Nordic countries (116, 118, 268). Although not totally in keeping, prevalence rates over 22 years in Paper I partly reflect a trend in depression and anxiety prevalence that is suggested to be stable globally (121) and across countries (117, 123, 269). Consistent findings on a higher prevalence of anxiety and depression in women than men (270, 271) align with the results from Paper I for anxiety but not depression. Of note, the HADS-D instrument is considered a generally robust test for depression symptoms across age groups, yet with minimal sex differences (272). These psychometric properties is likely to explain the small differences in depression prevalence in women and men, in contrast to many other studies (116, 269-271). However, increased prevalence of depression and anxiety symptoms observed in men and women with CVDs and, to a minor degree, DM, aligns with results from previous cross-sectional studies (273, 274) and corresponds with previous meta-analytic evidence that the prevalence and risk of these mental conditions (self-reported or clinically diagnosed) are higher in individuals with than without CVDs (152-155) or DM (172, 275) of both sexes.

The findings in Paper II suggest that among the CVDs population, the prevalence of depression symptoms was lower among ASA or statin users than ASA or stains no-users, whereas there were no prevalence differences for other cardiovascular agents or metformin. These results broadly support relevant large register-based Scandinavian studies (22, 23, 33, 203) while partly disagree with Australian cross-sectional studies of over 14 000 hypertensive adults (235) of cardiovascular agents and contradict results for metformin from two case-control studies of T2DM individuals (30, 254) and prospective study of total Danish population (28). Paper III showed a reduced 10-year risk of antidepressant drug initiation for adults aged 40-70 years at baseline using ASA or statin polytherapy, in keeping with prospective studies with corresponding outcomes (22, 23, 202), with more

consistency for the benefits of statins than ASA suggested by meta-analysis (32, 36, 190). Similar findings for study participants on ARBs or CCB monotherapy generally correspond to previous prospective studies using prescription records to measure drug use (20, 22, 227, 228). However, the results in Paper III showed no sound statistical evidence of an association with reduced risk of antidepressant initiation for ACEI monotherapy. This observation is similar to population-based data demonstrating ARBs as superior to ACEI in the protection or improvement of depression symptoms in population-based settings (227, 229); however, biological reasons for these differences are still not elucidated (276). However, differences in outcome measurement and reference groups challenge direct comparison and may be reasons for the discrepancy between the findings (228, 230, 234).

6.2 Interpretation of main findings - clinical and public health perspectives

Higher depression and anxiety symptom prevalence from 1995 to 2019 in adults with CVDs or DM than in the general population in Norway (Paper I) reflect the well-known increased burden of this physical-mental health comorbidity worldwide (154, 155, 160, 173, 174), pointing to the need for routinely mental health assessment and management strategies in CVDs and DM clinical practice. Furthermore, the results show that depression and anxiety symptom load in population with CVDs or DM differ by sex. Associations between CVDs and increased prevalence of depression symptoms throughout the study in men but not women correspond to sex-specific symptom courses of post-CVDs depression, where, unlike women, men experience greater and longer-lasting mental health burdens after a cardiovascular event (277). In contrast, an increased prevalence of depression symptoms observed only in women with DM in HUNT2 and HUNT4 may be result of diabetes-related stress accompanied by depression, which is suggested to be higher in women than men (278). In addition, almost twice the use of antidepressants among women than men observed in the second study (Paper II) confirms the well-established knowledge that women are more likely to seek help for mental conditions and to be diagnosed and treated for depression than men (279, 280).

Most importantly, the decision to stratify analyses by gender (Papers I and II) was done a-priory and not during the analyses phase, hence it was a pre-specified analytical decision to minimize the influence of possible sex differences on CVDs and depression prevalence based on the previous literature (116, 174, 269, 271). However, there could be several possible mechanisms underlying the observed sex differences in the associations between the use of ASA or statins and prevalence of depression symptoms in the first study period (HUNT3) but not in the second study period HUNT4 (Paper II). The observed pattern may result from the selection bias into the HUNT surveys, recruiting increasingly healthier samples from 1995 to 2019 (256, 257, 281). Furthermore, the transition from ICD-9 (ICD, the Ninth Revision) to ICD-10 (ICD, the Tenth Revision) at the end of HUNT2 (282) increased the number of disease diagnosis which may, at the same time, lower the diagnostic thresholds for CVDs and DM and contribute to a higher prevalence and "healthier" population with these conditions (283). As a result, this revision of the diagnostic criteria might also contribute to a general decline in HADS-scores and thus, depression and anxiety symptom prevalence in population with CVDs or DM from HUNT2 to HUNT4 (Paper I), which again might result in lower depression symptom levels among ASA or statin users of both sexes in HUNT4 (Paper II).

It has been also hypothesized that underlying level of inflammation related to physical conditions may play an important role in antidepressant effects of statins or ASA (23, 203); however their potential benefits on depression have been suggested in both women and men (284, 285). As so, the conflicting findings for ASA and statins between sexes (i.e., subgroups) may result from different prevalence of other underlying conditions or risk factors for depression between women and men that analysis in this study (Paper II) could not control for. However, the findings of subgroup analyses in observational studies that contradict previous research must be interpreted by a great causation because they may be influenced by bias, confounding, study design, analytical choices and data material (286). Therefore, generally speaking, the results in Paper II are not sufficient evidence to

redefine the hypothesis to state potential antidepressive effects of ASA or statins in women but not men.

The potential benefits of ASA or statins on depression have previously been suggested in individuals with more severe types of CVDs (e.g., myocardial infarct, angina, stroke and others) (23, 191, 203), characterized by higher levels of systemic inflammation than less complicated CVDs such as hypertension (136). Accordingly, there is the possibility that anti-inflammatory agents, including ASA and statins, may improve depression symptoms in individuals with increased systematic inflammation, such as specific CVDs sub-populations (287). Diagnosis, duration and severity of CVDs, which may be factors underlying observed negative associations of specific CVDs drug classes with depression symptoms (Paper II) and antidepressant initiation (Paper III), are not included in the analysis in the studies. However, the underlying assumption in the analysis (Papers II and III) is that prescriptions of different cardiovascular agents are not subject to prescription bias in terms of depression symptom level or other mental health conditions at the time of prescription. Evidence of the potential benefits of cardiovascular and antidiabetic agents on depression is still new and not widespread. Hence, it is unlikely that such knowledge has influenced the choice of drug prescribed for CVDs or DM treatment.

The lowest prevalence of depression symptoms (Paper II) and risk of antidepressant initiation (Paper III) for cardiovascular agents with known anti-inflammatory secondary effects (ASA and statins) (19, 34, 187), align with the notion that inflammation could be one of the shared mechanisms of depression with CVDs (131). Hence, inflammation could be a potential target for prevention and treatment of these conditions (14, 15). Mental health conditions negatively affect the prognosis and treatment outcome of CVDs (288), yet cardiovascular agents' possible positive psychological impact requires further investigation before consideration in clinical practice can be recommended.

It is important to emphasize that the results of Papers II and III are not sufficient evidence to suggest any of the studied drug classes as potential candidates for new drug targets in depression treatment or prevention. The purpose of these studies was purely descriptive, and the limitations of their designs may lead to selection and information bias, influencing the results.

Epidemiological studies with causal purposes (analytical observational and interventional studies) can aid in demonstrating causation with different levels of evidence. A well-designed RCTs provide the most substantial evidence for causal exposure-outcome associations, and causal language in reporting results from this type of epidemiological study is appropriate (289). This is because their design avoids confounding, balances differences between exposed and control groups, and minimises selection bias in the findings of this study. Since it is impossible to rule out the role of chance, bias or confounding with total certainty in an individual observational (non-experimental) study, the causal interpretation of the results is, in most cases, inappropriate (290). Using causal language in reporting results from observational analytic studies (e.g., cohort or case-control studies) may be appropriate only if the study design ensures no (or minimal) confounding, measurement and selection bias. However, observational analytic studies using a variety of statistics and strategies based on designs with distinct strengths and limitations and, in particular, sources and directions of bias may, if they survive multiple rejection attempts, lead to sufficiently robust causal inferences to justify policy or practice actions (233).

Depression, CVDs and DM, overlapping inflammatory conditions represent major global health problems (291, 292), and novel strategies for appropriate and effective prevention and treatment of these conditions would be of great importance to the general public health. Despite sex-specific associations between prevalence of depression symptoms and CVDs or DM (Paper I), these observations still indicate the importance of mental health monitoring of individuals with CVDs or DM in general. From a public health perspective, shared aetiological mechanisms could introduce

novel targets for improved public health strategies with benefits for mental and physical health in high-risk populations such as those with CVDs or DM. Such strategies could also be universal and involve non-pharmacological interventions in the general population, for example diets with low inflammatory index, regular sleeping habits, stress reduction and others (293).

6.3 Methodological considerations

6.3.1 Strengths and limitations of the study designs in Papers I-III

The general strengths in all three studies (Papers I, II and III) include large sample sizes and extensive sets of demographic, lifestyle and health data collected from community-dwelling adults living in a well-defined catchment area in the past 20 years. This ensured sufficient statistical power in most analyses, a good description of the study population and adjustment for the most known variables (i.e., covariates) that affect the outcome and may differ among study populations (i.e., lifestyle factors, BMI and others). Furthermore, all studies include a well-suited and validated instrument to measure depression and anxiety symptoms (HADS) that, at certain cut-off levels, shows a good correlation with the clinical diagnosis of depression and anxiety in the general population and adults with chronic diseases (87).

The strengths in Papers II and III include a linkage between the population-based study HUNT and the Norwegian Prescription Database (NorPD). This combination of two extensive databases has several advantages. First, to measure drug use (exposures) by dispensed prescriptions, a valid and reliable instrument with minimal risk for information bias (259). Second, to investigate the prevalence of depression symptoms (outcome) according to the use of various cardiovascular agents and metformin among adults with CVDs or DM at two-time points (Paper II). Third, to prospectively collect drug prescriptions and investigate the 10-year risk of antidepressant initiation (outcome) across several drug classes taking into account baseline levels of relevant health-related factors (depression symptoms and BMI) not available in prescription databases (Paper III). The longitudinal

design was applied in Paper III to reassess (replicate) results from Paper II, allowing an outcome closer to clinical depression. Finally, the strengths of the designs in Papers II and III were that both studies examined several cardiovascular agents and metformin simultaneously, unlike most studies within the field that investigated either cardiovascular (206, 230, 231) or antidiabetic agents separately (28, 43, 250).

A general limitation of the study designs in Papers I-III include a lack of information on clinical diagnoses of CVDs, DM, depression and anxiety, the gold standard in clinical assessment and research on treatment and pharmacotherapies. Moreover, the HADS mainly covers features of depression and generalized anxiety, the most common symptoms of mental distress, yet does not capture features of more specific anxiety disorders (e.g., social phobia, obsessive-compulsive disorder (OCD), panic disorder) or states of abnormally elevated mood (e.g., hypomania and mania) (260). Further, measurement points 10 years apart prevented the detection of fluctuation in levels of depression symptoms over time (Papers I and II). As CVDs and DM in these studies were self-reported and limited to several diagnoses, underreporting or misclassifying these diseases is likely to have influenced the results of these studies, possibly toward underestimation. Various diagnosis are indications for use of antidepressants, including anxiety, OCD, chronic neuropathic pain, fibromyalgia, and others. Therefore, relying solely on antidepressant prescriptions as a proxy for clinical depression due to the absence of clinical diagnoses in NorPD, may result in misclassification of the outcome in Paper III. Selection bias caused by the selection into the HUNT surveys is a limitation in all three studies, discussed under 6.3.3 External validity and generalizability. Importantly, the most studies using information from HUNT are considered “secondary analyses”, as data was collected for multiple purposes. Thus, findings in Papers I-III may have limited clinical and public health implications compared to the studies using diagnosis of CVDs, DM and depression (20, 22, 112, 113, 116, 250) or data primary collected for the purpose of answering a specific research questions (112, 116).

6.3.1 Precision (vs random error)

The considerable sample sizes of HUNT surveys (over 50 000 participants in each survey) allowed for reasonable high precision (i.e., low random error) of reported estimates (PR, PD and HR) in Papers I-III. The multivariable analysis included only HUNT variables previously described as relevant covariates for the analysis of the relationships between exposure and outcome of interests, the approach used to minimize the possibility of detecting significant associations by pure chance.

6.3.2 Internal validity

Selection bias influencing the results in Papers I-III could have resulted from the selection (i.e., exclusion and inclusion) criteria made in each study. Also, the exclusion of HUNT participants missing more than two items (i.e., item level missingness) on HADS-A and HADS-D subscale (outcome) and missing all items on CVDs or DM status (independent variables) will lead to selection bias if the missingness is not at random (MNAR) (i.e., depends on the values that are missing) whereas might lead to selection bias if the missingness is at random (MAR) (i.e., depends on observed characteristics of study participants), influencing the results in Papers I and II (294).

As MNAR depends on unobserved values, the selection bias caused by missing items on HADS subscales and CVDs or DM status cannot be determined (in terms of direction or magnitude) or ruled out from the observed data included in Papers I and II (294). However, the missing one or two items on each HADS subscale were handled by mean substitution, the method recommended to minimize the bias caused by item non-response on the HADS (295). Furthermore, the exploratory analysis in Papers I and II did not show a direct pattern between missing response to HADS, CVDs or DM items and other measured characteristic of study participants (i.e., age, sex, smoking and others), indicating low risk of bias in the analysis caused by MAR.

