Depression and migraine comorbid to diabetes

Epidemiological studies utilizing data from the Norwegian Prescription Database and the Hordaland Health Study

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Scientific environment

This project has been a collaboration between the Division of Psychiatry, Helse-Bergen, Department of Clinical Medicine, Section of Psychiatry and Department of Global Public Health and Primary Care at the Faculty of Medicine and Dentistry, University of Bergen. Until I received a PhD-position at the faculty, the project was funded by Division of Psychiatry, the Norwegian Diabetes Association and Mood-Net, a regional research network in mood disorders.

The project origins from ”Reseptgruppa”, a research group led by professor Anders Lund at ”Sandviken Sykehus”. This group is concerned with psychosomatic issues in pharmacoepidemiology and is affiliated both with the Department of Clinical Medicine, Section of Psychiatry and the Department of Research at Division of Psychiatry. In this environment, I worked part-time with the project the first 3 years of my training to be a psychiatrist.

The final 1.5 years of work with this project was undertaken at the Department of Global Public Health and Primary Care in the research group of lifestyle epidemiology. The primary focus of this group is epidemiological studies of risk factors for diseases as well as methodological issues, an is at present headed by professor Grethe S. Tell.

diabetesforbundet

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Abbreviations

ATC-classification system: Anatomical Therapeutic Classification System

BMI: Body mass index

HADS: Hospital Anxiety and Depression Scale

HADS-d: Hospital Anxiety and Depression Scale, subscale depression

HUNT: Nord-Trøndelag Health Study (Helseundersøkelsen I Nord Trøndelag)

HUNT 1: First HUNT survey, undertaken in 1984-1986

HUNT 2: Second HUNT survey, undertaken in 1995-1997

HUNT 3: Third HUNT survey, undertaken in 2006-2008

HUSK: The Hordaland Health Study

ICHD: International Classification of Headache Disorders

IHS: International Headache Society

NorPD: Norwegian Prescription Database

OR: Odds Ratio

SSB: Statistics Norway

Abstract

Background: Diabetes, depression and migraine are prevalent diseases in the Norwegian population, and have great impact on patients life in terms of disability. Diabetes is a systemic disease manifesting in a range of organ systems when the body not being able to either produce or effectively use insulin, whereas the exact pathophysiologic mechanisms leading to depression and migraine are not fully known. The understanding of the complexity of disorders in which the etiology and pathophysiology is not fully known might be improved by studying their comorbid conditions. Additionally, given the increasing life expectancy, information on how the risk of comorbid diseases to diabetes varies according to age can be important both in a public health perspective as well as for clinicians in the fields of family medicine, endocrinology, psychiatry and neurology.

Aims: Investigate depression and migraine treated with migraine agents as comorbid conditions to diabetes in the general Norwegian population, with emphasis on differences in risk according to age, sex and type of antidiabetic treatment.

Methods: Data on dispensions of prescriptions of antidiabetic, antidepressant and/or migraine agents in the total Norwegian population in 2006 was obtained from the Norwegian Prescription Database. As a measure of comorbidity, associations between type of antidiabetic and antidepressant agents according to age-group and sex were investigated in paper 1, while associations between type of antidiabetic agents and migraine agents according to age-group and gender were investigated in paper 3. Self-reported information from the population based survey "Helseundersøkelsen i Hordaland" (HUSK) was used in paper 2 to investigate how the association between diabetes and depression varied by presence and type of antidiabetic treatment in a community sample of middle-aged and older adults, and further study to which extent the association could be explained by known confounders. All studies were cross-sectional and the OR was used as a measure of the associations estimated by logistic regression models.

Results: Persons using antidiabetic agents had overall age and gender adjusted OR of about 1.5 of using antidepressant agents relative to persons not using antidiabetic agents (paper 1). Highest risk of using antidepressant agents was found for persons in their thirties using oral antidiabetic agents with an OR of about 4.5, and the risk decreased with increasing age to about 1.5 among persons aged 70 years and upwards. Persons using insulin in monotherapy had less variation in risk according to age, OR ranging from 1.7 for persons in their fifties years to 1.3 among persons aged 70 years and upwards. This finding of a higher risk of depression among middle aged persons with diabetes treated with oral antidiabetic agents relative to the non-diabetic population was confirmed in paper 2. The OR for depression defined as symptoms and/or antidepressant treatment for persons with diabetes in their forties using oral antidiabetic agents was attenuated from 3.79 to 2.92 after adjustments for gender, BMI, physical activity, alcohol consumption and education. This increased risk of depression among persons with diabetes contrasts the findings from paper 3, where persons with diabetes had an overall reduced risk of migraine treated with migraine agents relative to the non-diabetic population (age and gender adjusted OR: 0.72). Although young and middle aged persons using oral antidiabetic agents had, in fact, an increased risk of migraine, the risk decreased with increasing age to about the same reduced risk (OR: 0.4-0.6) for all types of antidiabetic treatment for persons aged 60-69 years. In both paper 1 and 3, no sex-specific differences in risk of the outcome were found.

Conclusion: Persons with diabetes have increased risk of depression and decreased risk of migraine treated with migraine agents. While no gender specific differences in risk were found, we found marked variation in risk according to age and type of antidiabetic treatment. The finding of an inverse association between diabetes and migraine could reflect an effect of presence of diabetes over time, inferring with the sensation of migraine pain. If possible preventive strategies in the general population are considered to reduce the prevalence and impact of depression comorbid to diabetes, one should first consider targeting middle-aged persons with diabetes type 2.

List of papers

Paper 1: Berge L.I., Riise T, Fasmer O.B., Lund A, Oedegaard K.J., Hundal Ø. "Risk of depression in diabetes is highest for young persons using oral anti-diabetic agents" Diabetic Medicine (2012), 29; 509-514.

Paper 2: Berge L.I., Riise T, Tell G.S., Iversen M.M., Østbye T, Lund A, Knudsen A.K. "Depression in persons with diabetes by age and antidiabetic treatment: The Hordaland Health Study". Submitted to Plos One.

Paper 3: Berge L.I., Riise T, Fasmer O.B., Hundal Ø, Oedegaard K.J., Midthjell K, Lund A. «Does diabetes have a protective effect on migraine?» Epidemiology (2013), 24; 129-134.

Contents

1.0. Background

Depression, diabetes and migraine are prevalent diseases in the general population, and are ranked the 3 th, 7th and 23th most important causes of disability adjusted life years (DALYs) in Norway in the 2010 global burden of disease study (1). An increase in DALYs for each of the three disorders since the last survey in 1990 was also found, reflecting the increasing impact these non-communicable diseases have on public health in Norway. While the prevalence of diabetes assessed in health surveys in Norway have increased the last 30 years (2), the International Diabetes Federation estimates the global prevalence of diabetes among adults to increase from 8.3% in 2013 to 10.1% in 2035 (3) (p 33). As one can expect the disability to increase with increasing number of comorbid conditions, knowledge on if and how other conditions are associated with diabetes is of importance in a public health perspective. The present thesis aims at investigating depression and migraine as comorbid conditions to diabetes in the general Norwegian population, with emphasis on differences in risk according to age, gender and type of antidiabetic treatment.

This background will give an introduction to the term "comorbidity", followed by definitions, measures, prevalence and risk factors for diabetes, depression and migraine, respectively. Finally, the current literature on studies investigating depression and migraine comorbid to diabetes are reviewed, with emphasis on risk according to gender and age.

Throughout the thesis the term *"risk"* is used as a measure of relative probability, i.e., the probability of an outcome when exposed relative to the probability of the outcome when unexposed, also in the context of cross-sectional designs**.** This implies that the OR is interpreted as a measure of risk.

1.1. Comorbidity

The presence of two or more medical conditions occurring in one person at the same time is common (4), and the prevalence of co-occurrence of chronic diseases is expected to rise worldwide as the proportion of older people increases. Yet, health care, education and research systems are to a large extent concerned about single and specific diseases. Patients with multiple medical conditions are often excluded from randomized controlled trials, limiting the external validity of studies addressing the effect of interventions. Consequently, guidelines for specific diseases often have limited applicability to patients with multiple conditions (5, 6). Chronic somatic disorders has been shown to account for as much as half of the excess mortality in persons with severe mental disorders (7), illustrating the importance of addressing multiple disorders both in the day to day clinical management, as well as in order to predict to outcome of diseases. Further, to study the co-occurrence of disorders might improve our understanding of the etiology behind the conditions. In particular, it has been argued that exploration of the co-occurrence of somatic and psychiatric disorders may contribute to our understanding of the pathophysiology and biologic treatment of psychiatric disorders (8).