Relative to the number of eligible participants in Papers I and II, the small proportion of participants with all missing items on CVDs or DM status (<5%) and sufficiently large number of valid HADS, suggest low risk of bias caused by missing data (294). It is important to note that the HADS questions were moved from Q1 (the questionnaire to be filled in before the clinical examination) in HUNT2, to Q2 (the questionnaire to be filled in after the clinical examination and to be returned by regular mail) in HUNT3 and HUNT4. Hence, this is the reason for the increased number of missing responses to all items in Q2, including HADS scales in last two HUNT surveys. Given that the participants were participating in Q1 and the clinical examination, it is believed that the HADS data from Q2 is missing at random due to lack of time to answer and return Q2. If HADS data is missing at random, likelihood-based methods (e.g. mixed models) used in analysis in Papers I and II will yield unbiased results (296). The final analysis in Paper I included only adjustment for age; all participants with information on CVDs or DM and outcomes were included. As such, missing data on other covariates (i.e., smoking, physical activity, and others) have not affected the reported results in this study.

Although antidepressant prescriptions were exclusion criteria in Papers II and III, participants with a history of depression diagnosis, non-pharmacological depression treatments, or other indications for antidepressant therapy might still be present in the analytic samples. It could be expected that this limitation could have influenced the results, possibly toward underestimation. An adjustment for the HADS-T in Paper III aimed to minimize the influence from the possible inclusion of participants with increased psychological symptoms at baseline in the analysis. Including younger adults (< 40 years), in whom CVDs or T2DM is less common, in the analysis would have reduced the power to detect associations between exposures and outcomes (Paper III).

Information bias is relevant for the measurement of both outcomes and exposures in this thesis. To minimize misclassification and reverse causality, the HADS covers psychological symptoms of depression and anxiety but excludes physical conditions often present in mental conditions (85). As

HADS questionnaires refer to the last week's feelings (93), recall bias is not likely to influence on the findings in Papers I-III. However, the HADS is a screening instrument which introduces the possibility of a high number of false-positive cases, while the number of false-negative cases is expected to be low (264). Accordingly, prevalence of HADS-defined depression and anxiety symptoms (outcomes) in Papers I and II may be overestimated compared to diagnostic thresholds.

The agreement between self-reported and medical records of diseases with well-established diagnostic criteria, including CVDs and DM, has proven to be substantial (297). However, the prevalence of these physical conditions could be underestimated because some individuals were unwilling to disclose their disease or, in the case of DM, were undiagnosed. The increasing prevalence of DM across study periods (HUNT2-4) (Paper I) may also indicate possibility of underreported DM among study participants due to lack of information of their disease status.

A definition of drug use (exposure) was simplified because of the large number of prescription records in data material and, thus, many possibilities for drug combinations which were difficult to classify and interpret. This approach to exposure measurement could have influenced the results in Papers II and III. In Norway, pharmacotherapy for chronic disease is dispensed in quantities to cover three months use. Paper II defined drug use as one or more drug dispensation during the last nine months before participation in HUNT, that should be a sufficient threshold (202). However, study participants with dispensations of large drug quantities before nine months or those who received drugs in the secondary healthcare facilities, could cause exposure misclassification, likely non-differential and possibly bias toward null. Analysis of drug dispensation patterns showed that most study participants in the exposed groups were dispensed three to four drug prescriptions over nine months, suggesting that possible misclassification of exposure and bias caused by the definition of drug use are less likely to affect the findings in Paper II significantly. Furthermore, a six-month treatment-free period can be expected to have sufficient sensitivity to capture the individuals not

using these drugs, as also indicated by the drug dispensation among the exposed participants in HUNT3 and HUNT4 (Paper II).

In addition, drug use definition did not differentiate between participants with mono- and polytherapy (Paper II) and possible changes in therapy (i.e., switching between drugs or deprescribing) (Paper III), which are factors potentially related to increased or decreased depression symptoms (i.e., outcome). This limitation in exposure measurement could have affected the results in Papers II and III, potentially leading to underestimation or overestimation of the true associations between exposure and outcome. Moreover, Papers II and III included only antidepressants, cardiovascular agents and metformin. There is the possibility that other drugs and corresponding indications could influence results in both directions; however, adjustment for chronic diseases aimed to some degree minimize this influence. Due to a lack of mortality data, participants included into exposure groups in Paper III 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 likely.

Confounding bias is a term reserved for studies with a causal aim. However, a descriptive study may or may not require covariate adjustments. The decision to execute analytical adjustments essentially depends on the goal of the descriptive study (298). In this thesis, both adjustments and stratification were used in the attempt to identify potential differences between the study groups (Paper I-III). All studies included age adjustment and sex stratifications (Papers I and II) or sex adjustment (Paper III). Of many available HUNT variables, a number of covariates were used as adjustment variables in the final models. These included smoking, chronic diseases (Paper II), HADS-T and BMI (Paper III). The purpose of all studies in this thesis (Papers I-III) was to explore and describe differences between different exposure groups and adjusting for too many covariates may mask important disparities between these groups. Therefore, the number of variables included in adjustment is expected to be

appropriate. Additional analysis in Paper III included age as a time-varying covariate. However, due to the design of the HUNT study this analysis could not account for the change of HADS-T and BMI or other time-varying covariates, (e.g., psychological or physical conditions, diseases severity, lifestyle) and competing risk factors (i.e., death) that could influence the findings in Paper III, possibly in both directions.

Confounding by indication (i.e., clinical indication influencing treatment options) is a complex, patient-specific source of bias that is difficult to control by non-experimental design. As many factors underline the choice of drug treatment, dealing with confounding by indication in the «real-world» settings requires more specific methods than standard statistical analysis (299*).* The definitions of CVDs and DM in Papers I and II were general and included various diagnoses. Therefore, restricting the analysis to participants with CVD or DM (Paper II) could not fully minimize differences and improve comparability between exposed (i.e. drug users) and unexposed (i.e. non-drug users as reference) participants. Moreover, distinct CVDs diagnoses (i.e., myocardial infarction, angina, stroke and heart failure) will require different drug treatments. Due to drug indications and clinical guidelines (300), some CVDs diagnosis could be more frequent among users and less frequent among non-users (reference) of specific cardiovascular agents. For example, stroke or myocardial infarction can be expected to be a more common diagnosis among users of ASA, whereas less common among no-users of ASA, leading to bias in the results, possibly in both directions.

Compared with T2DM, T1DM is a disease with potentially higher risk of depression (175), where the use of metformin is not primarily indicated. Thus, expected unequal distribution of DM diagnosis and possible underlying risks of depression between users (exposure group) and non-users (reference) of metformin may bias the results for this drug, possibly toward underestimation. However, the available data indicate a much higher prevalence of T2DM than T1DM among participants in HUNT2 and HUNT3. These results correspond with the DM prevalence among the Norwegian population

based on national health data (60), and a similar prevalence pattern is likely among participants in HUNT4. Furthermore, the higher prevalence of DM based on general practitioner records than prevalence of antidiabetic and insulin dispensations in Trøndelag county during HUNT3 (281) suggests adequate diabetes control by lifestyle changes for many patients with T2DM. As so, the magnitude of the bias influencing the results for metformin, although possible, may not be significantly large. Furthermore, participants with CVDs or DM included in the analysis in Paper II also may differ by other factors (for example, disease duration and severity, patient preferences and characteristics, risk factors, family history, and others) that determine the CVDs or DM drug option. This limitation in the selection of exposure groups can be expected to influence the results in Paper II, potentially in both directions. However, without available data, it is difficult to determine the exact direction and magnitude of this bias. As important mental health indicators, type, duration and severity of CVDs or DM could influence the association between drug use and outcomes in Papers II and III, which assessment required additional linkage to patient records and was outside the scope of these studies.

No use of CVDs or DM drugs may also reflect medication non-adherence due to depression. If so, the associations between cardiovascular agents or metformin and depression symptoms in Paper II may be underestimated even when comparing users and non-users of these drugs with the same CVDs or DM diagnosis. However, the majority of participants with CVD selected for the analysis (Paper II) received at least one or more cardiovascular agents, and all participants may have been using other drugs not included in this study. Although possible, depression-related medication nonadherence among study participants is not expected to significantly bias the analysis in Paper II.

Immortal time bias can happen in cohort studies when there is a time window between when a person enters a cohort and when treatment is initiated. The period between study entry and treatment initiation is called immortal time because a person must remain in the cohort without

experiencing the outcome long enough to receive the treatment (301). As participants included in the study population in Paper III could have experienced the outcome before exposure (i.e., their time before exposure was not immortal), the risk of immortal time bias in the analysis in this study is expected to be minimal.

6.3.3 External validity and generalizability

Selection bias caused by selection into the HUNT surveys, as described above, could compromise the external validity of all studies because the likelihood of participating in the HUNT surveys depended on age, health conditions (i.e., CVDs, DM and depression symptoms) and lifestyle factors (255-258), the variables of interest to Papers I-III. Participation rates in the HUNT differed by age and were lowest among young (20-29 years) and the highest among middle aged and older adults (40-79 years) (255-257). Health-related mechanisms were less likely to be the main reasons for non-participation among the younger population in HUNT (255-258). Given that CVDs or DM are more common among adults of higher age, the under-representation of the younger (<40 years) health population in HUNT is less likely to influence the study findings. However, the total CVDs or DM population is likely underrepresented in study populations in Papers I-III because many individuals aged >70 years were too ill to participate in HUNT (281), influencing reported estimates probably toward underestimation. Further, nonparticipants in HUNT3 and HUNT4 were characterised by a lower socioeconomic status and unhealthy lifestyles (i.e., smoking and physical activity), (257, 281), which are important factors for physical (48, 65) and psychological health (166, 182), potentially underestimating the results in all these studies.

The overall participation rate fell by over 15 percentage points from HUNT2 to HUNT3, and a separate nonparticipation study showed a higher prevalence of chronic physical diseases (e.g., CVDs or DM), depression symptoms, and to a lesser degree, anxiety symptoms among non-participants than participants (281). As ill health and old age (70+) were among the main reasons for non-

participation in HUNT (281), the distribution of both exposure and outcomes might differ between study populations and target population (i.e., general adult population) in Papers I-III, affecting the external validity and generalizability of findings in these studies. Thus, both participants defined as users (exposure group) and non-users (reference) of cardiovascular agents or metformin in Paper II may represent "the healthier part" of the CVDs and DM population with a lower prevalence of depression symptoms than the general adults with these conditions. Consequently, their comparison might underestimate the true association between these drugs and the prevalence of depression symptoms in Paper II. Similarly, the risk of initiating antidepressant therapy suggested by the results in Paper III might be underestimated by this selection into HUNT.

Participation rates in the HUNT surveys are generally considered high or acceptable (>50%) in most age groups and highest in the middle-aged and elderly (50-79 years) (255-257), which constitutes the large part of study populations in all three studies (Papers I-III). Furthermore, the most common reasons for non-participation in HUNT surveys were not health-related, but lack of time or inconvenience among all age groups, or a lack of personal benefits of participation among older participants (255, 281). Therefore, selection bias into HUNT which likely has influenced the results (Papers I-III), is not expected to be substantially large. It is also important to emphasize, that the sampling procedure and inclusion criteria were almost identical for all HUNT surveys (255-258).

Overall, results in Papers I-III are primarily generalizable to middle-aged and elderly (50-79 years), community-dwelling adults, but not to adults in same age group who are sickest, live in institutions or are hospitalized due to their illness, or those with frequent health care follow-ups who likely reported no personal benefits of examination in the HUNT (281). Due to the baseline exclusion criteria (70 years) in Paper III, the low participation rate and the health-related reasons for non-participating among the oldest population (> 80 years) (255-257), inference from the results to this age group requires even more caution. Overall, the ethnically homogeneous population in HUNT limits the generalizability of study findings (Papers I-III) to adults of non-European ancestry.

Prevalence of anxiety and depression symptoms, CVDs, DM and risk factors for these conditions may vary between study populations, countries, and cultures. The HADS has proven valid across cultures and study settings (87). Therefore, it is unlikely that observed prevalence of depression and anxiety symptoms among adults with and without CVDs and DM in the Norwegian population would radically differ from other countries. Since CVDs and DM treatment in Norway (302, 303) corresponds to international guidelines (300, 304), findings related to cardiovascular agents and metformin are expected to have considerable validity outside Norway. The prescription of antidepressants in Norway corresponds to other Nordic countries with similar health policies, but might be lower than in other parts of Europe (126). Thus, differences in factors that may influence drug prescription patterns and use across countries (e.g., accessibility of drugs, available treatment alternatives, pharmaceutical economics, healthcare policies and practices) needs to be considered.

6.3.4 Comparison of the study designs in Papers I-III with the designs of previous studies

Similar to Paper I, the trend in prevalence of depression and anxiety symptoms in most population-based studies within the field was measured by self-report (118, 268, 269, 273, 274). These studies provided mixed evidence of a trend in prevalence compared with no change in the prevalence of depression and anxiety suggested by several population-based studies using diagnostic *interviews* (116, 117, 123). Moreover, several studies (268, 269, 274) have used a more suitable design to describe the variations in symptom prevalence and symptom levels over time compared to Paper I. For example, an American study measured self-reported depression symptoms on six occasions two years apart and divided them into three depression categories (mild, moderate and severe) and age groups (20-39, 40-64 and ⩾65 years)(269). Depression symptoms measured by a single cut-off approach, used in Paper I and two prevalence studies (273, 274) is common; however often results in identifying a group with symptoms at a subclinical level compared to clinically significant depression (depressive disorders)(116, 117).

A recent cross-sectional study (235) and several register-based cohort studies (23, 203, 228, 254) examined the association between cardiovascular or antidiabetic agents and depression in adults with specific CVDs diagnoses, including acute coronary syndrome (ACS) (23), stroke (203), and hypertension (228, 235) or T2DM (254). This selection of study population in the previous studies (23, 203, 228, 254) may result in more comparable exposure and reference groups and findings at a lower risk of bias compared to Papers II and III. On the other hand, two cross-sectional studies of cardiovascular agents that examined only adults ≥ 70 years old excluding those with a history of CVDs, established CVDs or severe hypertension (206, 235), provide findings with a very limited generalizability to the large patient group with established CVDs.

While a few register-based cohort studies have not accounted for any change in drug treatments during the follow-up (202, 227), other studies applied different approaches to address time-varying nature of drug prescriptions (20, 22, 28, 33). A large Swedish study used a self-controlled designed to compare the incidence rate of various psychiatric disorders between periods with and without statin use within each individual (33). A self-control study designs (e.g., within-individual design) would offer the advantage of controlling for time-invariant factors (i.e., individual specific underlying factors and risk such as genetics, psychiatric history and others) and accounting for changes of exposure after treatment initiation, contrary to study design in Paper III (305). Due to the lack of mortality data, the challenge of using a self-controlled study design in Paper III will be to deal with death as a competing risk factor that directly affects treatment status. Previous prospective studies have controlled for various competitive factors that may interfere with the detection of primary outcomes (20, 22, 23, 28, 33, 202, 203, 205, 227, 234); however design applied in most of these studies, as in Paper III, could not address the influence of relevant time-varying factors on the findings (20, 23, 28, 33, 202, 203).

Similar to Paper I, non-response of individuals with severe physical and psychological conditions to health surveys likely leads to selection bias and prevalence underestimation in the previous population-based studies within the field (116, 117, 123, 268, 269, 273, 274), threatening external validity of study findings. However, in prospective registry-based studies of cardiovascular or antidiabetic agents where the study population is all or a large part of the country's population (20, 22, 23, 28, 33, 203, 205, 228, 230), this selection bias is minimal or not of concern and is, therefore an advantage of their designs compared to Papers II and III. Findings from the studies using diagnostic codes for depression from primary or secondary health records alone (33, 227, 228, 230, 250) or with an antidepressant prescription (20, 22, 28, 205, 234) as an outcome are likely more transferable to a true diagnosis of depression compared to results relying only on antidepressant prescriptions as in Paper III. However, the diagnosis of depression may still be underestimated among individuals who do not regularly use health services or seek help for their mental health in Paper III and other studies within the field (20, 22, 28, 33, 205, 227, 228, 234, 250).

7. Conclusions and further research

The findings in this thesis add to the growing literature regarding the relationships of depression and anxiety symptoms with CVDs and DM prevalence and drug treatments. The results may indicate possibility that prevalence of depression and anxiety symptoms declined from 1995 to 2019, whereas prevalence rates of both symptoms were generally higher in the population with than without CVDs or DM. However, the prevalence of depression and anxiety symptoms differed by CVDs and DM status and between sexes, where men with CVDs and, to a lesser extent, women with DM had a higher depression symptom prevalence compared to no-disease (CVDs or DM) adults of same sex. Several cardiovascular agents, the majority with anti-inflammatory effects, were statistically associated with a reduced prevalence of depression symptoms and risk of antidepressant drug initiation. A reduced prevalence of depression symptoms and risk of antidepressant therapy initiation

was observed for ASA or statin general use and monotherapy, respectively. ARBs or CCB monotherapy was associated with a reduced risk of initiating antidepressant use.

Further clarification of the associations between use of cardiovascular agents or metformin and depression, whether it suggests protective effects or unwarranted concerns about the safety of these drugs, could have important implications for public mental health. Study designs in Papers II and III are not appropriate to imply any evidence of causal relationships between use of these drugs and depression. As such, consistent evidence from large and methodologically robust population-based studies, including real-world data, is still warranted and may be sufficient for replication or reassessment of results and can aid in bridging the gap from randomized clinical trials (RCTs). Observational state-of-the-art study design, an active-comparator new-user (ACNU) design (306) more closely approximates RCTs than traditional observational study designs (i.e., prevalent-user design and non-drug user comparator design) and thus, is suggested as a gold standard for examining drug effectiveness in "real-world" settings. Moreover, a more precise approach to the design of population-based studies within the field is required to identify and describe the populations affected by cardiovascular or antidiabetic agents for depression. This may include analysis of specific target populations with different medical or inflammatory conditions (e.g., obesity, hyperlipidaemia, or specific CVDs diagnosis), level of inflammation, dose and duration of individual drugs, or specific depression phenotypes.

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Paper I

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Prevalence trends of depression and anxiety symptoms in adults with cardiovascular diseases and diabetes 1995–2019: *The HUNT studies, Norway*

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Abstract

Background: Symptoms of depression and anxiety are common in adults with cardiovascular diseases (CVDs) and diabetes mellitus (DM). The literature on depression and anxiety in CVDs and DM populations is extensive; however, studies examining these relationships over time, directly compared to adults without these conditions, are still lacking. This study aimed to investigate trends in depression and anxiety symptom prevalence over more than 20 years in adults with CVDs and DM compared to the general population.

Methods: We used data from the population-based Trøndelag Health Study (HUNT), Norway, including adults (≥ 20 years) from three waves; the HUNT2 (1995–97; n = 65,228), HUNT3 (2006–08; n = 50,800) and HUNT4 (2017–19; n = 56,042). Depressive and anxiety symptom prevalence was measured independently by the Hospital Anxiety and Depressions scale (HADS) in sex-stratified samples. We analyzed associations of these common psychological symptoms with CVDs and DM over time using multi-level random-effects models, accounting for repeated measurements and individual variation.

Results: Overall, the CVDs groups reported higher levels of depression than those free of CVDs in all waves of the study. Further, depressive and anxiety symptom prevalence in adults with and without CVDs and DM declined from HUNT2 to HUNT4, whereas women reported more anxiety than men. Positive associations of depression and anxiety symptoms with CVDs and DM in HUNT2 declined over time. However, associations of CVDs with depression symptoms remained over time in men. Moreover, in women, DM was associated with increased depression symptom risk in HUNT2 and HUNT4.

Conclusions: Depression and anxiety symptoms are frequent in adults with CVDs. Further, our time trend analysis indicates that anxiety and depression are differentially related to CVDs and DM and sex. This study highlights the importance of awareness and management of psychological symptoms in CVDs and DM populations.

Keywords: Cardiovascular diseases, Diabetes mellitus, Depression symptoms, Anxiety symptoms, Prevalence, Multilevel models

Introduction

Cardiovascular diseases (CVDs) and diabetes mellitus (DM) represent major public health challenges, and their prevalence rates are steadily rising globally. World Health Organization (WHO) estimate that 17.8 million

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people die from CVDs each year, representing 31% of all global deaths [1]. The global population with DM in 2013 is estimated at 382 million (ages 20 to 79), the number expected to rise to 592 million by 2035 [2]. Simultaneously, a growing prevalence of depression and anxiety has been reported worldwide. In 2017, more than 264 million people of all ages worldwide suffered from depression [3]. The rates varied across studies and countries, yet a systematic review from 2016 concluded that the anxiety prevalence was generally high (3.8–25%) and particularly in women (5.2–8.7%) and individuals from European countries (3.8–10.4%) [4]. Higher prevalence rates and risk of depression and anxiety in women compared to men have been well documented [5, 6]. However, whether depression and anxiety prevalence is increasing over time is still debated [7, 8].

CVDs and DM populations are often affected by higher depression and anxiety symptom load than the general population [9, 10]. Research suggests common biological pathways of CVDs and DM with depression and anxiety, focusing on the autonomic and hypothalamic-pituitary-adrenal (HPA) axis and immuno-inflammatory dysregulation [11, 12]. Depression and anxiety have different clinical manifestations; however, these psychological conditions often overlap [13] and appear together with CVDs and DM [9, 10], further increasing the burden of symptoms in these wide-spread physical illnesses [14].

Worldwide, studies consistently report on increased prevalence rates and risk of depression and anxiety in adults with CVDs compared to people free from these conditions [9, 15–20]. WHO has estimated the prevalence of clinical depression in CVDs populations to range between 3 and 9% worldwide [9] in the last two decades, yet rates between 35 and 46% in China [15] and rates as high as 47% have been reported from Iran [18]. A recent meta-analysis found that of 10,785 acute myocardial patients, approximately one of five were diagnosed with major depression, whereas one of three reported mild to moderate symptoms of depression [19]. A study using data on population-based adults from 17 countries demonstrated a higher odds ratio (OR) for depression (adjusted OR 2.1; 95% CI 1.9–2.5) and anxiety (adjusted OR 1.4; 95% CI 1.0–1.9) in participants with CVDs than those with no such conditions [9]. Likewise, symptoms of depression and anxiety are frequently present in adults with DM [21–23]. Epidemiological evidence suggests that the prevalence of depression is more than three times higher in adults with type 1 DM and almost twice as high in adults with type 2 DM [21]. In line with this, a meta-analysis of longitudinal studies showed that people with DM had an average of 30% higher risk of developing depression than those without [24]. A recent systematic review shows that anxiety disorders and anxiety symptoms are present in 14% and 40% of patients with DM [22]. These findings correspond to a systematic review that reported positive associations between DM and both anxiety disorders (pooled OR 1.20; 95% CI 1.10–1.30) and elevated anxiety symptom levels (pooled OR 1.48; 95% CI 1.02–1.93) [25].

Unfortunately, depression and anxiety symptoms often go undetected and untreated in CVDs and DM populations [26, 27]. In turn, this may contribute to poor treatment outcome of the primary disease [28, 29], reduced quality of life [30, 31] and increased health care costs [32, 33]. Recently, there has, therefore, been a growing interest in CVDs and DM populations' psychological conditions and how to improve the clinical practice of detection and treatment [34, 35]. Despite the increasing literature on depression and anxiety in adults with CVDs and DM, studies examining secular trends in depression and anxiety symptom levels are lacking. Thus, this study aims to investigate the development of depression and anxiety symptom levels in CVDs and DM groups, using population-based data from three waves of the Trøndelag Health Study (HUNT) over more than two decades (HUNT2, HUNT3, and HUNT4). The objectives of this study are: (1) to describe depression and anxiety symptom load in the populations according to CVDs and DM status (2) to investigate time trends of these psychological symptoms over 22-years, and to (3) examine the associations of CVDs and DM with depression and anxiety symptom risk.

Methods

Study population

The HUNT Study is a repeated, serial-entry health study of an entire population residing in Nord-Trøndelag county (recently included in the larger Trøndelag County), Norway, carried out in four waves: HUNT1 (1984–86), HUNT2 (1995–97), HUNT3 (2006–08), and HUNT4 (2017–19). The serial-entry participation means that all county inhabitants eligible to participate (aged 19 years and more) were invited every 10 years—regardless of whether they had participated before or not. This study used data from the HUNT2, HUNT3 and HUNT4 waves, where all county adults (aged $\geq$ 20 years) received questionnaires (Q1) to fill out before the clinical screening test. A second questionnaire (Q2) was distributed to be filled out and returned by mail after clinical examination. Of all invited, the number of respondents whose data material was available to this study was 65,228 (69.5%) in HUNT2, 50,800 (54.1%) in HUNT3, and 56,042 (54%) in HUNT4. The number of participants and the respective participation rates (in %) is per point of data collection, as the number of eligible adults in the county changed over time. Information on

the participation of cohorts over time is available on the HUNT official website [36]. The population in HUNT is considered representative of general Norwegian adults [37]. All 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 (reference2019/30292/REK Nord) and the Norwegian Centre for Research Data (reference 30292/NSD).

Data material

This study used data from the main questionnaires (Q1 and Q2) covering a wide range of variables on health condition, lifestyle, sociodemographic characteristics, and clinical measurements. The participants yielding valid data on self-reported depression and anxiety questions (outcome) and CVDs and/or DM status (exposure) were eligible, while those with missing values on both exposures were excluded. The study population was analyzed by diseases status (CVDs and DM) independently in sex-stratified samples. Analysis by CVDs status was carried out in 61,284 participants from HUNT2, 40,508 participants from HUNT3 and 40,443 participants from HUNT4, including individuals with and without CVDs. Samples analyzed by DM status were 61,229 participants from HUNT2, 40,504 participants from HUNT3 and 41,371 participants from HUNT4, including individuals with and without DM. Samples of individuals with both CVDs and DM were too small (i.e., 204, 164 and 182 among women and 262, 283 and 385 among men in HUNT2, HUNT3 and HUNT4, respectively) to provide the necessary statistical power and were therefore not analyzed as a separate group. Figure 1 shows the flow chart of the study participants selected for this study.

Measurements

Outcome variables: Anxiety and Depression symptoms

The Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of depression and anxiety. The HADS is a brief self-report questionnaire consisting of 14 items, seven for anxiety subscale (HADS-A) and seven for depression subscale (HADS-D), each scored on a Likert-scale from 0 (no symptoms) to 3 (symptoms maximally present) [38]. For this study, valid ratings of the HADS-D and HADS-A were defined as at least five completed items on both subscales. The score of those who filled in five or six items was based on the sum of completed items multiplied by 7/5 or 7/6, respectively. We assessed anxiety and depression with the categorical approach, using a conventional cut-off threshold of 8 on both the HADS subscales. This cut off value is found to provide optimal sensitivity and specificity (about 0.80) and a good correlation with the case of clinical depression based on DSM-III and ICD-8/9 diagnostic criteria [39]. Additionally, these conventional cut-offs are often used for decision-making purposes, such as rating the severity of depression or the need for treatment [40]. 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) [41]. The HADS-subscales has been confirmed as reliable for detecting symptoms of anxiety and depression independently and describing symptom severity among the CVDs and DM populations [42, 43].

Exposure variables

CVDs status was measured with questions on the history of heart diseases (myocardial infarct or angina) or stroke (yes/no). Question on heart failure was excluded from HUNT2, and thus, this condition was not used in the definition of CVDs in this study. History of diabetes, including type 1 DM, type 2 DM and other DM types, were criteria for defining DM (yes/no). Missing data on CVDs and DM were defined as an absence of the diseases.