Comorbidity has been suggested to represent one of the greatest challenges to academic medicine (9). The term was first introduced in 1970 by Feinstein, a doctor of internal medicine and epidemiologist, who suggested the following definition: “any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study” (10). A common interpretation of this description has been “the presence of two or more medical conditions occurring simultaneously but independently of the index disease”. The “index disease” is understood as the main condition under study, the “reference disease”, and is often dependent on the branch of medicine the caregiver represents. For instance, an oncologist might consider arrhythmia and depression as comorbid conditions to cancer mamma, while a psychiatrist could be more likely to think of cancer and heart disease comorbid to a major depressive episode. In primary care, the term “multimorbidity” is often used to describe the presence of multiple diseases,

possibly reflecting a more general approach to complex and partly overlapping conditions (11).

One of the challenges of defining comorbidity is to agree upon how the conditions should be related in order to be termed comorbid. In 2009, Valderas suggested that the term comorbidity should be reserved to "2 or more medical conditions occurring simultaneously that is somehow related to the index disease" (12), while Jakovljevic in 2013 argued that the term also should include conditions existing simultaneously regardless of their causal relationship (9) . In addition, he introduced "subtypes" of comorbidity, suggesting the term "complicated comorbidity" to refer to situations where one disease is caused by another disease, and the term "prognostic comorbidity" when a disorder predisposes an individual to develop other disorders. This is contrasted by the definitions proposed by Ording in 2013, suggesting that the term "comorbidity" only should refer to conditions that are not a direct consequence of the index disease (no known causality"), while the term "complication" should imply a strong evidence of causality, and that complications should be regarded as endpoints or intermediate steps on the causal pathway from exposure to endpoint (13).

Figure 1 attempts to give an overview over possible explanations for why we observe associations between disorders, and under which conditions these associations can be regarded as examples of comorbidity. For the purpose of this thesis, comorbidity is understood as two disorders observed at the same point of time, regardless of the direction of the association between the disorders, and when the association observed is not expected to be explained by causality.

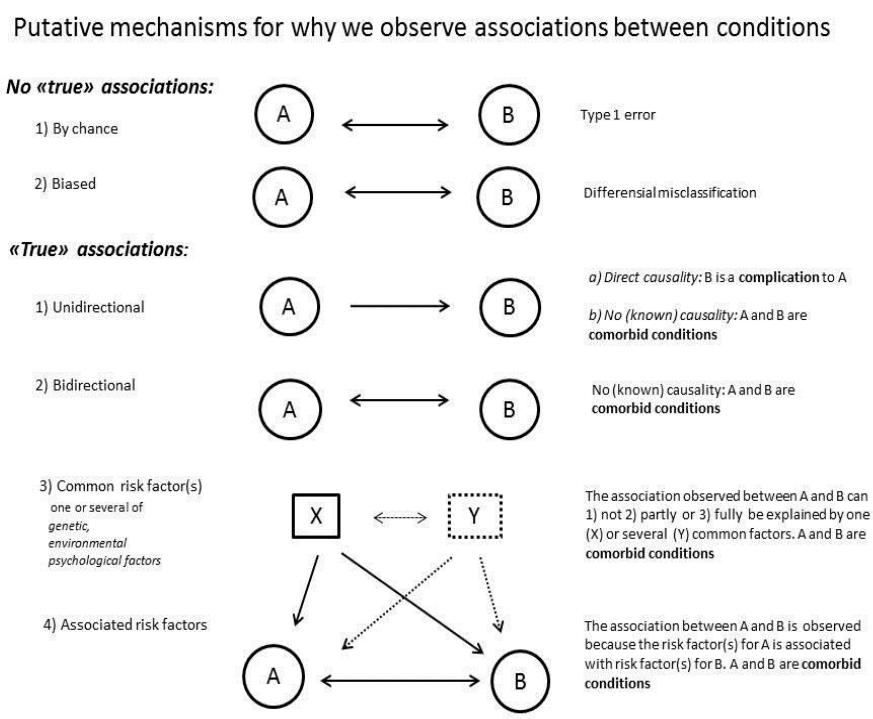

Figure 1: Examples of situations illustrating the various associations

No «true» associations:

1) By chance: Type 1 error with a 95% confidence interval implies a 5% risk of wrongly keeping the null hypothesis.

2) Biased: Differential misclassification due to recall bias in case-control studies with self-reported exposure.

«True» associations:

1) Unidirectional a) Direct causality: Neuropathy regarded as a complication to diabetes, b) No (known) causality: Diabetes associated with increased risk of breast cancer (14), while breast cancer is not known to be associated with increased risk of diabetes.

2) Bidirectional: No known causality: Diabetes type 2 is associated with increased risk of depression, while depression is associated with increased risk of diabetes type 2 (15, 16).

3) Common risk factor(s): Obesity is associated with both diabetes type 2 (17)(p 24) (3)(p 23) and depression (18), and is expected to explain some of the association.

4) Associated risk factors: Smoking is associated with high alcohol consumption. Smoking increases risk of lung cancer, alcohol increases risk of liver cirrhosis, explaining (partly or completely) the association found between lung cancer and liver cirrhosis (12).

Presence of comorbid diseases can be assessed by a variety of methods in epidemiological studies (19-21). The source of data can be medical charts and clinical examination (primary or secondary health care), self-report questionnaires (population based surveys), and administrative data from for example national health registries. It has been emphasized that in order to use pharmacy databases to study comorbidity, all participants must have uniform access to reimbursement (21). The ordering of data is often subdivided in listing the number of diseases in a "disease count" (with possibility of weighting) or "comorbidity indexes" (20), often specific for a particular index-disease, population or outcome of interest.

1.2. The diseases under study

1.2.1. Diabetes

Diabetes is a chronic, systemic disease manifesting when the body is not able to either produce or effectively use the hormone insulin, leading to altered glucose uptake in the cells (3)(p 12). In general, diabetes type 1 is understood as an autoimmune disease causing sudden drop in insulin production, while diabetes type 2 is by far considered a "lifestyle disease" caused by insulin resistance due to relative lack of insulin to meet the body's increasing demand. The International Diabetes Federation estimates that diabetes type 2 accounts for about 85%-95% of all diabetes cases in high income countries (3)(p 34).

Since 2012, the Norwegian Directorate of Health has recommended HbA1c as the primary tool for diagnosing diabetes, with a cut-off of 6.5% for manifest diabetes (22). HbA1c reflects the average concentration of serum glucose the last 8-12 weeks. In contrast to s-glucose, the HbA1c value is not affected by diurnal variation and time since last meal. Two separate tests with values above cut-off are required for the diagnosis if the patient is asymptomatic. The test is not regarded valid if the patient has acute current illness, recent trauma or surgery, or if conditions altering erythrocyte turnover are present, such as iron deficiency anemia, hemolytic anemia, chronic malaria and recent larger bleedings and transfusions. Under these conditions, the previous diagnostic criteria for diabetes must be applied: 1) fasting s-glucose $\geq$ 7.0

mmol/L or 2) s-glucose 2 hour after 75 gr oral glucose tolerance test (OGTT) ≥11.1 mmol/L or 3) random s-glucose ≥ 11.1mmol/L when symptoms of hyperglycemia are present (22). Two tests meeting the diagnostic criteria for diabetes are required for the diagnosis if the person has no symptoms or clinical signs of diabetes.

Assessment of diabetes in epidemiological studies

Presence of diabetes is assessed by a variety of methods in epidemiological studies. In studies utilizing data from population based health surveys, presence of diabetes is usually determined based on self-report of the diagnosis ("Do you have diabetes?", "Has a doctor ever told that you have diabetes?") or by measuring glucose in blood samples (s-glucose, fasting s-glucose, s-glucose 2 hours after oral glucose tolerance test). In the Norwegian population based Nord Trøndelag Health (HUNT) Study, participants answering affirmative to whether they had diabetes in survey 2 (HUNT 2) and 3 (HUNT 3) were given a second diabetes-specific questionnaire and had a fasting serum sample analyzed for glucose, c-peptide and anti-GAD antibodies (23). Further, presence of diabetes is often defined as a physician based ICD code for diabetes or diabetes related complications in studies using data from national health registries such as the Norwegian Patient Registry (24) and the Causes of Death Registry (25). Further, information on use of antidiabetic agents as a proxy for medically treated diabetes can be obtained from The Norwegian Prescription Database (26, 27) . Finally, in Norway, data on physician diagnosed diabetes is available in both the national consent-based Norwegian Diabetes Register for Adults (28) and the Norwegian Childhood Diabetes Registry (29).

- **Prevalence of diabetes in Norway**

Despite the range of methods available to determine the presence of diabetes in different samples of the population, the current prevalence of diabetes in Norway is difficult to determine (30). Utilizing data from 9 population based regional health surveys in Norway in the time span 1995-2001, Stene and colleagues estimated the age and gender adjusted prevalence of known diabetes to 3.4% for persons aged 30 years and above (31). The prevalence increased with age, reaching 8% among persons in

their seventies. Utilizing additional data from international studies, the estimated prevalence of undiagnosed diabetes was expected to be almost as high as the prevalence of known diabetes among persons ≥ 30 years. The prevalence of diabetes is fairly equal in men and women, a slightly higher prevalence in men compared to women in HUNT 1 was no longer evident in HUNT 2 (2). Prevalence of known diabetes in one of the most recent population based studies in Norway, HUNT 3 (2006-2008) was 4.1% among persons ≥20 years (32), while the International Diabetes Federation (IDF) estimated the prevalence of diabetes in Norway to be 5.9% in 2013 (3) (p 122).