Other independent variables

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). The HUNT3 database lacks direct data describing socioeconomic status (e.g., education level). Therefore, we used the lifestyle variable "current smoking" (yes/no) as an indicator of socioeconomic status in multivariate analysis. Other lifestyle measurements included monthly alcohol consumption (no or low drinking versus moderate to frequent) and physical activity (inactive versus active). Alcohol consumption in HUNT2 was described numerically (i.e., times drinking per month) whereas in HUNT3 and HUNT4 with categories. In this study, never or ≤ one time per week was defined as no or low drinking, while drinking two-three times or ≥ four times per week was 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/let physical activity were physically active. Of clinical anthropometric measurements, we used Body mass index (BMI) as a general indicator of overweight and obesity, which are significant risk factors for cardio-metabolic diseases [44], depression [45] and anxiety [46]. Body mass index (BMI) included two categories: underweight to normal

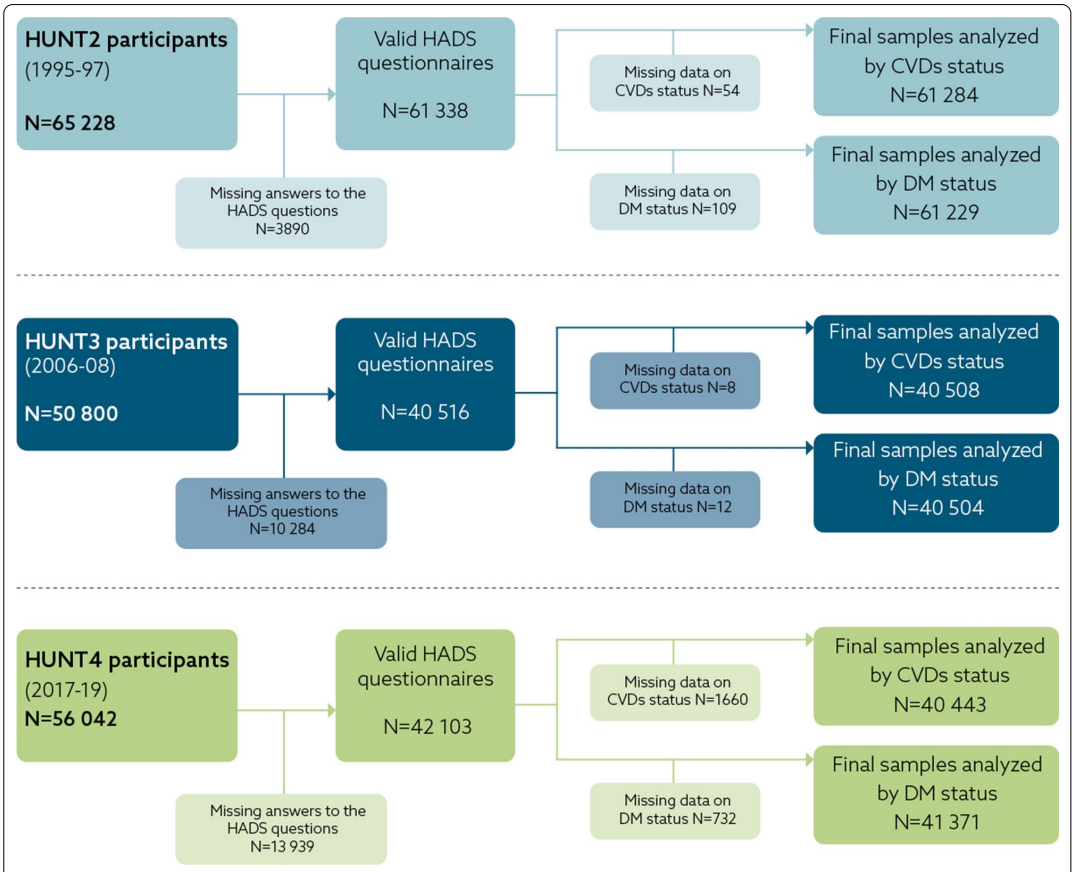

Fig. 1 Flow chart showing the selection criteria[a] for participants. [a]Hospital Anxiety and Depression Scale (HADS) questionnaires, cardiovascular diseases (CVDs) and diabetes mellitus (DM) Status. CVDs status defined as CVDs or no-CVDs; DM status was defined as DM or no-DM

(< 25 kg/m^2) and overweight to obese (≥ 25 kg/m^2), defined according to WHO BMI cut-off for overweight and obesity classification [47].

Statistical analysis

The prevalence of self-reported anxiety and depression symptoms was evaluated using cross-sectional data from three HUNT surveys performed with an 11-years' interval. Descriptive statistics regarding baseline characteristics included frequencies and percentages. The study population's characteristics stratified by sex are presented for the sample with a report on CVDs (Table 1) and DM status (Table 2) separately. The groups with positive disease status in Tables 1 and 2 are bolded. Prevalence of depression and anxiety was described separately by disease status and across sexes. Estimates were age-standardized (using the age categories < 55, 55–64 and ≥ 65 years) by the direct standardization using the age distribution of participants attending the screening in HUNT3 as the standard population. The associations of self-reported depression and anxiety with CVDs and DM were analyzed using multi-level logistic models. Multi-level models were specified to account for repeated measurements on the same participants (i.e., non-independent observations). To derive risk ratios (RR) and risk differences (RD), we used predictions from the multi-level models. Specifically, the RR was formed as the ratio between the mean predicted probability, whereas RD was the difference in mean predicted probability. We calculated RR and RD for three specific ages, 40, 60 and 80. We present findings for age 60 in the results section and age 40 and 80 in the supplementary information

Table 1 The characteristics of HUNT2, HUNT3 and HUNT4 participants according to CVDs status stratified by sex

Total n (%)	HUNT2 (1995–98) n = 61,284				HUNT3 (2006–08) n = 40,508				HUNT4 (2017–19) n = 40,443			
	CVDs n = 4484 (7.3)		No-CVDs n = 56,800 (92.7)		CVDs n = 3472 (8.6)		No-CVDs n = 37,036 (91.4)		CVDs n = 3531 (8.7)		No-CVDs n = 36,912 (92.3)	
	Women n = 1746 (38.9)	Men n = 2738 (61.1)	Women n = 30,552 (53.8)	Men n = 26,248 (46.2)	Women n = 1324 (38.1)	Men n = 2148 (61.9)	Women n = 21,359 (57.7)	Men n = 15,677 (42.3)	Women n = 1354 (38.4)	Men n = 2177 (61.6)	Women n = 21,690 (58.8)	Men n = 15,222 (41.2)
Variables												
Depression[a]												
No	**1344 (77.0)**	**2181 (79.7)**	27,538 (90.1)	23,560 (89.8)	**1092 (82.5)**	**1805 (84.0)**	19,583 (91.7)	14,122 (90.1)	**1187 (87.7)**	**1854 (85.2)**	19,806 (91.3)	13,773 (90.5)
Yes	**402 (23.0)**	**557 (20.3)**	3014 (9.9)	2688 (10.2)	**232 (17.5)**	**343 (16.0)**	1776 (8.3)	1555 (9.9)	**167 (12.3)**	**323 (14.8)**	1884 (8.7)	1449 (9.5)
Anxiety[b]												
No	**1231 (70.5)**	**2228 (81.4)**	23,196 (75.9)	21,701 (82.7)	**1044 (78.8)**	**1914 (89.1)**	17,695 (82.8)	14,068 (89.7)	**1077 (79.5)**	**1929 (88.6)**	17,120 (78.9)	13,190 (86.7)
Yes	**515 (29.5)**	**510 (18.6)**	7356 (24.1)	4547 (17.3)	**280 (21.2)**	**234 (10.9)**	3664 (17.2)	1609 (10.3)	**277 (20.5)**	**248 (11.4)**	4570 (21.1)	2032 (13.3)
Age (years)												
Mean (Sd)[c]	**71.6 (10.8)**	**68.0 (15.6)**	47.6 (16.3)	47.1 (10.7)	**70.4 (11.9)**	**68.8 (10.8)**	52.5 (15.6)	53.5 (14.6)	**70.5 (14.0)**	**70.8 (10.7)**	53.6 (16.8)	55.2 (16.1)
<55	**137 (7.9)**	**353 (12.9)**	21,014 (68.8)	18,454 (70.3)	**137 (10.4)**	**222 (10.3)**	11,686 (54.7)	8096 (51.7)	**174 (12.9)**	**167 (7.7)**	11,018 (50.8)	7036 (46.2)
55–64	**257 (14.7)**	**566 (20.7)**	4162 (13.6)	3649 (13.9)	**257 (19.4)**	**525 (24.4)**	4903 (23.0)	4097 (26.1)	**197 (14.5)**	**355 (16.3)**	4574 (21.1)	3442 (22.6)
≥65	**1352 (77.4)**	**1819 (66.4)**	5376 (17.6)	4145 (15.8)	**930 (70.2)**	**1401 (65.3)**	4770 (22.3)	3484 (22.2)	**983 (72.6)**	**1655 (76.0)**	6098 (28.1)	4744 (31.2)
Cohabitation												
Living with someone	**780 (44.7)**	**1889 (69.0)**	21,610 (70.7)	17,237 (65.7)	**778 (58.8)**	**1766 (82.2)**	17,147 (80.3)	13,064 (83.3)	**785 (58.0)**	**1737 (79.8)**	16,810 (77.5)	12,466 (81.9)
Living alone	**966 (55.3)**	**849 (31.0)**	8942 (29.3)	9011 (34.3)	**546 (41.2)**	**382 (17.8)**	4212 (19.7)	2613 (16.7)	**569 (42.0)**	**440 (20.2)**	4880 (22.5)	2756 (18.1)
Current smocking												
No	**1361 (78.0)**	**2034 (74.3)**	20,755 (67.9)	18,380 (70.1)	**999 (75.5)**	**1650 (76.8)**	15,673 (73.4)	11,947 (76.2)	**1182 (87.3)**	**1978 (90.8)**	19,408 (89.5)	13,985 (91.9)
Yes	**314 (18.0)**	**661 (24.1)**	9226 (30.2)	7544 (28.7)	**257 (19.4)**	**436 (20.3)**	5135 (24.0)	3363 (21.5)	**161 (11.9)**	**189 (8.7)**	2216 (10.2)	1203 (7.9)
Missing	**71 (4.0)**	**43 (1.6)**	571 (1.9)	324 (1.2)	**68 (5.1)**	**62 (2.9)**	551 (2.6)	367 (2.3)	**11 (0.8)**	**10 (0.5)**	66 (0.3)	34 (0.2)
Physical activity												
Inactive[d]	**252 (14.4)**	**212 (7.8)**	1511 (5.0)	1493 (5.7)	**135 (10.2)**	**189 (8.8)**	730 (3.4)	871 (5.6)	**130 (9.6)**	**139 (6.4)**	631 (2.9)	628 (4.1)
Active[e]	**948 (54.3)**	**2057 (75.1)**	25,941 (84.9)	22,924 (87.3)	**1130 (85.3)**	**1911 (89.0)**	20,293 (95.0)	14,602 (93.1)	**1177 (86.9)**	**1986 (91.2)**	20,761 (95.7)	14,414 (94.7)
Missing	**546 (31.3)**	**469 (17.1)**	3100 (10.1)	1831 (7.0)	**59 (4.5)**	**48 (2.2)**	336 (1.6)	204 (1.3)	**47 (3.5)**	**52 (2.4)**	298 (1.4)	180 (1.2)
Alcohol consumption												
No or low[f]	**1522 (87.2)**	**2127 (77.7)**	25,814 (84.5)	20,008 (76.2)	**977 (73.8)**	**1286 (59.9)**	14,202 (66.5)	8329 (53.2)	**1159 (85.6)**	**1641 (75.4)**	17,946 (82.7)	11,014 (72.4)
Moderate to frequent[g]	**44 (2.5)**	**311 (11.4)**	2275 (7.4)	4615 (17.6)	**257 (19.4)**	**802 (37.3)**	6570 (30.8)	7092 (45.2)	**157 (11.6)**	**499 (22.9)**	3516 (16.2)	4074 (26.7)

Table 1 (continued)

Total n (%)	HUNT2 (1995–98) n = 61,284				HUNT3 (2006–08) n = 40,508				HUNT4 (2017–19) n = 40,443			
	CVDs n = 4484 (7.3)		No-CVDs n = 56,800 (92.7)		CVDs n = 3472 (8.6)		No-CVDs n = 37,036 (91.4)		CVDs n = 3531 (8.7)		No-CVDs n = 36,912 (92.3)	
	Women n = 1746 (38.9)	Men n = 2738 (61.1)	Women n = 30,552 (53.8)	Men n = 26,248 (46.2)	Women n = 1324 (38.1)	Men n = 2148 (61.9)	Women n = 21,359 (57.7)	Men n = 15,677 (42.3)	Women n = 1354 (38.4)	Men n = 2177 (61.6)	Women n = 21,690 (58.8)	Men n = 15,222 (41.2)
Missing	**180 (10.3)**	**300 (10.9)**	2463 (8.1)	1625 (6.2)	**90 (6.8)**	**60 (2.8)**	587 (2.7)	256 (1.6)	**38 (2.8)**	**37 (1.7)**	228 (1.1)	134 (0.9)
BMI[h] (kg/m^2)												
Under-weight to normal	**471 (27.0)**	**740 (27.0)**	13,942 (45.7)	9405 (35.8)	**333 (25.2)**	**447 (20.8)**	8317 (38.9)	3915 (25.0)	**396 (29.3)**	**446 (20.5)**	8522 (39.3)	4141 (27.2)
Overweight to obese	**1178 (67.5)**	**1939 (70.8)**	16,323 (53.4)	16,685 (63.6)	**974 (73.6)**	**1682 (78.3)**	12,978 (60.8)	11,725 (74.8)	**927 (68.5)**	**1689 (77.6)**	13,052 (60.2)	11,007 (72.3)
Missing	**97 (5.5)**	**59 (2.2)**	287 (0.9)	158 (0.6)	**17 (1.2)**	**19 (0.9)**	64 (0.3)	37 (0.2)	**31 (2.2)**	**42 (1.9)**	116 (0.5)	74 (0.5)

CVDs, Cardiovascular diseases; HUNT, The Trøndelag Health Study

[a] Depression symptoms defined by HADS-D ≥ 8, HADS-D Hospital Anxiety and Depression-subscale Depression

[b] Anxiety symptoms defined by HADS-A ≥ 8, HADS-A Hospital Anxiety and Depression-subscale Anxiety

[c] Sd = standard deviation

[d] Inactive = never or no light/hard physical activity per week

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

Light physical activity (no sweating or heavy breathing) vs hard physical activity

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

[g] Moderate (2–3 times/week) to frequent (≥ 4 times/week)

[h] BMI = Body mass index; underweight to normal: BMI < 25 kg/m^2; overweight to obese: BMI ≥ 25 kg/m^2

Table 2 The characteristic of HUNT2, HUNT3 and HUNT4 study participants according to DM stratified by sex

Total n (%)	HUNT2 (1995–98) n = 61,229				HUNT3 (2006–08) n = 40,504				HUNT4 (2017–19) n = 41,371			
	DM n = 1707 (2.8)		No-DM n = 59,522 (97.2)		DM n = 1872 (4.6)		No-DM n = 38,632 (95.4)		DM n = 2569 (6.2)		No-DM n = 38,802 (93.8)	
	Women n = 847 (49.6)	Men n = 860 (50.4)	Women n = 31,435 (52.8)	Men n = 28,087 (47.2)	Women n = 904 (48.3)	Men n = 968 (51.7)	Women n = 21,776 (56.4)	Men n = 16,856 (43.6)	Women n = 1217 (47.4)	Men n = 1352 (52.6)	Women n = 22,436 (57.8)	Men n = 16,366 (42.2)
Variables												
Depression[a]												
No	**692 (81.7)**	**710 (82.6)**	28,182 (89.7)	25,004 (89.0)	**791 (87.5)**	**836 (86.4)**	19,881 (91.3)	15,091 (89.5)	**1052 (86.4)**	**1171 (86.6)**	20,469 (91.2)	14,713 (89.9)
Yes	**155 (18.3)**	**150 (17.4)**	3253 (10.3)	3083 (11.0)	**113 (12.5)**	**132 (13.6)**	1895 (8.7)	1765 (10.5)	**165 (13.6)**	**181 (13.4)**	1967 (8.8)	1653 (10.1)
Anxiety[b]												
No	**631 (74.5)**	**702 (81.6)**	23,791 (75.7)	23,192 (82.6)	**748 (82.7)**	**866 (89.5)**	17,988 (82.6)	15,115 (89.7)	**936 (76.9)**	**1181 (87.4)**	17,702 (78.9)	14,184 (86.7)
Yes	**216 (25.5)**	**158 (18.4)**	7644 (24.3)	4895 (17.4)	**156 (17.3)**	**102 (10.5)**	3788 (17.4)	1741 (10.3)	**281 (23.1)**	**171 (12.6)**	4734 (21.1)	2182 (13.3)
Age (years)												
Mean (Sd)[c]	**66.1 (14.9)**	**63.6 (14.5)**	48.4 (16.8)	48.6 (16.3)	**64.7 (13.2)**	**64..6 (11.3)**	53.1 (15.9)	54.8 (15.0)	**65.0 (14.6)**	**67.5 (11.4)**	52.3 (17.1)	56.4 (16.5)
<55	**194 (22.9)**	**232 (27.0)**	20,952 (66.6)	18,564 (66.1)	**189 (20.9)**	**174 (18.0)**	11,633 (53.4)	8144 (48.3)	**270 (22.2)**	**183 (13.5)**	11,075 (49.4)	7105 (43.4)
55–64	**123 (14.5)**	**157 (18.3)**	4291 (13.7)	4048 (14.4)	**244 (27.0)**	**309 (31.9)**	4916 (22.6)	4312 (25.6)	**242 (19.9)**	**292 (21.6)**	4634 (20.7)	3566 (21.8)
≥65	**530 (62.6)**	**471 (54.7)**	6192 (19.7)	5475 (19.5)	**471 (52.1)**	**485 (50.1)**	5227 (24.0)	4400 (26.1)	**705 (57.9)**	**877 (64.9)**	6727 (29.9)	5695 (34.8)
Cohabitation												
Living with someone	**427 (50.4)**	**565 (65.7)**	21,950 (69.8)	18,536 (66.0)	**618 (68.4)**	**798 (82.4)**	17,306 (79.5)	14,031 (83.2)	**804 (66.1)**	**1070 (79.1)**	17,204 (76.7)	13,351 (81.6)
Living alone	**420 (49.6)**	**295 (34.3)**	9485 (30.2)	9551 (34.0)	**286 (31.6)**	**170 (17.6)**	4470 (20.5)	2825 (16.8)	**413 (33.9)**	**282 (20.9)**	5232 (23.3)	3015 (18.4)
Current smoking												
No	**695 (82.1)**	**647 (75.3)**	21,408 (68.1)	19,739 (70.3)	**696 (77.0)**	**768 (79.3)**	15,974 (73.4)	12,827 (76.1)	**1070 (87.9)**	**1241 (91.8)**	20,024 (89.3)	14,997 (91.6)
Yes	**118 (13.9)**	**192 (22.3)**	9419 (30.0)	8003 (28.5)	**167 (18.5)**	**180 (18.6)**	5224 (24.0)	3620 (21.5)	**133 (10.9)**	**105 (7.8)**	2321 (10.3)	1318 (8.1)
Missing	**34 (4.0)**	**21 (2.4)**	608 (1.9)	345 (1.2)	**41 (4.5)**	**20 (2.1)**	578 (2.6)	409 (2.4)	**14 (1.2)**	**6 (0.4)**	91 (0.4)	51 (0.3)
Physical activity												
Inactive[d]	**102 (12.0)**	**66 (7.7)**	1660 (5.3)	1639 (5.8)	**76 (8.4)**	**85 (8.8)**	788 (3.6)	976 (5.8)	**87 (7.2)**	**99 (7.3)**	701 (3.1)	683 (4.2)
Active[e]	**504 (59.5)**	**656 (76.3)**	26,374 (83.9)	24,291 (86.5)	**801 (88.6)**	**868 (89.7)**	20,620 (94.7)	15,643 (92.8)	**1099 (90.3)**	**1226 (90.7)**	21,387 (95.3)	15,456 (94.4)
Missing	**241 (28.5)**	**138 (16.0)**	3401 (10.8)	2157 (7.7)	**27 (3.0)**	**15 (1.5)**	368 (1.7)	237 (1.4)	**31 (2.5)**	**27 (2.0)**	348 (1.6)	227 (1.4)
Alcohol consumption												
No or low[f]	**746 (88.1)**	**666 (77.5)**	26,572 (84.5)	21,435 (76.3)	**719 (79.5)**	**627 (64.8)**	14,458 (66.4)	8988 (53.3)	**1089 (89.5)**	**1091 (80.7)**	18,515 (82.5)	11,809 (72.2)
Moderate to frequent[g]	**26 (3.1)**	**106 (12.3)**	2293 (7.3)	4816 (17.2)	**146 (16.2)**	**323 (33.4)**	6680 (30.7)	7570 (44.9)	**97 (8.0)**	**241 (17.8)**	3649 (16.3)	4385 (26.8)

Table 2 (continued)

Total n (%)	HUNT2 (1995–98) n = 61,229				HUNT3 (2006–08) n = 40,504				HUNT4 (2017–19) n = 41,371			
	DM n = 1707 (2.8)		No-DM n = 59,522 (97.2)		DM n = 1872 (4.6)		No-DM n = 38,632 (95.4)		DM n = 2569 (6.2)		No-DM n = 38,802 (93.8)	
	Women n = 847 (49.6)	Men n = 860 (50.4)	Women n = 31,435 (52.8)	Men n = 28,087 (47.2)	Women n = 904 (48.3)	Men n = 968 (51.7)	Women n = 21,776 (56.4)	Men n = 16,856 (43.6)	Women n = 1217 (47.4)	Men n = 1352 (52.6)	Women n = 22,436 (57.8)	Men n = 16,366 (42.2)
Missing	**75 (8.8)**	**88 (10.2)**	2570 (8.2)	1836 (6.5)	**39 (4.3)**	**18 (1.8)**	638 (2.9)	298 (1.8)	**31 (2.5)**	**20 (1.5)**	272 (1.2)	172 (1.0)
BMI[h] (kg/m^2)												
Under-weight to normal	**154 (18.2)**	**198 (23.0)**	14,251 (45.3)	9945 (35.4)	**140 (15.5)**	**139 (14.4)**	8508 (39.1)	4222 (25.1)	**214 (17.6)**	**200 (14.8)**	8907 (39.7)	4454 (27.2)
Overweight to obese	**651 (76.9)**	**646 (75.1)**	16,841 (53.6)	17,952 (63.9)	**751 (83.1)**	**819 (84.6)**	13,200 (60.6)	12,588 (74.7)	**989 (81.3)**	**1131 (83.7)**	13,397 (59.7)	11,817 (72.2)
Missing	**42 (4.9)**	**16 (1.9)**	343 (1.1)	190 (0.7)	**13 (1.4)**	**10 (1.0)**	68 (0.3)	46 (0.2)	**14 (1.1)**	**21 (1.5)**	132 (0.6)	95 (0.6)

DM, Diabetes mellitus; HUNT, The Trøndelag Health Study

[a] Depression symptoms defined by HADS-D ≥ 8, HADS-D Hospital Anxiety and Depression-subscale Depression,

[b] Anxiety symptoms defined by HADS-A ≥ , HADS-A Hospital Anxiety and Depression-subscale Anxiety

[c] Sd = standard deviation

[d] Inactive = never or no light/hard physical activity per week

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

Light physical activity (no sweating or heavy breathing) vs hard physical activity

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

[g] Moderate (2–3 times/week) to frequent (≥ 4 times/week)

[h] BMI = Body mass index; underweight to normal: BMI < 25 kg/m^2; overweight to obese: BMI ≥ 25 kg/m^2

(see Additional files 1 and 2 for CVDs and DM analysis, respectively). Associations of diseases status (i.e., CVDs and DM) and self-reported depression and anxiety are reported with 95 per cent confidence intervals (95% CI). All statistical models were sex-stratified. The models considered first age adjustment (age and age squared), followed by the inclusion of other sociodemographic variables (i.e., smoking and cohabitation) and finally, lifestyle measurements (i.e., alcohol consumption, physical activity and BMI). First we adjusted for BMI using categorical approach with cut-off at 25 kg/m^2. Second, we used BMI as a continuous variable with restricted cubic splines and tested for possible non-linear associations between the continuous change of BMI and the outcome (anxiety and depression symptoms) at four prespecified locations according to percentiles of BMI distribution (i.e., 5th, 25th, 75th and 95th) that correspond to different BMI values (i.e., 20.7 kg/m^2, 24.1 kg/m^2, 26.3 kg/m^2, 28.9 kg/m^2, and 34.9 kg/m^2, respectively).Statistically significant associations of self-reported depression and anxiety with CVDs (Table 3) and DM (Table 4) are highlighted in bold. The statistical software STATA® (version 16) was used in the analysis.

Results

Study population characteristics

Table 1 shows the HUNT2, HUNT3 and HUNT4 study participants' characteristics within sex-stratified samples according to CVDs status. Overall, the prevalence of CVDs was relatively stable from HUNT2 to HUNT4 (range from 7.3 to 8.7%) and higher in women than men. CVDs groups consistently reported higher rates of depression than the no-CVDs group across age, sexes and study waves, yet for anxiety, this pattern was only observed in women and limited to the first two waves of the study. In contrast, DM prevalence consistently increased from HUNT2 to HUNT4 (range from 2.8 to 6.2%), with rates slightly higher in men than women, whereas differences in depression and anxiety symptom load between DM and no-DM groups were less prominent (Table 2). Participants reporting disease (i.e., CVDs or DM) were often 65 years and older, non-smokers, physically active, reported no to low monthly alcohol consumption and were more often overweight or obese.

Figure 2 shows the age-standardized anxiety and depression symptom prevalence of participants with CVDs compared to the no-CVDs group for the study period 1995–2019. Within CVDs groups, the symptom of depression decreased consistently in women whereas initially declined and subsequently increased in men, the trends resulting in an overall decrease in both sexes over the total study period (from HUNT2 to HUNT4). On the other hand, the trend in depressive symptom prevalence in groups with no CVDs was stable. Anxiety symptom prevalence declined in the first (1995–2008) and

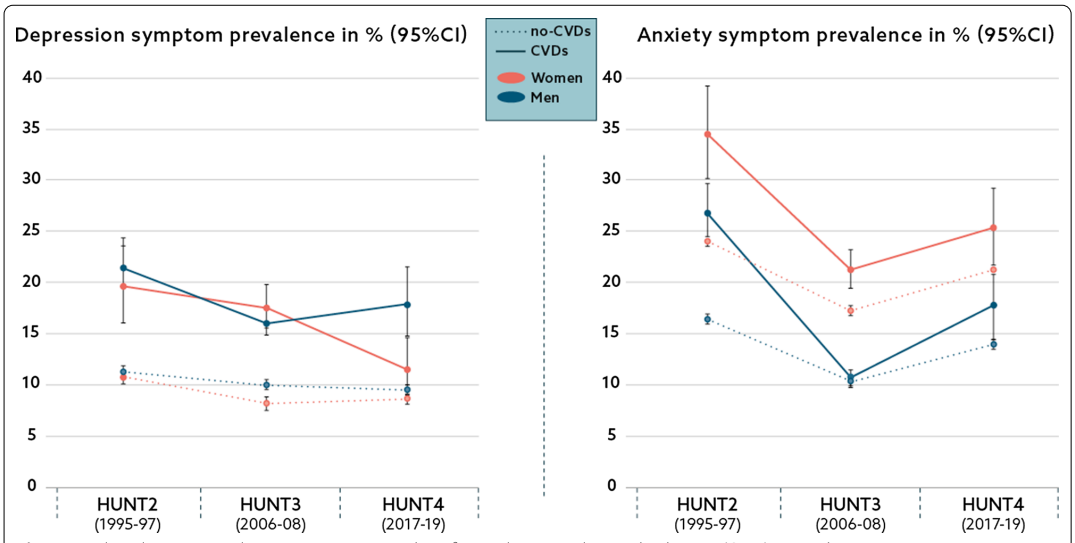

Fig. 2 Trends in depression and anxiety symptom prevalence[a] according to cardiovascular diseases (CVDs) status, the HUNT 1995–2019.
[a]Age-standardized using the age distribution of participants attending a screening in HUNT3 as the standard population. HUNT, The Trøndelag Health Study

increased in the last study period (2008–2019) across all study groups and sexes, resulting in an overall decrease in participants with CVDs and relative stability in groups without this condition. Women reported higher anxiety scores than men, a trend observed across all study groups and periods.