- **Risk factors, comorbid conditions and complications**

Manifesting in several organ systems, diabetes is a systemic disease with complex etiology. **Figure 2** attempts to give an overview of risk factors for diabetes, comorbid conditions to diabetes and complications of diabetes. It is important to emphasize that this figure does not capture the complete and detailed picture on how diabetes is related to virtually all other conditions; the figure must be understood as an overview of possible associations with a complex, multisystem disease. In this context, no distinction between type 1 and 2 diabetes are made, which is more challenging for the overview of "risk factors" rather than for "comorbidities", and "complications". Known risk factors for type 1 diabetes includes genetic susceptibility (first degree relative with type 1 diabetes) and younger age, while it is debated whether viral infections, early exposure to cow's milk and living in cold areas/high latitudes is associated with increased risk (33). Further, the different conditions are only listed once in the figure, however, some of the conditions listed under the main headings, especially under either "risk factors" or "complications", could undoubtedly be listed under the other heading as well. In particular, one could argue that the "risk factors" metabolic syndrome, hypertension and obesity and virtually all of the "diseases" also could be regarded as "comorbid conditions ".

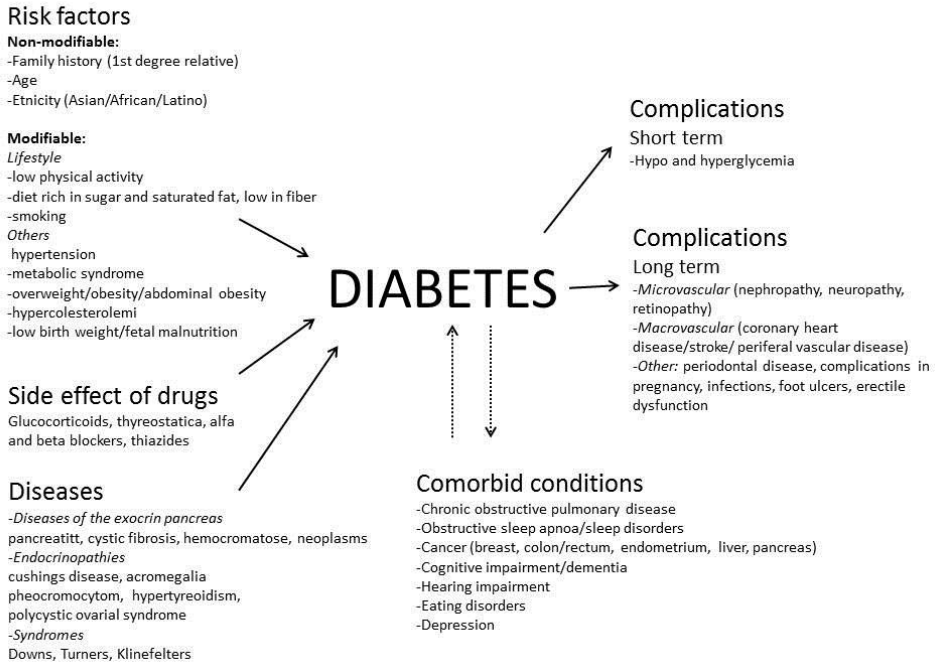

Figure 2: Risk factors for diabetes, comorbid conditions to diabetes and complications of diabetes.

A range of factors are associated with increased risk of diabetes type 2 (17, 34)(p 29). Most attention has been paid to factors regarding unfavorable lifestyle, possibly due to the high prevalence of these modifiable factors in the general population, however, the use of certain systemic drugs and the presence of some endocrinological diseases and congenital syndromes also increase the risk of diabetes (35) (p16). In addition, persons with diabetes more often suffer from comorbid somatic and psychiatric conditions (36) (p49). Examples include obstructive respiratory disorders (37), cancers (14, 38-41), cognitive dysfunction/dementia (42, 43), eating disorders and depression (44). Further, the development of macro and microvascular complications (amongst others) (17) (p 96) (3) (p 24) further illustrates the impact of this systemic disease.

1.2.2. Depression

The term "affective disorders" or "mood disorders" as used by ICD-10 characterizes a range of disorders with disturbances in mood, such as bipolar affective disorders, depressive episode, recurrent depressive disorders, and persistent mood disorders (45). In the present thesis, the term "depression" is used in accordance with the Norwegian Directorate of Health as "a heterogeneous group of disorders with core symptoms such as impaired mood and loss of interest and energy" (46). Other symptoms associated with depression include impaired concentration and attention, reduced self-esteem and self-confidence, ideas of guilt and unworthiness, bleak and pessimistic views of the future, ideas or acts of self-harm or suicide, disturbed sleep and diminished appetite (46). One has not succeeded in determining one single biologic mechanism explaining why some are affected by depression. Yet, a range of alterations have been shown to be associated with depression, leading to hypothesis regarding (amongst others) synaptic monoamine deficiency and impaired neurogenesis due to increased levels of cortisol as a response to various forms of stress (47, 48).

- **Assessment of depression in epidemiological studies**

Psychiatric disorders such as depression are defined by the presence of certain symptoms without any apparent single physical cause, making them particularly challenging to measure. Such diseases that cannot be measured directly are understood as *latent constructs*, and instead, several indicators assumed to represent the latent construct has to be measured (49)(p 605-608). These indicators are to a large extent self-reported, and to ensure precision, they must be both valid (measure what it sets out to measure) (50) (p 251) and reliable (consistent measure when applied under different circumstances) (50) (p 214). Data concerning these indicators further has to be operationalized as categorical or dimensional. Symptoms of depression on a continuous scale from absent to maximum intensity represent a dimensional measure of depression and is relatively easy to assess with self-reported questionnaires or screening tools measuring symptoms during a recent, short time span such as the Hospital Anxiety and Depression scale, subscale depression (HADS-d) and the Beck

Depression Inventory (BDI). Yet, these tools often provide different cut-off values defining "caseness" of depression, thereby employing a categorical approach when measuring depression. Today, psychiatric diagnoses as defined by the DSM-V and ICD-10 classification system is determined by a categorical approach; one have to meet a minimum of the disease specific criteria, often within a defined time span, in order to fulfil the diagnostic criteria. A categorical measure of depression can be obtained with diagnostic interviews, such as depression specific modules in the Mini International Neuropsychiatric Interview (M.I.N.I.) and the Composite International Diagnostic Interview (CIDI). In general, screening tools often give a higher number of "false positive cases" than diagnostic interviews. Further, it has been argued that comorbidity between psychiatric disorders to a large extent is a result of applying categorical thresholds on series of continuous dimensions of psychopathology in an effort to narrowly define disorders rather than to "lump" them together in few broadly defined categories (51).

Additionally challenging when attempting to measure psychiatric disorders in general, and depression in particular, is the often naturally fluctuating course. A consequence of this relapsing and remitting of symptoms over time is that persons meet the diagnostic criteria for depression only at certain times with high symptom load, and risk being wrongly classified if the measurement is undertaken at times with low symptom load. This risk of misclassification can be reduced in epidemiological studies utilizing information from registries on physician based ICD-10 codes regarding depression, or combine measures of symptoms with measures of treatment such as use of antidepressant agents (52).

- **Prevalence of depression in Norway**

Given the challenges measuring depression, the Norwegian Institute of Public Health estimates the lifetime prevalence of depression in Norway to 25%, while 10% of the adult population is expected to suffer from depression during the last 12 months (53) (p 15-22) (54). These estimates are based on results from population based studies employing diagnostic interviews to measure psychiatric disorders. One of these, the

"Oslo-study" undertaken in 1994-1997 found a 12 month prevalence of major depression and dysthymic disorder of about 7% and 4% respectively, in a random sample of about 2000 persons aged 18-65 years (55). In comparison, about 10% of participants in HUNT 2 had HADS-d ≥8, indicating possible cases of depression (56).

- **Risk factors for depression**

Depression is a multifactorial disorder with a range of risk factors with complex interactions. First degree relative with affective disorders, adverse childhood events, experiences of loss, comorbid substance use, somatic, other psychiatric disorders and low education and income are probably the most important risk factors in the general population (46, 53, 57). Generally, one recons that women have twice has high prevalence of depression compared to men (46, 55), suggesting female gender to be a risk factor for depression. However, it is discussed whether the diagnostic criteria used to assess depression could be biased toward detecting symptoms of depression that are more prevalent in women. A recent study employing a scale that also included symptoms of anger attacks/aggression, substance abuse and risk taking behavior found an equal prevalence of depression in men and women (58). Given the chronic and recurrent nature of depression, the interpretation of risk according to age is complex. Using data on depression assessed with the diagnostic interview C.I.D.I. from the National Comorbidity Survey Replication in the US, recent major depressive episode was found to be less prevalent among persons aged ≥65 years (59). Mean age of onset of depression in this study was 26 years, while the World Mental Health Study assessing depression with C.I.D.I. in about 85 000 persons worldwide estimated median age of onset of mood disorders between late 20s and early 40s (60). The previously mentioned "Oslo-study" found no significant variation in either 12 month or lifetime prevalence of depression between age-group 18-29, 30-39 or 40-49 years (55). An increase in both mean HADS-d score and proportion of participants with HADS-d ≥8 with age was found in HUNT 2 (61), even in the most adjusted models (62).