Similarly, Fig. 3 shows the age-standardized prevalence of symptoms of anxiety and depression in participants according to DM status. Within DM groups of both sexes, depressive symptom prevalence showed an overall decline in the first period yet increased slightly in women and remained largely unchanged in men throughout the study period. Such trend resulted in an overall depressive symptom decrease in men with DM and relative symptom stability in women with this condition. From HUNT2 to HUNT3, anxiety symptom prevalence declined across all study groups and sexes and subsequently increased again in HUNT4, so that anxiety prevalence rates in DM groups remained largely unchanged in women and declined in men. As in CVDs analyses, depression symptom prevalence remained relatively stable in no-DM participants of both sexes, whereas anxiety symptoms increased in the first and declined in the last period.

Associations of cardiovascular diseases and diabetes with depression and anxiety symptoms at age 60

Table 3 shows associations of CVDs with symptoms of depression and anxiety at age 60 years for men and women in HUNT2, HUNT3 and HUNT4. Overall, the risk differences between individuals with and without CVDs declined over time for both sexes yet remained statistically significant in men. Among women, RD for depression decreased from 0.08 (95% CI 0.07–0.1) in HUNT2 to 0.05 (95% CI 0.04–0.07) in HUNT3. In HUNT4, there was no statistical evidence for any difference between those with and without CVDs on either depression or anxiety symptoms among women. Men with CVDs in HUNT4 had a 26% higher risk for symptoms of depression than males with no CVDs, with an absolute RD of 0.03 (95% CI 0.01–0.04). In contrast, there was no statistical evidence for any difference between CVDs groups and anxiety symptoms among men in HUNT4.

Table 4 shows that among adults at the age of 60 with DM in HUNT2, the risk for depression and anxiety symptoms above cut-off levels was raised by 36% compared to no-DM groups as a reference, with an RD of 0.04 (95% CI 0.02–0.07). There was no difference between DM and anxiety or depression risks in either sex in HUNT3, whereas 11 years later (HUNT4), DM was associated with a 24% increased risk for depression and 13% increased risk for anxiety in women but not in men. Further adjustment for sociodemographic and lifestyle variables yielded minimal changes in risk estimates in both CVDs and DM analysis (Tables 3, 4), and thus, these variables were not included in the final model.

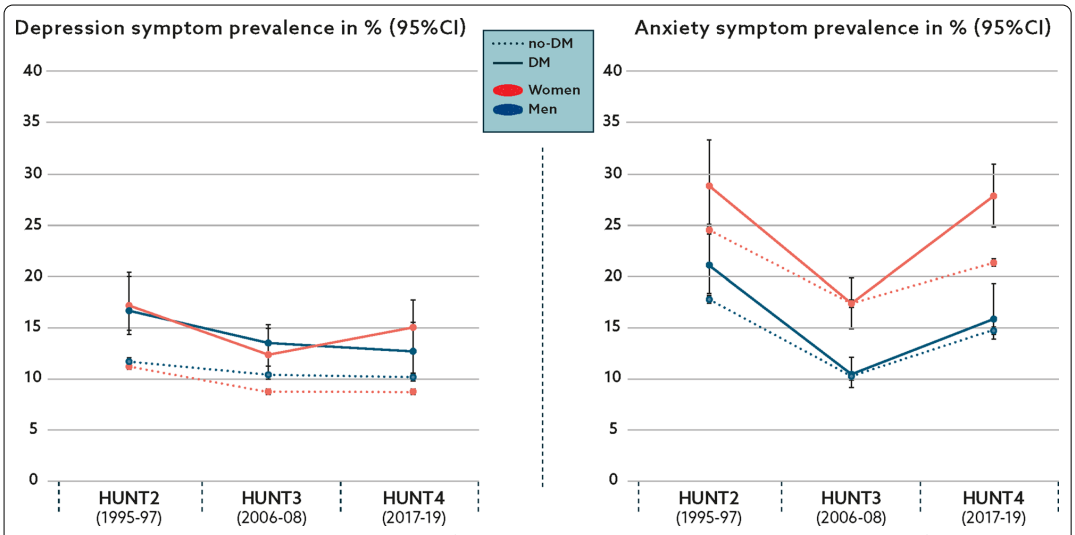

Fig. 3 Trends in depression and anxiety symptom prevalence[a] according to diabetes mellitus (DM) status, the HUNT 1995–2019. [a]Age-standardized using the age distribution of participants attending a screening in HUNT3 as the standard population. HUNT, The Trøndelag Health Study

Table 3 Associations of CVDs with depression and anxiety symptoms in HUNT2 (1995–97), HUNT3 (2006–08) and HUNT4 (2017–19), multi-level logistic analysis

	HUNT2 (1995–97) RR (95% CI)	HUNT3 (2006–08) RR (95% CI)	HUNT4 (2017–19) RR (95% CI)	HUNT2 (1995–97) RD (95% CI)	HUNT3 (2006–08) RD (95% CI)	HUNT4 (2017–19) RD (95% CI)
Depression						
Women n = 45,726	**1.72 (1.55–1.88)**	**1.57 (1.37–1.76)**	1.10 (0.94–1.26)	**0.08 (0.07–0.10)**	**0.05 (0.04–0.07)**	0.01 (− 0.01 to 0.03)
Men n = 39,012	**1.45 (1.33–1.57)**	**1.25 (1.12–1.38)**	**1.26 (1.12–1.39)**	**0.06 (0.04–0.07)**	**0.03 (0.01–0.04)**	**0.03 (0.01 to 0.04)**
Anxiety						
Women n = 45,095	**1.39 (1.28–1.49)**	**1.28 (1.15–1.40)**	1.03 (0.93–1.14)	**0.09 (0.07–0.11)**	**0.05 (0.03–0.07)**	0.01 (− 0.01 to 0.03)
Men n = 38,754	**1.37 (1.25–1.48)**	**1.28 (1.12–1.43)**	1.07 (0.95–1.19)	**0.06 (0.04–0.08)**	**0.03 (0.01–0.04)**	0.01 (− 0.01 to 0.03)

Adjusted for age and age squared. Risk Ratio (RR) and Risk Difference (RD) between individuals reporting CVDs and no-CVDs (ref.) at age 60

CVDs, Cardiovascular diseases; HUNT, The Trøndelag Health Study; RR, Risk ratio; RD, Risk difference; CI, Confidence Interval

Table 4 Associations of DM with depression and anxiety symptoms in HUNT2 (1995–97), HUNT3 (2006–08) and HUNT4 (2017–19), multi-level logistic analysis

	HUNT2 (1995–97) RR (95% CI)	HUNT3 (2006–08) RR (95% CI)	HUNT4 (2017–19) RR (95% CI)	HUNT2 (1995–97) RD (95% CI)	HUNT3 (2006–08) RD (95% CI)	HUNT4 (2017–19) RD (95% CI)
Depression						
Women n = 45,844	**1.36 (1.17–1.56)**	1.18 (0.98–1.38)	**1.24 (1.06–1.42)**	**0.04 (0.02–0.07)**	0.02 (− 0.00 to 0.04)	0.02 (0.01 to 0.04)
Men n = 39,095	**1.22 (1.04–1.40)**	1.07 (0.90–1.24)	1.09 (0.94–1.23)	**0.03 (0.01–0.05)**	0.01 (− 0.01 to 0.03)	0.01 (− 0.01 to 0.03)
Anxiety						
Women n = 45,219	1.12 (1.00–1.25)	1.05 (0.91–1.19)	**1.13 (1.02–1.24)**	0.03(− 0.00 to 0.06)	0.01 (− 0.02 to 0.03)	**0.03 (0.01–0.05)**
Men n = 38,838	**1.21 (1.04–1.38)**	1.13 (0.93–1.33)	1.12 (0.97–1.26)	**0.03 (0.01–0.06)**	0.01 (− 0.01 to 0.03)	0.02 (− 0.00 to 0.04)

Adjusted for age and age squared. risk ratio (RR) and risk difference (RD) between individuals reporting DM and no-DM (ref.) at age 60

DM, diabetes mellitus; HUNT, The Trøndelag Health Study; RR, risk difference; RD, risk ratio; CI, confidence interval

Discussion

Findings from three waves (1995–2019) of this population-based study of more than 140,000 adults showed higher depression and anxiety symptom prevalence in groups with CVDs and DM than no-disease groups, and differences were generally more pronounced in CVDs than DM. Overall, there was a general decline in depression symptom prevalence in the same period for all study groups. Anxiety symptom prevalence decreased initially and increased in the last decade across study groups and sexes; still, there was an overall symptom reduction in participants with and without CVDs or DM. These trends are not in keeping with a meta-analysis that suggested no change in the global prevalence of depression and anxiety in the general populations in 21 world regions between 1990 and 2010 [7]. Nevertheless, our results partially reflect patterns of depression and anxiety prevalence in other Scandinavian countries [48–50] and confirm existing evidence of the higher prevalence of depressive and anxiety symptoms in populations with CVDs or DM than in the general adults [9, 10].

Prevalence of depression and anxiety symptoms according to cardiovascular disease and diabetes status

Depression and anxiety symptoms and disorders often overlap with CVDs and DM [17, 24, 25, 51] and are more frequent in people with these wide-spread physical conditions than in the general population [9, 10]. Largely in line with our findings, worldwide population-based survey data from 17 countries, showed that the prevalence of clinically diagnosed depression and anxiety is generally higher in CVDs and DM populations than those with no such conditions, consistently across countries, sexes, and

age [9, 10]. However, although not directly comparable, the depressive symptom prevalence in CVDs groups for the period 2006–08 (HUNT3) in our data was closer to the prevalence reported for the corresponding period in the recent US studies—ranging from 15.8 to 18.3% [52, 53], than the pooled depressive symptom prevalence in community-dwelling adults with CVDs in China and Iran ranging from 35 to 47% [15, 18]. Thus, our findings broadly agree with the evidence on the prevalence of depression (i.e., self-reported or clinically diagnosed) in the people with CVDs and the general public to be lower in Western countries than in non-Western world region [54, 55].

Secular trends in the prevalence of depression and anxiety symptoms

Although it is well established that depression and anxiety prevalence is generally higher in people with chronic medical conditions than those without, findings on time changes in depression and anxiety symptom prevalence in the general population and groups with CVDs or DM have been inconsistent. Epidemiological studies from the last two decades have observed an overall increase in depression and anxiety prevalence in the general population [48, 56, 57] and CVDs and DM populations [10, 57, 58]. In contrast, other studies report that these mental conditions are on the rise in general adult populations [7, 59, 60] and populations with CVDs and DM [23, 53, 61].

In contrast to our findings, studies from the USA showed that depressive symptom prevalence increased in the general population from 2005 to 2016 [57], while no change was found in community-dwelling adults with heart disease (aged 20–80 years) in the same period [53]. Moreover, our prevalence rates of non-disease groups align with the literature review and meta-analysis of studies on the global prevalence of depression and anxiety symptoms, revealing relative stable rates from 1990 through 2005 to 2010 [7]. However, the overall decline of depression symptoms across CVDs/DM groups in this study corresponds to a general reduction in the pooled global prevalence of depression symptoms and disorders observed in various outpatient groups from 1995 to 2010, from 83 cross-sectional studies mainly from Europe, Asia and North America [54]. This change was partly explained by improved treatment and awareness of these psychological conditions [54]. Similarly, the decline in depressive symptom rates was observed in a population-based sample of Mexican adults with DM (aged $\geq$ 50 years) from 2001 to 2015 [23].

A decrease in anxiety symptom prevalence from 1995 to 2008 in our data is not in keeping with a meta-analysis that relied on data from 44 countries and concluded no change in the global prevalence of anxiety in adults (clinically diagnosed or self-reported) for the period 1990–2010 [8]. On the other hand, Swedish findings from 1980 to 2005 showed a general increase in self-reported anxiety rates among adults aged 16–63 years [48]. Nevertheless, the same study also observed a decline in anxiety symptom prevalence in the oldest female groups (aged 64–71 years), in line with trends observed in our data. Similarly, another population-based Swedish study that examined time trends in self-reported anxiety from 1997 to 2006 reported an increase in participants aged $\leq$ 24 years, whereas a decrease or stable estimates in the other adult groups (25 years and more) from 2001 and onwards [49]. A study of national representative Dutch adults (aged 18–64 years) observed no change in the prevalence of clinically diagnosed anxiety and depression from 1995 to 2009 [50].

Variations in instruments and criteria, sampling, study location/country, and characteristics of underlying populations make it difficult to directly compare and interpret study findings [62, 63]. In sum, changes in depression and anxiety symptom prevalence for the period 1995–2019 (HUNT2 to HUNT4) within a national representative sample of Norwegian adults are in keeping with comparable studies reporting on depression and anxiety symptom trends in the same age groups in other Scandinavian countries [48, 50]. Moreover, anxiety symptom rates for the period 2006–19 (HUNT3 to HUNT4) showed a marked increase across all study groups and in both sexes. The increase in anxiety symptoms has been linked to the global rise in psychological stressors such as work-life stress [64], urbanization [65] and social media use [66] observed in past decades. However, understanding the extent to which our findings on increasing anxiety prevalence reflect the growing trend in stress-related risk factors for anxiety, particularly within specific subgroups, requires further investigation. On the other hand, the overall reduction in symptoms of depression and anxiety in our study over two decades may, in addition to the above-mentioned cohort effect, to some degree be a result of altered lifestyle behaviour (i.e., non-smoking, physical activity and no-low alcohol use) of study participants becoming "healthier" from HUNT2 to HUNT3, particularly in those with a diagnosis of CVDs and DM, which in turn could have contributed to improved mental health outcomes [67–69]. However, the overall decrease or relative stability of mental health symptoms in our data may reflect an overall improved public recognition of common mental conditions, particularly in groups with wide-spread physical conditions or increased awareness of people with such diseases to seek mental health help [60, 70].

Importantly, the diagnostic criteria for several physical illnesses have changed around the time of HUNT2

[71]. These changes lowered the thresholds for CVDs and DM diagnosis, contributing to higher prevalence and a "healthier" population with these conditions [72, 73]. This change might, at least partly, contribute to the general decline of the existing depression symptom burden across the three HUNT surveys and the drop in anxiety symptoms from HUNT 2 to HUNT3. Nevertheless, these changes have most likely affected CVDs and DM populations similarly in most of the world—both in terms of physical and mental symptom burden.

Higher prevalence, severity, and burden of anxiety and depression have consistently been documented in women compared to men in general, CVDs and DM populations [5, 6, 21, 22, 52]. Our study confirmed existing evidence that anxiety symptoms were more common in women than in men, irrespectively of CVDs or DM status. In contrast, the analysis of our data generally yielded marginal sex-differences in depressive symptom prevalence, except in the CVDs population in HUNT4, where men reported more depression than women. This can largely be attributed to the psychometric properties of the HADS-D subscale, also confirmed in a previous study of the HUNT2 cohort [74].

Associations of anxiety and depression symptoms with cardiovascular diseases and diabetes

In our study, CVDs or DM was positively associated with depression and anxiety symptom risk in HUNT2 (1995–97). However, over 22 years, these associations declined, except for CVDs and symptoms of depression in men that remained across studies. Moreover, in women, DM was associated with an increased risk of psychological symptoms, greater for depression than anxiety in HUNT2 and HUNT4.

The findings that CVDs are significantly associated with symptoms of depression and anxiety are consistent with literature showing that these psychological symptoms are common after CVDs [16, 20, 75]. A literature review and meta-analysis of studies examining several vascular risk factors of late-life depression (clinically diagnosed or self-reported) found positive associations of CVDs with depression (pooled OR 1.76; 95% CI 1.52–2.04) [68]. Similarly, a meta-analysis reporting on post-stroke anxiety found self-reported anxiety in one of five stroke survivors [16]. The strength and significance of the associations of CVDs with depression and anxiety symptoms in our data changed over time across sexes, the results inconsistent compared to previous research. However, research has addressed that psychological reactions following CVDs events differ in women and men. Results from a meta-analysis of studies examining depression after CVDs diagnosis/events across sexes suggested that women experience a higher level of depression initially after a coronary heart event than men. However, in most women, symptoms tend toward improving over time, whereas men typically reported more long-lasting distress and depressive symptom burden [76].

It has been documented that several psychological conditions related to diabetes, such as stress followed by the diagnosis, feeling of the burden caused by demanding lifestyle and self-care behavior, fear of hypoglycemia, diabetes complication, and invasive procedures, may impose depression and anxiety [77]. Moreover, a meta-analysis showed that DM is associated with, on average, a 30% increased risk for both self-reported and clinically diagnosed depression [24], which partly correspond to our findings. However, these associations remained statistically significant only in women in two study waves about 20 years apart. These findings agree with a literature review on diabetes stress, an emotional state characteristical for type 2DM, that reported diabetes stress is more frequent in women than men and often followed by depression [78].

Strengths and limitations

This study has several strengths. First, it used an internationally renowned health database to examine changes in depression and anxiety symptoms over more than 20 years in people with CVDs, DM, and adults residing in the same area without these diseases. Second, the study sample is relatively large and comprises an adult population representative of the general Norwegian adult population. Of note, HADS was specifically designed to detect anxiety and depression in patients with cardiovascular/physical conditions. Therefore, it covers core psychological symptoms of depression and anxiety, yet excludes all physical conditions (i.e., dizziness, fatigue, insomnia, and others) frequently present in both mental and physical disorders to avoid misclassification and reverse causality [13, 79].

This study also has some limitations. Depression and anxiety symptoms were based on self-rating rather than clinical interviews. This makes direct comparison with studies of diagnostic categories of anxiety and depression difficult. However, it is quite time consuming to perform diagnostic interviews, and this method is hardly feasible in large scale studies such as HUNT. In addition, using self-reported instruments with cut-off values to measure anxiety and depression levels might represent a possible source of bias, and using continuous scores could have utilized the available information along the whole range of the HADS scale. Thus, the definitive diagnosis of depression must be based on the results from the clinical interviews and the assessment of functional and somatic symptoms. However, the HADS instrument has been

used in various settings, and cut-off levels have been well defined in the literature [39].

Furthermore, decreasing participation rates from HUNT2 to HUNT3 (i.e., on average, by 15.4%) may also have influenced the results. However, it should be noted that participation rates alone do not necessarily indicate selection bias [80]. Further, CVDs and DM were self-reported, which introduce the possibility that reporting bias and misclassification may have affected our results.

Overall, this study's results can mainly be generalized to middle-aged and elderly community-dwelling adults [37]. The overall prevalence rates of CVDs, DM, anxiety and depression, are likely underestimated as some individuals were too ill to participate. However, we argue that this study provides valid, up-to-date information on time trends in anxiety and depression symptoms in a nationally representative sample of adults over 22 years, across CVDs and DM status and age.

Conclusion

We observed a declining trend in symptoms of depression and anxiety for the last two decades, irrespectively of age, sex, and CVDs or DM status. Women reported consistently more anxiety than men, whereas associations of CVDs with depression symptom remained over time in men. However, our findings indicate that depression and anxiety symptom load is still higher in people with CVDs or DM than in the general public. Anxiety and particularly depression are negatively associated with help-seeking, adherence to treatment and outcomes of CVDs and DM. Therefore, more attention to those with coexisting mental health problems during the treatment of these physical diseases should be warranted. Further research should focus on how the treatment of depression and anxiety might improve CVDs and DM outcomes, and vice versa.

Abbreviations

CI: Confidence interval; CVDs: Cardiovascular diseases; DM: Diabetes mellitus; HADS: The Hospital Anxiety and Depression Scale; HUNT: The Trøndelag Health Study; RR: Risk ratio; RD: Risk difference.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40359-021-00636-0.

Additional file 1. Associations of CVDs with depression and anxiety symptoms in HUNT2 (1995–97), HUNT3 (2006–08) and HUNT4 (2017–19) at age 40, 60 and 80, multi-level logistic analysis[a].

Additional file 2. Associations of DM with depression and anxiety symptoms in HUNT2 (1995–97), HUNT3 (2006–08) and HUNT4 (2017–19) at age 40, 60 and 80, multi-level logistic analysis[a].

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Authors' contributions

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

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Availability of data and materials

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 the included permission from the HUNT, The Regional Ethical Committee and Norwegian Data Protection Authority. The dataset used in this study, are 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 approval of a research protocol by the Regional Ethical Committee and HUNT Research Centre. To protect participants' privacy, HUNT Research Centre aims to limit storage of data outside HUNT databank and cannot deposit data in open repositories. HUNT databank has precise information on all data exported to different projects and are able to reproduce these on request. There are no restrictions regarding data export give approval of applications to HUNT Research. For more information about HUNT data see: https://www.ntnu.edu/hunt/data.

Declarations

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.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests in the manuscript.

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Publisher's Note

Supplementary material

Additional file 1. Associations of CVDs with depression and anxiety symptoms in HUNT2 (1995-97), HUNT3 (2006-08) and HUNT4 (2017-19) at age 40, 60 and 80, multi level logistic analysis [a]

		HUNT2	HUNT3	HUNT4	HUNT2	HUNT3	HUNT4
	Age (years)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RD (95% CI)	RD (95% CI)	RD (95% CI)
Depression							
Women	40	1.79 (1.61-1.97)	1.61 (1.40-1.83)	1.11 (0.93-1.28)	0.07 (0.05-0.09)	0.04 (0.03-0.06)	0.01 (-0.00-0.02)
	60	1.72 (1.55-1.88)	1.57 (1.37-1.76)	1.10 (0.94-1.26)	0.08 (0.07-0.10)	0.05 (0.04-0.07)	0.01 (-0.01-0.03)
	80	1.64 (1.50-1.79)	1.52 (1.34-1.69)	1.09 (0.94-1.24)	0.10 (0.08-0.12)	0.07 (0.04-0.09)	0.01 (-0.01-0.03)
Men	40	1.50 (1.36-1.64)	1.27 (1.13-1.42)	1.28 (1.13-1.43)	0.05 (0.03-0.06)	0.02 (0.01-0.03)	0.02 (0.01-0.03)
	60	1.45 (1.33-1.57)	1.25 (1.12-1.38)	1.26 (1.12-1.39)	0.06 (0.04-0.07)	0.03 (0.01-0.04)	0.03 (0.01-0.04)
	80	1.41 (1.30-1.52)	1.23 (1.11-1.35)	1.24 (1.11-1.36)	0.07 (0.05-0.08)	0.03 (0.02-0.05)	0.03 (0.02-0.05)
Anxiety							
Women	40	1.36 (1.77-1.46)	1.26 (1.14-1.38)	1.03 (0.94-1.13)	0.09 (0.07-0.12)	0.05 (0.03-0.08)	0.01 (-0.01-0.03)
	60	1.39 (1.28-1.49)	1.28 (1.15-1.40)	1.03 (0.93-1.14)	0.09 (0.07-0.11)	0.05 (0.03-0.07)	0.01 (-0.01-0.03)
	80	1.43 (1.31-1.54)	1.30 (1.16-1.44)	1.04 (0.93-1.15)	0.08 (0.06-0.10)	0.04 (0.02-0.06)	0.01 (-0.01-0.03)
Men	40	1.34 (1.24-1.44)	1.26 (1.12-1.40)	1.06 (0.95-1.18)	0.07 (0.05-0.09)	0.03 (0.02-0.05)	0.01 (-0.01-0.03)
	60	1.37 (1.25-1.48)	1.28 (1.12-1.43)	1.07 (0.95-1.19)	0.06 (0.04-0.08)	0.03 (0.01-0.04)	0.01 (-0.01-0.03)
	80	1.44 (1.30-1.58)	1.32 (1.14-1.50)	1.08 (0.94-1.22)	0.04 (0.03-0.05)	0.02 (0.01-0.03)	0.01 (-0.00-0.02)

Abbreviations: CVDs, Cardiovascular diseases; HUNT, The Trøndelag Health Study; RR, Risk ratio; RD, Risk difference; CI, Confidence Interval.

[a]Adjusted for age and age squared. Risk Ratio (RR) and Risk Difference (RD) between individuals reporting CVDs and no-CVDs (ref.) at age 40, 60 and 80.

Additional file 2. Associations of DM with depression and anxiety symptoms in HUNT2 (1995-97), HUNT3 (2006-08) and HUNT4 (2017-19) at age 40, 60 and 80, multi-level logistic analysis [a]

		HUNT2	HUNT3	HUNT4	HUNT2	HUNT3	HUNT4
	Age (years)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RD (95% CI)	RD (95% CI)	RD (95% CI)
Depression							
Women	40	1.40 (1.18-1.62)	1.20 (0.98-1.42)	1.26 (1.06-1.45)	0.04 (0.02-0.06)	0.01 (-0.00-0.03)	0.02 (0.00-0.03)
	60	1.36 (1.17-1.56)	1.18 (0.98-1.38)	1.24 (1.06-1.42)	0.04 (0.02-0.07)	0.02 (-0.00-0.04)	0.02 (0.01-0.04)
	80	1.32 (1.15-1.50)	1.17 (0.99-1.35)	1.22 (1.06-1.38)	0.05 (0.03-0.08)	0.02 (-0.00-0.05)	0.03 (0.01-0.05)
Men	40	1.24 (1.04-1.44)	1.08 (0-89-1.77)	1.09 (0.93-1.26)	0.02 (0.00-0.04)	0.01 (-0.01-0.02)	0.01 (-0.01-0.02)
	60	1.22 (1.04-1.40)	1.07 (0.90-1.24)	1.09(0.94-1.23)	0.03 (0.01-0.05)	0.01 (-0.01-0.03)	0.01 (-0.01-0.03)
	80	1.20 (1.04-1.35)	1.07 (0.91-1.22)	1.08 (0.94-1.21)	0.03 (0.01-0.06)	0.01 (-0.01-0.03)	0.01 (-0.01-0.03)
Anxiety							
Women	40	1.12 (1.00-1.24)	1.05 (0.92-1.18)	1.13 (1.02-1.23)	0.03 (-0.00-0.06)	0.01 (-0.02-0.04)	0.03 (0.01-0.05)
	60	1.12 (1.00-1.25)	1.05 (0.91-1.19)	1.13 (1.02-1.24)	0.03 (-0.00-0.06)	0.01 (-0.02-0.03)	0.03 (0.01-0.05)
	80	1.13 (0.99-1.27)	1.05 (0.91-1.20)	1.14 (1.02-1.26)	0.03 (-0.00-0.05)	0.01 (-0.01-0.03)	0.03 (0.00-0.05)
Men	40	1.20 (1.04-1.35)	1.12 (0.94-1.31)	1.11 (0.98-1.24)	0.04 (0.01-0.07)	0.02 (-0.01-0.04)	0.02 (-0.00-0.04)
	60	1.21 (1.04-1.38)	1.13 (0.93-1.33)	1.12 (0.97-1.26)	0.03 (0.01-0.06)	0.01 (-0.01-0.03)	0.02 (-0.00-0.04)
	80	1.24 (1.05-1.44)	1.15 (0.92-1.37)	1.13 (0.97-1.30)	0.03 (0.01-0.05)	0.01 (-0.00-0.02)	0.01 (-0.00-0.03)

Abbreviations: DM, Diabetes mellitus; HUNT, The Trøndelag Health Study; RR, Risk difference; RD, Risk Ratio; CI, Confidence Interval.