1.2.3. Migraine

Migraine is a chronic and episodic primary headache. Recently updated in 2013, the International Headache Society (IHS) defines the diagnostic criteria for migraine in the International Classification of Headache Disorders (ICHD) (63). Migraine without aura manifest in attacks of 4-72 hours duration, have a unilateral pulsating pain of moderate to severe intensity which is aggravated by routine physical activity and is associated with nausea and/or photophobia and phonophobia. Migraine with aura is defined by recurrent attacks, lasting for minutes, of unilateral fully reversible symptoms of visual, sensory or other central nervous system character. The aura is then accompanied, or followed within an hour, by unilateral headache and other associated migraine symptoms.

- **Assessment of migraine in epidemiological studies**

Migraine is suggested to be a disorder of neuronal hyperexcitability associated with cortical spreading waves of neuronal depression and activation of trigeminovascular system (64). However, as for depression, one has not succeeded in determining exact pathophysiological mechanism explaining migraine and therefore no "diagnostic test" measuring a "biologic correlate" of the disease can be used, such as laboratory or radiologic procedures. Accordingly, the diagnosis of migraine relies on self-reported symptoms, thereby facing the many of the same challenges described above on how to measure psychiatric disorders. Interestingly, few studies have addressed methodological challenges on how to measure the presence of migraine in epidemiological studies until the past 5-10 years. To improve the methodological quality of population based surveys of headache prevalence, an expert consensus group was established around 2011 in association with the charitable nongovernmental UK organization "Lifting the burden" and "Global Campaign against Headache", an official collaborator with the World Health Organization. (65, 66). Of particular interest was to agree upon case definition and time frame to be applied for a diagnosis of migraine, as well as how to select and systematically report appropriate study populations. Prevalence of migraine in epidemiological studies has been reported with

respect to various time frames such as 1, 3 or 12 months, the "whole life" (i.e. lifetime prevalence) or not specified (67), possibly hampering the interpretation of the estimates. As a result of this work, the HARDSHIP (Headache-Attributed Restriction, Disability, Social Handicap and Impaired Participation) questionnaire was recently developed (68). Both developed and validated in African, Asian and European countries, this lay administered questionnaire aims at providing a standard method for assessing the prevalence of migraine according to the ICHD.

Only a few population based studies have applied personal interview and examination by neurologist (regarded as the "gold standard") to estimate the prevalence of migraine. In Denmark, an early study from 1991 employed interview questions based on the IHS criterion in addition to examination by a neurologist to assess the prevalence of migraine (69). A follow-up and a replicate of this study was undertaken in the same geographical area in 2001 using approximately the same methods of assessment, except that medical doctors instead of neurologist performed the clinical examination (70).

In 1995-1997, assessment of various forms of headache was made by one single (and local) neurologist who employed an interview based on the IHS criteria, followed by a brief routine cranial nerve examination in the population based "Vågå Study" in Norway (71). The extensive interview with each participant lasted from 45 to 90 minutes, and a full neurological examination was carried out if indicated by the anamnesis or brief examination. In the first and second "head-HUNT", a sample of participants in HUNT 2 (age ≥20) and HUNT 3 (age ≥13) were given a "headache-specific" questionnaire assessing self-reported headache the last 12 months and caseness of migraine were defined according to liberal (self-reported) , moderate or restrictive criteria (ICHD) (72).

- **Prevalence of migraine in Norway**

Present 12 months prevalence estimates of migraine in the Norwegian population are derived from the HUNT Studies. In HUNT 3, the age adjusted prevalence using liberal ICHD 2010 diagnostic criteria was about 13%, while the prevalence reached 12%

when applying the most restrictive criteria (73). In contrast, the age adjusted prevalence in HUNT 2 using the liberal ICHD 1999 criteria was 12.0, while only about 2% filled the most restrictive criteria (74). The discrepancies in prevalence using the most restrictive criteria might be a result of change in diagnostic criteria for restrictive migraine. To meet the 1999 criteria, the headache attack had to last for 4-72 hours, while the duration of the attack had to be less than 72 hours according to the 2010 criteria, thereby possibly including a higher number of persons who terminate the attack with medications in this category than earlier. Further, the population based Akershus sleep apnea project estimated an overall *lifetime* prevalence of self-reported migraine to 27% in a sample of about 21 000 participants (75).

- **Risk factors for migraine**

Relative to the general population, persons with a first degree relative with migraine have increased risk of migraine (76-78). Familiar hemiplegic migraine, a rare subtype of migraine with aura, has an autosomal dominant pattern of inheritance (79) (p144). This implies that offspring's of a parent with the disorder have 50% risk of inheriting the gene; however, the risk of developing the disease is usually lower, due to incomplete penetrance. Twin studies have indicated that shared rearing environment during child and adulthood has little impact on the risk of developing migraine (80). On the contrary, low socioeconomic status defined by education and occupation among persons from 20 years of age was associated with increased risk of migraine at 11 years of follow up in HUNT (81), while no vocal education was associated with increased risk of incident migraine in a population based study of headache in Denmark with 12 years of follow up (78). In cross-sectional studies, an association between migraine and obesity has been found in middle-aged adults (82, 83), however, no prospective studies have addressed whether obesity increased the risk of incident migraine. Some argue that stressful time periods might precipitate the debut of migraine among persons with increased risk due to genetic factors (84), as frequent tension-type headache and high work load has been associated with incident migraine (78). Interestingly, an association between depression and migraine in the general

population has been found in both cross-sectional studies (85-87) and in some (88, 89), but not all (86), prospective studies.

In 1991, a population based study of persons aged 12-29 years from found that, based on self-reported debut of symptoms, the incidence of migraine reached a peak several years earlier among boys than girls, suggesting that migraine is more common in boys than girls before puberty (90). From adulthood and upwards, the incidence and prevalence of migraine has consistently been found to be higher among females than males (73, 78). The previously mentioned population based study in Denmark found an OR higher than 6 when comparing females versus males risks of incident migraine after adjustment for age (78), while the cross-sectional estimates from both HUNT 2 and 3 showed a more than twice as high prevalence among woman than men (73). Similarly, both incidence and prevalence of migraine are reckoned to be highest among younger adults. Highest incidence in the Danish study was found among the youngest, aged 25-34 years, and the incidence further decreased with increasing age (78). In HUNT 2 and 3, highest prevalence of migraine was found among persons aged 20-49 years, with a peak in age-group 30-39. The prevalence decreased with increasing age, reaching the lowest prevalence among persons in their eighties (73, 74). Interestingly, the substantial variations in prevalence of migraine according age have been difficult to explain, and theories related to the aging of the brain have been proposed (91).

1.3. Review of the literature

1.3.1. Diabetes and depression

Around 1684, Doctor Willis, who first identified glycosuria as a sign of diabetes, proposed that diabetes may be caused by “sadness or long sorrow (…) and other depressions” (92, 93). Psychiatrist Maudsley quoted in 1899 that “Diabetes is a disease which often shows itself in families in which insanity prevails; whether one disease predisposes in any way to the other or not, or whether they are independent outcomes of a common neurosis, they are certainly found to run side by side, or alternately with one another more often than can be accounted for by accidental coincidence” (93, 94).

Further, the term “diabetic personality” was introduced in 1935 by psychiatrist Menninger, suggesting clinical characteristics such as weakness, irritability, hypochondriasis and frequent mood swings, in particular depression, to characterize persons with diabetes (93, 95).

- **Impact of depression on diabetes**

In the more recent decades, a range of studies have underlined that comorbid depression increases the risk of adverse outcomes among persons with diabetes. Utilizing data from the World Health Surveys, Moussavi et al showed that the effect of combined depression and diabetes on decrements in health was interactive, suggesting an additional negative effect on health beyond that expected by adding the effects of the two disorders (96). Two recent systematic reviews have established an association between depression and impaired quality of life among persons with diabetes (97, 98). In particular, when symptoms of depression were present among persons with diabetes, generic quality of life (independent of any disease) and domain specific quality of life (on specific areas of functioning) were found to be mild to moderately reduced, while a severe reduction in diabetes specific quality of life was shown (97). The association between depression and diabetes specific quality of life has further been shown to persist after adjustments for gender, age, duration of diabetes, treatment regimen and socio-demographic status (99). In addition, depression has been associated with poorer self-care and nonadherence to diabetes treatment, especially pronounced for “patient-initiated behaviors” which can be considered most difficult to maintain (100-102). In a meta-analysis, the effect of depression was strongest for missed medical appointments, however, an association between depression and typically “patient-initiated behaviors” such as lack of adherence to diet, medication, exercise and glucose monitoring was also found (103).

A meta-analysis from 2001 of cross-sectional studies demonstrated an association between depression and a variety of complications to diabetes such as retinopathy, nephropathy, neuropathy, macrovascular complications and erectile dysfunction, effect-size ranging from small to moderate (104). Often cited, a prospective study with

data from older Mexican Americans not only confirmed an association between depression and complications among persons with diabetes type 2, it found evidence of both an interaction between depression and diabetes as well as a dose-response pattern were risk of macro and microvascular complications increased with increasing severity of depression (105). The results persisted after adjustments for sex, age, education and marital status, and in addition, similar results were found when disability and mortality were regarded as outcomes. Further, major depression was associated with 36% higher risk of macrovascular and 24% increased risk of microvascular complications after adjustments for prior complications, demographic, clinical and diabetes self-care variables in a cohort of persons with diabetes type 2 requited from primary care (106). The effect of depression on glycemic control measured as HbA1c are more contradictory. While an early meta-analysis of cross-sectional studies (107) and one prospective study (108) showed a significant association with small effect sizes, a recent prospective study was not able to show an association between depression and HbA1c, blood pressure and lipids among persons with diabetes (109). In addition, although a cross-sectional study reported an association between depression and glycemic control among persons using 3 or more injections of insulin daily, no association was found among persons treated with diet/exercise, oral antidiabetic agents or oral antidiabetic agents and 1-2 injections of insulin daily (110). Finally, in 2013, 3 different meta-analyses including slightly different studies all reported a hazard rate of all-cause mortality for depression comorbid to diabetes compared to diabetes with no depression of about 1.4-1.5 in the most adjusted models (111-113). This estimate is however in the range of estimates of excess mortality due to depression in the general population (114), suggesting no increased mortality due to depression among persons with diabetes relative to the non-diabetic population.

- **Risk factors for depression in diabetes**

In general, risk factors for developing depression among persons with diabetes are regarded as either diabetes-specific or shared with the general population. Analyzing data from HUNT 2 in a cross-sectional design, factors associated with depression

among persons with diabetes were shared with the non-diabetic population; female sex, low education, living alone, smoking, high BMI, physical inactivity and impairment as well as more than one somatic disease or complaint (115). Some of these findings have been confirmed in prospective studies. Physical impairments of daily activities, in addition to low health related quality of life, were associated with depression in a cohort of elderly persons with diabetes type 2 over 2 years follow up (116), while female sex, younger age and presence of comorbid conditions were associated with incident depression after 18 months follow up of a cohort of persons with diabetes (117). Further, female sex and low education, in addition to previous history of depression were found to predict incident depression over 2-3 years among persons with diabetes type 2 in primary care (118). Interestingly, in this latter study, baseline macro and microvascular complications as well as comorbidities did not predict incident depression. In a study with 5 year follow up of patients with diabetes, depression at baseline was the strongest predictor of depression at follow up (119), consistent with studies suggesting depression among persons with diabetes to have a chronic and recurrent course (118). After adjustment for depression at baseline, depression at follow up was associated with coronary procedures during follow up, number of diabetic symptoms (such as cold or numb hands or feets, polyuria, excessive hunger or thirst, shakiness, blurred vision or feeling faint or sleepy) and retinopathy at baseline, while no associations with HbA1c, nephropathy or macrovascular complications were found. Finally, two studies have shown a temporary increase in antidepressant use around time of diagnosis of diabetes (120, 121), suggesting that the burden of being diagnosed with diabetes is associated with increased risk of depression.

Few prospective studies have addressed whether the risk of incident depression among persons with diabetes varies according to groups of age. An inverse association between age and risk of incident depression was found in the sample of persons with diabetes type 2 aged 21-75 years followed for 18 months (117), while no differences in risk of incident depression was found between persons aged over or under 60 years of age in the sample of persons with diabetes aged 18 years or above followed for 5 years (119). Comparing risk factors for depression in cohorts of persons in their forties and

sixties, presence of diabetes has been found to predict depressive symptoms only among those in their forties (122). Nevertheless, a recent review of the epidemiology of depression and diabetes concludes that "the relationship between age and risk for depression in people with diabetes remains complicated and needs further exploration" (123).

- **Population based cross-sectional studies on the association between diabetes and depression.**

The first review attempting to assess the prevalence of depression among persons with diabetes was made by Lustman in 1983, simply to conclude that the prevalence of depression in diabetes remains unknown (124). By June 2014, at least 12 studies have estimated the risk of depression among persons with diabetes compared with the non-diabetic population using population based cross-sectional designs, in addition to studies included in 4 systematic reviews/meta-analyses. Overview of these is presented in **Table 1** (found after the references in main part of this thesis), with focus on risk according to age and gender. It must be underlined that Table 1 only aims at summarizing cross-sectional studies were diabetes is the main exposure and depression is the main outcome, therefore, one study by Holt et al from 2009 (125) and one by Golden et al in 2007 (126) both defining depression as exposure are not included in the table. Further, in the recent years, many studies in this field are prospective or even bidirectional (127-130), investigating the risk of developing incident depression among persons with diabetes relative to the non-diabetic population (15, 131), and vice versa, assessing the risk of incident diabetes among persons with depression relative to the non-depressed population (16, 132). The results of these studies are further discussed in section *5.2.4. Issues on causality* in the discussion of this thesis.

Even though some of the studies listed in Table 1 find no increased risk of depression among persons with diabetes (133-135), or no increased risk among men with diabetes (136), the majority of the studies support an association between diabetes and depression in the general population (115, 137-148). Often cited, the meta-analysis by Anderson et al in 2001 concluded that the presence of depression doubles the odds of

depression, and determined that the estimate did not differ according to sex, type of diabetes, clinical or community settings or method of assessment of depression (146). In 2006, a meta-analysis by Ali et al estimated a somewhat lower odds of 1.6 for depression among persons with type 2 diabetes (147), while yet another systematic review concluded that it was not possible to determine whether the prevalence of depression among persons with type 1 diabetes was increased relative to the population without diabetes due to a nonsignificantly increased OR of 2.36 (148). Further, the World Mental Health study assessing psychiatric diagnoses in a worldwide sample of about 85 000 persons found an even lower OR of 1.38 of major depression among persons with any type of self-reported diabetes compared to the non-diabetic population (141).

As discussed earlier, one recognizes that women have higher prevalence of depression than men in the general population. In the meta-analysis by Anderson, the OR of depression among persons with diabetes compared to the non-diabetic population were similarly increased among men and women (146), while the meta-analysis by Ali suggested that the increased risk of depression among persons with type 2 diabetes compared to the non-diabetic population was higher in males than females (147). Both men and women with type 1 diabetes had a higher risk of depression relative to non-diabetic men and women respectively, however, among persons with type 1 diabetes, women were found to have higher risk of depression compared to men (142). Although women with type 2 diabetes had increased risk of depression compared to women with normal glucose metabolism, no such association was found among men in the study by Adriaanse et al (136). In this study, with overlapping confidence intervals for the estimates presented for men and women, the authors claim statistically significant effect modification by sex, although no formal test for interaction gender-diabetes is presented. Interestingly, older men with previously undiagnosed diabetes type 2 had a reduced risk of depression compared to non-diabetic males, suggested to be explained by low awareness of both somatic and psychiatric symptoms (134).

The majority of studies investigating the risk of depression among persons with diabetes provide age-adjusted estimates, thus concealing potential variations in risk

according to age. Age-stratified risk estimates of depression are presented in the study by Egede et al, showing that persons with diabetes under the age of 65 years had a higher risk of depression than those ≥65 years, after adjustment for a range of covariates (138). After adjustment for diabetes and selected covariates, Osborn et al find a significant decreased risk of depression with increasing age from 40 years in the general population (144). To our best knowledge, no population based studies have investigated the age-group stratified risk of depression among persons with diabetes compared to the non-diabetic population.

1.3.2. Diabetes and migraine

Relative to the association between diabetes and depression, the association between diabetes and migraine has received little attention. In 1933, Critchley suggested an etiological classification of migraine, which interestingly also included a "dietetic type" of migraine (149). The impression that attacks of migraine could be precipitated by hypoglycemia has been supported by a few clinical studies (150, 151) and case-reports (152, 153), while another study suggested that persons both with and without established migraine could tolerate a high degree of hypoglycemia before a migraine attack is triggered (154). The first study suggesting a possible effect of diabetes of the clinical course of migraine was published in 1970 (151). Of 36 patients with both diabetes and migraine requited after an advertisement in a diabetic journal, 5 reported disappearing or greatly reduction of the migraine attacks after onset of diabetes, additional 5 participants reported a moderate reduction in severity and frequency of the attacks, while the remaining could not confirm any change in the clinical course of migraine after the onset of diabetes.