[a]Adjusted for age and age squared. Risk Ratio (RR) and Risk Difference (RD) between individuals reporting DM and no-DM (ref.) at age 40, 60 and 80

Paper II

Drugs - Real World Outcomes
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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

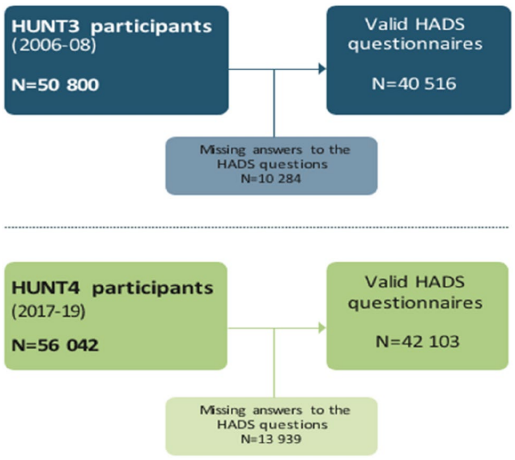

Fig. 1 Flow chart showing the selection criteria for study participants based on valid Hospital Anxiety and Depression Scale (HADS) questionnaires for selecting the study participants. Participants with five or more answers on the HADS-Depression subscale (HADS-D) and HADS-Anxiety subscale (HADS-A) questionnaires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

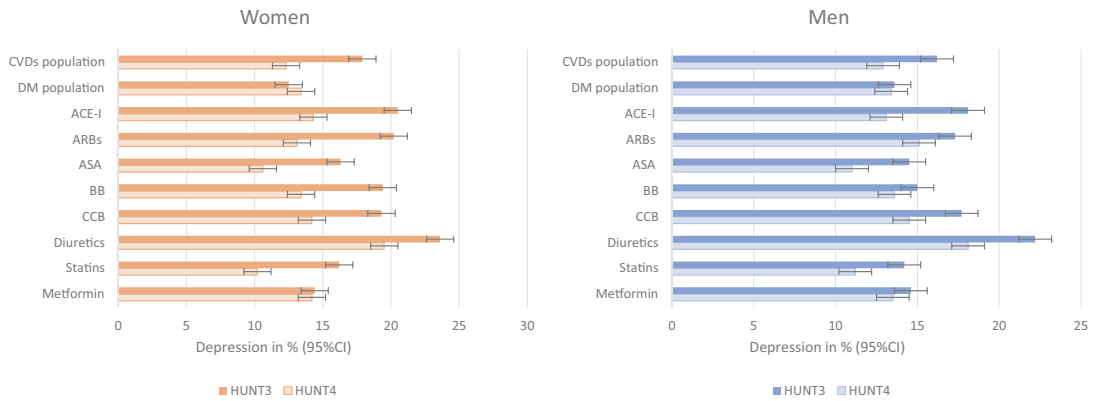

Fig. 2 Depression symptom prevalence (Hospital Anxiety Depression-subscale Depression [HADS-D] ≥ 8) among participants with cardiovascular diseases (CVDs; myocardial infarction/angina/stroke/heart failure) or diabetes mellitus (DM) stratified by sex, presented in total, and by prescriptions of cardiovascular 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 $\geq$ 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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Conflicts of interest/Competing interests Ivana Bojanić, Ottar Bjerkeset, Lana J. Williams, Michael Berk, Erik R. Sund, and Hege Sletvold have no conflicts of interest that are directly relevant to the content of this article.

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.

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Supplementary material

Supplementary Table 1 Associations between drug use (ref=non-users) and depression symptoms among participants with cardiovascular diseases (CVDs) and/or diabetes mellitus (DM) in HUNT3 and HUNT4 studies. Risk ratio (RR) and Risk difference (RD) with 95 per cent confidence intervals (95% CI).

	HUNT3 (2006-08)			**HUNT4** (2017-19)			**HUNT3** (2006-08)			**HUNT4** (2017-19)		
Drug group	**RR^0 (95%CI)**	**RR^1 (95%CI)**	**RR^2 (95%CI)**	**RR^0 (95%CI)**	**RR^1 (95%CI)**	**RR^2 (95%CI)**	**RD^0 (95%CI)**	**RD^1 (95%CI)**	**RD^2 (95%CI)**	**RD^0 (95%CI)**	**RD^1 (95%CI)**	**RD^2 (95%CI)**
ACE-I												
Women	1.17 (0.83-1.51)	1.31 (0.91-1.71)	1.38 (0.89-1.88)	1.16 (0.76-1.55)	1.20 (0.79-1.60)	1.38 (0.84-1.91)	0.03 (-0.02-0.07)	0.04 (-0.01-1.00)	0.05 (-0.01-0.10)	0.02 (-0.02-0.06)	0.02 (-0.02-0.06)	0.03 (-0.01-0.08)
Men	1.06 (0.80-1-32)	1.06 (0.80-1.31)	1.03 (0.75-1.31)	1.07 (0.80-1.35)	1.03 (0.78-1.28)	1.02 (0.73-1.31)	0.01 (-0.03-0.04)	0.01 (-0.03-0.04)	0.00 (-0.03-0.04)	0.01 (-0.02-0.04)	0.00 (-0.03-0.04)	0.00 (-0.03-0.04)
ARBs												
Women	1.10 (0.76-1.44)	1.08 (0.71-1.45)	1.19 (0.70-1.68)	1.04 (0.68-1.40)	0.98 (0.64-1.32)	1.30 (0.79-1.81)	0.01 (-0.03-0.06)	0.01 (0.04-0.06)	0.02 (-0.04-0.08)	0.00 (-0.03-0.04)	-0.00 (-0.04-0.04)	0.03 (-0.02-0.07)
Men	1.05 (0.75-1.36)	1.05 (0.74-1.35)	1.14 (-0.77-1.50)	1.05 (0.79-1.31)	1.06 (0.80-1.31)	1.12 (0.82-1.42)	0.01 (-0.03-0.05)	0.01 (0.04-0.05)	0.02 (-0.03-0.06)	0.01 (-0.03-0.04)	0.01 (-0.03-(-0.04)	0.01 (-0.02-0.05)
ASA												
Women	0.85 (0.71-1.00)	0.82 (0.62-1.02)	0.85 (0.59-1.10)	0.81 (0.62-1.01)	0.76 (0.55-0.97)	0.70 (0.47-0.94)	-0.02 (-0.05-0.00)	-0.03 (-0.07-0.01)	-0.02 (0.06-0.02)	-0.02 (-0.05-0.00)	-0.03 (-0.06-0.00)	-0.03 (-0.06-(-0.00)
Men	0.74 (0.59-0.89)	0.80 (0.63-0.96)	0.76 (0.59-0.94)	0.66 (0.52-0.80)	0.69 (0.55-0.83)	0.67 (0.52-0.82)	-0.04 (-0.07-(-0.01)	-0.03 (-0.06-(-0.00)	-0.04 (-0.07-(-0.00)	-0.06 (-0.08-(-0.03)	-0.05 (-0.09(-0.02)	-0.05 (-0.08(-0.02)
BB												
Women	1.18 (0.91-1.46)	1.24 (0.93-1.54)	1.26 (0.88-1.64)	0.78 (0.57-1.00)	0.78 (0.57-1.00)	0.78 (0.52-1.03)	0.02 (-0.01-0.06)	0.03 (-0.00-0.07)	0.03 (-0.01-0.07)	-0.03 (-0.05-0.00)	-0.03 (0.06-0.00)	-0.02 (-0.05-0.01)
Men	0.83 (0.67-1.00)	0.79 (0.64-0.95)	0.78 (0.61-0.96)	0.99 (0.79-1.19)	0.93 (0.74-1.11)	0.93 (0.72-1.14)	-0.03 (-0.05-0.00)	-0.03 (-0.06-(-0.00)	-0.03 (-0.06-0.00)	-0.00 (-0.03-0.02)	-0.01 (-0.04-0.02)	-0.01 (-0.03-0.02)
CCB												
Women	1.03 (0.85-1.21)	1.07 (0.77-1.36)	1.13 (0.76-1.50)	0.79 (0.56-1.03)	0.77 (0.52-1.02)	0.69 (0.41-0.98)	0.01 (-0.02-0.03)	0.01 (-0.03-0.05)	0.02 (-0.03-0.06)	-0.03 (-0.06-0.00)	-0.03 (-0.06-0.00)	-0.03 (-0.06-(-0.00)
Men	1.09 (0.84-1.34)	1.05 (0.80-1.29)	1.03 (0.76-1.31)	1.09 (0.84-1.33)	1.07 (0.83-1.30)	1.12 (0.85-1.40)	0.01 (-0.02-0.05)	0.01 (-0.03-0.04)	0.00 (-0.03-0.04)	0.01 (-0.02-0.04)	0.01 (-0.02-0.04)	0.01 (-0.02-0.05)
Diuretics												
Women	1.35 (1.04-1.67)	1.31 (0.99-1.64)	1.31 (0.91-1.70)	1.32 (0.93-1.71)	1.25 (0.88-1.63)	1.28 (0.82-1.74)	0.05 (0.01-0.09)	0.04 (-0.00-0.09)	0.04 (-0.01-0.08)	0.03 (-0.01-0.07)	0.03 (-0.01-0.07)	0.03 (-0.02-0.07)
Men	1.36 (1.05-1.67)	1.29 (1.00-1.59)	1.31 (0.97-1.64)	1.34 (1.00-1.67)	1.22 (0.92-1.52)	1.12 (0.79-1.45)	0.05 (0.01-0.09)	0.04 (0.00-0.08)	0.04 (-0.00-0.08)	0.04 (0.00-0.08)	0.03 (-0.01-0.07)	0.01 (-0.02-0.05)
Statins												
Women	0.83 (0.64-1.02)	0.91 (0.69-1.13)	0.99 (-0.69-1.29)	0.75 (0.54-0.95)	0.72 (0.52-0.92)	0.66 (0.44-0.87)	-0.03 (-0.06-0.01)	-0.01 (-0.05-0.02)	-0.00 (-0.04-0.04)	-0.03 (-0.06-(-0.00)	-0.04 (-0.07-(-0.00)	-0.04 (-0.07-(-0.01)
Men	0.73 (0.58-0.88)	0.76 (0.60-0.91)	0.70 (0.54-0.86)	0.67 (0.52-0.82)	0.69 (0.54-0.83)	0.67 (0.51-0.84)	-0.04 (-0.07-(-0.01)	-0.04 (-0.07-(-0.01)	-0.05 (-0.08-(-0.01)	-0.05 (-0.09-(-0.02)	-0.06 (-0.09-(-0.02)	-0.05 (-0.09-(-0.02)
Metformin												
Women	1.39 (0.89-1.88)	1.47 (0.94-1.99)	1.70 (0.87-2.53)	1.12 (0.79-1.45)	1.13 (0.79-1.47)	1.26 (0.79-1.73)	0.04 (-0.00-0.08)	0.04 (0.00-0.08)	0.04 (0.00-0.08)	0.01 (0.02-0.05)	0.01 (-0.02-0.05)	0.02 (-0.01-0.06)
Men	1.18 (0.77-1.58)	1.18 (0.77-1.59)	1.33 (0.79-1.87)	0.85 (0.60-1.09)	0.91 (0.66-1.16)	0.95 (0.66-1.24)	0.02 (-0.02-0.05)	0.02 (-0.02-0.05)	0.03 (-0.01-0.06)	-0.02 (-0.05-0.01)	-0.01 (-0.04-0.02)	-0.01 (0.04-0.03)

CVDs, Cardiovascular diseases; MI, Myocardial infarction; HF, Heart Failure; DM, Diabetes mellitus; HUNT, Trøndelag Study; ACE-I, Angiotensin-converting enzyme inhibitors; ARBs, Angiotensin II receptor blockers; ASA, Acetysalicylic acid; BB, Beta-blockers; CCB, Ca-channel blockers.

[0]Adjusted for age and age squared; n women=2 574 , n men=3 915 for all cardiovascular agents; n women=1 708, n men=1 898 for metformin
[1] Adjusted for age and age squared, smoking, impairment due to a long-lasting diseases and antidepressant use; n women=2 452, n men=3 822 for all cardiovascular agents; women n=1 644 ; n men=1 858 for metformin
[2] Adjusted for age and age squared, smoking, impairment due to a long-lasting diseases and participants with antidepressant use were excluded; n women=2 027, n men=3 540 for all cardiovascular agents; n women=1 382 n men=1 723 for metformin

Risk ratio (RR) and Risk difference (RD) between individuals with any dispensed drug prescription vs no drug prescriptions nine months before HUNT (ref.) at age 55.
Depression symptoms defined by HADS-D ≥8. HADS-D; Hospital Anxiety and Depression Scale -Depression subscale.

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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