A few cross-sectional studies have investigated the association between diabetes and migraine in clinical samples. In 1984, cases with diabetes recruited from a diabetes outpatient clinic had lower age and gender adjusted prevalence of migraine compared with controls from a surgery unit (155). The prevalence was lower among the cases with diabetes in all age-groups, age ranging from 10-90 years. In contrast, among persons with non-insulin dependent diabetes aged 30-65 years also selected from a

diabetes outpatient clinic, as many as 61% filled the IHS criteria for migraine, compared to 15% among controls requited when attending periodic health examinations required for employment (156). Interestingly, compared to controls, the debut of migraine among the persons with diabetes in this study occurred at a higher age.

- **Population based, cross-sectional and prospective studies on the association between diabetes and migraine**

By June 2014, 10 population based studies have investigated the association between diabetes and migraine. An overview of these is presented in **Table 2** (found after the references in the main part of this thesis) showing that only the study by Aamodt (157) defined diabetes as the exposure while the remaining 9 studies defined migraine as the exposure. Only two of the studies had both diabetes and migraine as the exposure and primary outcome (157, 158), the rest presented results on the association between diabetes and migraine in secondary analyses. For the purpose of this overview, only the results regarding the association between diabetes and migraine are reported in Table 2. In addition to the studies listed in the table, one further population based study investigating the association between migraine and self-reported gestational diabetes is published, finding no increased risk of gestational diabetes among persons with migraine compared to persons without migraine (159).

In general, 5 of the studies found no association between diabetes and migraine in the general population (160-164), three studies report a positive association (165-167), while an inverse association between diabetes and migraine was evident in two studies (157, 158). Restricting the sample to participants in the Women Health Study, Kurth (161) and Burch (158) found no association and an inverse association among females, respectively. Only the case-control study by Bigal (166) reported the association stratified by gender, finding that relative to the controls, both males and females with migraine had increased risk of diabetes, possibly with a stronger effect among men than women (OR men: 1.75 (95% CI: 1.42, 2.16), OR women: 1.28 (95% CI: 1.10, 1.49)), although no formal test of interaction was presented.

While the studies showing no association between diabetes and migraine by Kurth (161), Fernandez-de-las Penas (163) and Le (164) presented crude estimates, not adjusting for age and gender, the crude estimates presented by Chuang (167) showed a positive association. Of these, the study by Kurth (161) included middle aged and older women, whereas Fernandez-de-las Penas (163) and Le (164) in addition included younger persons. The age-range included was not specified in the study by Chuang (167). The study by Davey (160) matching on age and gender reported no increased risk of being prescribed antidiabetic agents for persons with migraine relative to persons without migraine, neither the study by Bensenor (162) including persons from 65 years and adjusting for age found that the risk of diabetes differed by migraine status. On the contrary, including women from 45 years and adjusting for age in addition to lifestyle, use of medications, somatic conditions and family history of diabetes, Burch (158) showed that persons with migraine had a reduced risk of diabetes compared to non-migraineours in the baseline, cross-sectional analysis. Sillanpaa (165) found that the prevalence of diabetes was higher among adolescents with migraine compared to controls without migraine. Despite the contradicting results on the overall direction of the association in the studies by Aamodt (157) and Bigal (166), both suggested a possible trend with stronger associations in younger age-groups and weaker in the older age-groups. In particular, compared to the non-diabetic population, Aamodt (157) reported an overall decreased risk of migraine among persons with diabetes, strongest effect found among persons with type 1 diabetes. No interaction between diabetes and age was detected; however, a trend with lower prevalence of migraine among persons with diabetes in all age groups except for persons in their thirties was found. Further, the most reduced risk of migraine among persons with diabetes was found among those with highest HbA1c, leading the authors to speculate whether changes in vascular reactivity and nerve conduction associated with diabetes might have a protective effect on migraine.

2.0. Rationale and aims

Given the high prevalence of diabetes, depression and migraine in the Norwegian population, information on if and how depression and migraine are comorbid to diabetes can be useful in a public health perspective as well as for clinicians in the field of family medicine, endocrinology, psychiatry and neurology. Further, our understanding of the complexity of disorders in which the etiology and pathophysiology is not fully known can be improved by studying their comorbid conditions. Given the known positive associations found in population based studies between depression and diabetes, and depression and migraine, one could hypothesize that, despite the conflicting findings shown in the literature review, a positive association would also exist between diabetes and migraine. Further, we could not find any reason to expect the strength of the associations to vary substantially by age, possibly with the exception of weaker strength of the associations between diabetes and migraine at higher ages if duration of diabetes somehow reduces the sensation of migraine pain. The overall aim of this thesis was to describe how depression and migraine are associated with diabetes in a cross-sectional design in the Norwegian population.

Specific aims:

Paper 1: Investigate how the prevalence of medically treated depression varied according to antidiabetic drug treatment, sex and age in the complete Norwegian population.

Paper 2: Investigate how the association between diabetes and depression varied by presence and type of antidiabetic treatment in a large community based sample of middle-aged and older adults, and further study to which extent the association can be explained by known confounders.

Paper 3: Investigate how the prevalence of migraine treated with migraine agents varied according to antidiabetic drug treatment, sex and age in the complete Norwegian population.

3.0. Material and methods

3.1. The Norwegian Prescription Database (NorPD)

With legal authority in the "Regulation on the Norwegian Prescription Database" (168) and the "Personal Health Data Filing System Act"(169), NorPD was established 1st of January 2004 as a national health registry at the Norwegian Institute of Public Health (27). Until then, information on drug use in the population was only available at aggregated level from the Norwegian wholesale statistics on drugs, while no information at individual level was recorded. Main objectives of NorPD were to provide data to describe *individual* drug use patterns, surveillance of drug prescription for both doctors and authorities, and to promote research on safety and effectiveness of drug use, for instances with linkages to health surveys or other health registries (170-172).

The automated data flow into the NorPD is illustrated in **Figure 3**. When a patient collects a prescribed drug at the pharmacy, data is recorded via "NAF Data" and passed forward to the trusted third party center Statistics Norway (SSB). NAF Data is a company owned by the Norwegian Pharmacy Association which is accountable for the IT systems used at all Norwegian pharmacies. Due to encryption by NAF Data, SSB cannot read any of the prescription data except the patient's personal identification number and the prescriber's health personnel number. Both these numbers are replaced with a pseudonymised identifier, making NorPD the first pseudonymous health register in Norway. The tem "Pseudonymous health data" is defined according to the "Personal Health Data Filing System Act"(169) as "personal health data in which the identity has been encrypted or otherwise concealed, but nonetheless individualized so that it is possible to follow each person through the health care system without his identity being revealed".

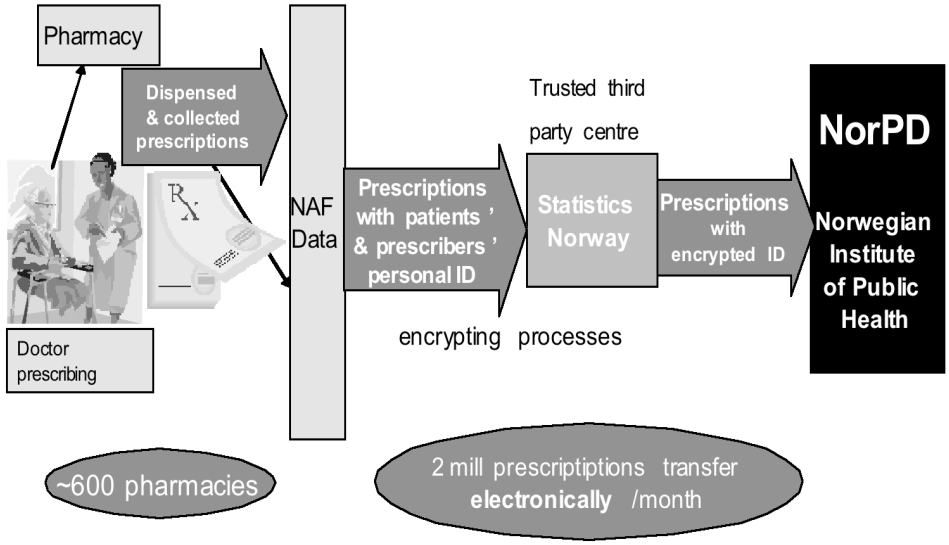

Figure 3: Automated data flow in NorPD. Reprinted with permission from Furu K: Establishment of the nationwide Norwegian Prescription Database (NorPD)- new opportunities for research in pharmacoepidemiology in Norway. Norwegian Journal of Epidemiology 2008; 18 (2): 129-136 (171).

Each record in the registry contains data on the following variables on individual patients receiving prescriptions in ambulant care: 1) *the patient* (encrypted person-identifier, date of birth and death, gender, place of residence), 2) *the prescriber* (encrypted person-identifier, data of birth, gender, profession, specialty), 3) *the drug* (Nordic article number (brand name, strength, package size), number of packages dispersed, ATC-code, Defined Daily Doses (DDD),code of reimbursement, dispensing data, price and free-text for information on area of application and dose), 4) *the pharmacy* (name, license number, location) (171). For patients residing in institutions (i.e. nursing homes and hospitals), information is still only available on aggregate level.

3.2. The Hordaland Health Study (HUSK)

HUSK is a population based health study undertaken in 1997 to 1999 in Hordaland County in the western part of Norway (173). The study was a collaboration between the University of Bergen, the Norwegian Health Screening Service (SHUS, now part of the National Institute of Public Health) and the local health service in Hordaland. The main objective of HUSK was to determine prevalence of diseases and its risk factors with special emphasis on cardiovascular and lifestyle factors in order to target preventive strategies at population level.

All persons born 1953-1957 who resided in Hordaland County on December 31, 1997 were invited to participate (n= 29400). In addition, 4849 persons born 1950-1951 and 4338 persons born 1925-1927 who had participated in a previous local health study (the Hordaland Homocysteine Study) in 1992-1993, were invited. Data collection was conducted in three steps, consisting of two sets of questionnaires and one brief physical health examination. The first questionnaire was included with a mailed personal invitation to take part in the study (copy of form in appendix of this thesis). Participation in HUSK was defined as signing the informed consent when attending the health examination at one of the local HUSK centers in their own municipality, at which height, weight, hip and waist circumference, blood pressure and a non-fasting blood sample was drawn. Participants were then given a second questionnaire to be returned by mail in a pre-paid envelope.

While 63% of the invited persons born 1953-1957 took part in the study, the participation rate in both the 1950-1951 and 1925-1927 cohorts were 77%, yielding a final sample of HUSK participants of 25232. Of these, about 87% returned the second questionnaire. Persons who did not meet at the examination or did not return the second questionnaire received one reminder by mail.

3.3. Methods

3.3.1. Design

All 3 studies included in this thesis have a population-based, cross-sectional design. This descriptive, epidemiological design utilizes data collection from *a predefined population* at one *specific point of time*. In paper 1 and 3, the population under study was the total Norwegian population in 2006. Information on all persons in living in Norway 1st of January 2006 was obtained from Statistics Norway, while information on number of persons receiving prescriptions of drugs included in our study during 2006 was obtained from NorPD. In paper 2, the study population was HUSK participants who gave their informed consent at the time of participation between 1997 and 1999.

3.3.2. Measures

Diabetes:

In paper 1 and 3, data on dispension of prescriptions of antidiabetic agents from NorPD was considered a proxy for diabetes. Antidiabetic agents were defined according to the ATC-classification system in 2006 as A10A (insulins) and A10B (oral antidiabetic agents) **(Table 3**, found after the references in the main part of this thesis**).** Persons were classified according to whether they had received at least one dispension of antidiabetic agents during 2006 in 1) no antidiabetic agents, 2) oral antidiabetic agents but no insulin (oral antidiabetic agents monotherapy), 3) insulin, but no oral antidiabetic agents (insulin monotherapy) and 4) combination of insulin and oral antidiabetic agents. Persons were classified regardless of prescribed doses of the medications, duration of treatment, other prescriptions received, and irrespective of information regarding the prescriber.

In paper 2, presence of diabetes was assessed with the item «have you or have you had diabetes? ». Persons answering affirmative were further classified according to self-reported use of type of antidiabetic treatment as 1) un-medicated diabetes (no use of antidiabetic agents), 2) orally treated diabetes (with or without use of insulin) and 3)

insulin treated diabetes (and no use of oral antidiabetic agents). Antidiabetic agents were defined according to the 1997 anatomical therapeutic chemical (ATC) classification system and includes agents categorized under A10A (insulins), A10B (metformin, glibenklamid, klorpropramid, glipizid, glucobay) and AX2 (glimeperid).

Depression:

In paper 1, data on dispension of prescriptions of antidepressant agents from NorPD was considered a proxy for medically treated depression. Antidepressant agents were defined according to the ATC-classification system in 2006 as N06A **(Table 3).** Persons were classified according to whether or not they had received at least one prescription of antidepressant agents in 2006. Again, persons were classified regardless of prescribed doses of the medications, duration of treatment, other prescriptions received, and irrespective of information regarding the prescriber.

Two measures of depression were used in paper 2; symptoms of depression during the last week assessed by HADS-d and self-reported use of antidepressant agents the day before completing the first questionnaire.

HADS was originally developed by Zigmond and Snaith in 1983 as a screening tool to determine both the presence and severity of anxiety and depression among patients in a non-psychiatric, general medical outpatient clinic (174). HADS consists of 14 four-point Likert-scaled items, 7 measuring symptoms of depression (HADS-d) and 7 measuring symptoms of anxiety (HADS-a). It is considered a convenient and easy to administer screening tool that takes only a few minutes to complete, and good case-finding properties for anxiety and depression has been shown among both psychiatric, somatic and primary care patients as well as in the general population (175).

HADS-d **(Table 4)** mainly covers anhedonia and loss of interest, symptoms regarded as "core depressive symptoms" (45). Items assessing features such as hopelessness, guilt and suicidal preoccupation are not included. As HADS originally was designed for symptom screening in hospital settings, it does not include items that may be attributed to somatic illness to reduce the likelihood of false-positive cases among

individuals with somatic diseases. Therefore, items assessing symptoms often associated with depression such as insomnia, anergia, fatigue, sleep and appetite disturbances are not included.

Table 4: The 7 items in the Hospital Anxiety and Depression scale, subscale depression:

Item	Item label
1	I still enjoy the things I used to enjoy
2	I can laugh and see the funny side of things
3	I feel cheerful
4	I feel as if I am slowed down
5	I have lost interest in my appearance
6	I look forward with enjoyment to things
7	I can enjoy a good book or radio or TV program

Responses are given on a four-point scale from 0 to 3. Items 1, 2, 3 and 6 are reversed before summation.

In paper 2, HADS-d was used as a dichotomous variable with cut-off level of ≥8 for "caseness of depression", which has been shown to yield a sensitivity and specificity of about 0.8 each (175) . To avoid misclassification of persons with recent depression now in remission due to treatment, we also classified persons reporting use of antidepressant agents the day before completing the questionnaire as depressed (52). Antidepressant agents were defined according to the 1997 ATC-classification system, and encompassed all agents categorized under N06A (including tricyclic and tetracyclic antidepressant agents, SSRI) and NX5 (SNRI). Three depression variables were computed based on these two depression measures: 1) HADS-d ≥8 (reference group: HADS-d <8), 2) use of antidepressant agents (reference group: no use of antidepressant agents) and 3) HADS-d ≥8 and/or use of antidepressant agents (reference group: HADS-d <8 and no use of antidepressant agents).

Migraine:

In paper 3, data on dispension of prescriptions of migraine agents from NorPD was considered a proxy for medically treated migraine. Migraine agents were defined

according to the ATC-classification system in 2006 as N02CA (ergotamines) and N02CC (triptans) **(Table 3).** Persons using clonidine (N02CX02) in monotherapy were not included as migraineours, as clonidine has a number of other indications in addition to migraine, and seldom is recommended as first-line treatment of migraine in monotherapy (176). Further, we did not include persons receiving medications used in prophylactic treatment of migraine, such as antiepileptic agents, beta-adrenoceptor blockers, angiotensin-converting enzyme (ACE) inhibitors, serotonin antagonists (pizotifen) and antidepressant agents, unless they also required ergotamines and triptans during 2006. Again, persons were classified regardless of prescribed doses of the medications, duration of treatment, other prescriptions received, and irrespective of information regarding the prescriber.

Covariates:

A factor is considered a confounder for an association if it is associated with both the exposure and outcome and further not expected to be on the causal pathway between them (50) (p 49). In study 1 and 3 we could only utilize information on sex and age in 10 year groups as possible confounders. Based on previous knowledge (130, 177, 178), we *a priori* selected musculoskeletal pain, smoking, body mass index (BMI), physical activity, alcohol consumption, education and cohabiting as possible confounders in paper 2. Weight (in kilograms) and height (in meters) were measured at the health examination, while self-reported information on other variables included in this study was obtained from the questionnaires. Musculoskeletal pain was defined as a history of painful and/or stiff muscles or joints of at least 3 months duration during the last 12 months. Smoking was categorized as "never", "former" and "current". Body mass index (BMI) was calculated as weight (kg)/height $(m)^{2,}$ and categorized as underweight (≤19.9), normal, (20.0-24.9), overweight (25.0-29.9) and obese (≥30). Information on light physical activity (no sweating or getting out of breath) and hard physical activity (sweating or getting out of breath) was reported as hours per week in four groups (none, ≤1, 1-2, and ≥ 3). No physical activity was given the value 1, ≤1hour value 2, 1-2 hours value 3, and ≥ 3 value 4, and a summary score of physical activity was computed multiplying the value of hard physical activity by two, and

adding light physical activity, yielding a continuous score ranging from 3-12. Alcohol consumption was defined as number of alcoholic units consumed per fortnight and categorized as ≤1, 2-5 and ≥6, as these values approximately corresponded to the tertiles of the distribution. Cohabiting was defined as being married or living with a partner, as opposed to being unmarried, widowed, separated or divorced. Highest achieved education was categorized as compulsory school only (up to ten years), high school and higher education (college or university).

3.3.3. Study samples

In paper 1, the study sample included all persons residing in Norway in 2006 aged ≥20 years (n= 3 434 233). In paper 3, the study sample included all persons residing in Norway in 2006, all ages (n= 4 640 219). In paper 2, we included persons who signed the informed consent (n=25532). The HADS-d subscale was included in the second questionnaire, and persons who did not return this form had to be excluded from the sample, as well as those responding to 4 or fewer of the 7 items assessing depression (n=3671(14.4%)). We further excluded 16 persons who reported a history of all six somatic conditions assessed in the first questionnaire (infarction, angina, stroke, diabetes, asthma and multiple sclerosis), as these persons were assumed to have misinterpreted the form. The final sample for paper 2 thus consisted of 21 845 persons, 85.6% of the total number of HUSK participants. Of these, 18948 were 40-47 years and 2897 were 70-72 years.

3.3.4. Missing data

Missing data refers to the situation were a person included in one of the study samples have missing data on some of the variables of interest for the study. The NorPD avoids the problem with missing data as the pharmacists are not able to complete the expedition of the dispension of the prescription without filling in the required information. Thus, the analysis in paper 1 and 3 were not challenged by missing data. Utilizing data from a health survey in paper 2, we had to handle missing data to reduce the magnitude of bias introduced. A total of 220 (1.0%) persons had missing responses on the question assessing diabetes. We classified these as not having diabetes. A total

of 128 (0.6%) persons had valid responses on 5 of the 7 items on HADS-d, while 2064 (8.3%) had valid responses on 6 of the 7 items. These persons were given imputed values based on the mean value of the non-missing responses. Missing values on any of the confounding factors were handled as follows in the final regression analysis: 1) imputed mean value on physical activity if valid response on the other item regarding this topic (n=784 (4.1%)), 2) missing as separate category on variable alcohol consumption (n=496 (2.6%)), and 3) exclusion of cases with otherwise missing values (n=321 (1.7%)).

3.3.5. Analyses

Descriptive statistics was used in all three papers. As a measure of 1-year prevalence, we estimated the number of persons with dispensions of prescriptions for insulin monotherapy, oral antidiabetic agents monotherapy, insulin and oral antidiabetic agents combined and for antidepressant agents (paper 1) and migraine agents (paper 3). In paper 2, Pearson Chi-square test and independent sample t-test were employed to test differences in distribution between the exposure (diabetes) and categorical and continuous covariates. P-value of ≤ 0.05 indicated significant different distributions between groups.

Logistic regression was in all three papers used to examine the association between exposure (diabetes) and outcome (depression or migraine). In paper 1 and 3, we estimated overall OR adjusted for sex and age group for receiving antidepressant agents (paper 1) and migraine agents (paper 3) for persons in all three treatment groups for diabetes. Effect estimates were given as OR with 95% confidence intervals. In addition, we estimated age-specific ORs adjusted for sex and sex-specific ORs adjusted for age. In paper 1 and 3, we estimated age-specific ORs for women and men separately. Test for age-diabetes interaction was performed in paper 3.

Although not a formal indication in Norway, metformin can additionally be used to treat polycystic ovarian syndrome (PCOS). In paper 1 and 3 we therefore performed sensitivity analyses excluding both men and women aged 20-39 years who received metformin in monotherapy. In paper 3, we conducted an additional sensitivity analysis

including only participants with 2 or more dispensions of antidiabetic and migraine agents.

In paper 2, stratified analyses by age groups were performed to examine the effect of diabetes on the three measures of depression. To test for possible differences in the effect estimate between age groups, we included an interaction term between age group and diabetes in the model. We then examined the association between the three different types of antidiabetic treatment and the three depression variables among persons aged 40-47 years. The final model examined the association between the three different types of antidiabetic treatment and depression defined as HADS-d ≥8 and/or use of antidepressant agents among persons aged 40-47 years. Presence of a statistical significant association between both diabetes and depression (defined as HADS-d ≥8 and/or use of antidepressant agents yesterday) were examined for the covariates selected a priori, and covariates with statistically significant associations with both diabetes and depression were considered as confounders and included in the final model

All statistical analyses were performed using SPSS, version 15 (paper 1 and 3) and version 20 (paper 2). An overview of the materials and methods employed in the three papers in this thesis are presented in **Table 5 (**found after the references in the main part of this thesis)**.**

3.4. Ethical considerations

As the information from NorPD is pseudonymous, and since we have only obtained data regarding sex, age and ATC-code for the prescriptions, we did not have to obtain permission from the Data Inspectorate or the Regional Ethics Committee for the studies in paper 1 and 3. The HUSK protocol was approved by the Regional Ethics Committee (REK) of Western Norway and by the Data Inspectorate. Participation in HUSK was voluntary, and written information about the survey was sent together with the personal invitation and the first questionnaire. Written informed consent was obtained from all participants at the time of the health examination, specifying that no specific time limit applied for storage of data. Copies of the permits from REK and the

Data Inspectorate as well as the consent statement are included in the appendix of this thesis.

4.0. Results

4.1. Paper 1

A total of 121 392 persons (3.5% of the Norwegian population ≥20 years) received minimum one dispension of prescriptions of antidiabetic agents in 2006. Oral antidiabetic agents were prescribed to 91 781 persons (2.7%), of these, 76 387 persons (2.2%) used oral antidiabetic agents in monotherapy, while 15 394 (0.4%) used the combination of insulin and oral antidiabetic agents. Insulin in monotherapy was prescribed to 29 611 persons (0.9%), antidepressant agents were used by 253 668 persons (7.4%). No major differences in prevalence of dispensions of antidiabetic agents according to gender were found (men: 65 231 (3.8% of the male population), women: 56 161(3.2% of the female population), while women had about twice as high prevalence of dispensions of antidepressant agents relative to men (men: 86 558 (5.1%), women: 167 110 (9.5%)). Prevalence of dispensions of both oral antidepressant agents, insulin and antidiabetic agents increased with age, particularly for antidepressant and oral antidiabetic agents used in monotherapy.

A total of 12.8% (n= 15 511) of persons using antidiabetic agents also received antidepressant agent, compared to 7.2% (n=238 157) in the rest of the population, yielding an age and gender adjusted OR of 1.53 (95% CI: 1.50, 1.56). Relative to persons not using the specific agent, OR of using antidepressant agents for persons receiving insulin in monotherapy, oral antidiabetic agents in monotherapy and the combination of insulin and oral antidiabetic agents were 1.47 (95% CI: 1.42, 1.53), 1.44 (95% CI: 1.41, 1.47) and 1.82 (95% CI: 1.80, 1.97) respectively. Women using antidiabetic agents had in general a higher risk of using antidepressant agents relative to men using antidiabetic agents, reflecting the sex differences in the general population. Stratified analysis on gender revealed no sex specific differences in risk (OR men 1.57 (95% CI: 1.53, 1.62), OR women 1.51 (95% CI: 1.48, 1.55). A formal test of an interaction between antidiabetic agents and sex gave a p-value of 0.75 (not reported in the paper).

The risk of using antidepressant agents among persons using antidiabetic agents varied by type of antidiabetic agents and age. Little (but still significant due to large numbers) variation in risk according to age was found for persons using insulin in monotherapy. Marked differences in risk by age were found for persons using oral antidiabetic agents, with an inverse association from age 30-39 years and upwards. A formal test of these differences by introducing the relevant interaction terms in the model gave $p<0.001$ for all interactions (not reported in the paper).

Stratifying on age-groups, the risk of using antidepressant agents was equally increased among men and women, with the exception of a higher risk of antidepressant agents' use among men aged 20-29 years using oral antidiabetic agents in monotherapy relative to women. However, when repeating the analyses excluding 2898 women and 716 men aged 20-39 years using metformin in monotherapy, no differences in risk by gender were found.

4.2. Paper 2

While 175 of 18 733 (0.9%) participants aged 40-47 years reported having diabetes, 178 of 2719 (6.5%) reported diabetes in the 70-72 year group. For persons aged 40-47 years, positive associations between diabetes and all 3 depression variables were found, while the corresponding associations were lower and did not reach statistical significance among persons aged 70-72. Differences in the OR's between the two age groups were not significant when evaluated by interaction terms in the model (≥ 0.05 for all measures of depression).

Compared to participants without diabetes, persons aged 40-47 years with un-medicated diabetes had an increased OR of 2.33 (95% CI: 1.07, 5.07) for use of antidepressant agents, while no association was found with HADS-d ≥ 8 and/or use of antidepressant agents. Oral treatment of diabetes was significantly associated with all three measures of depression, the strongest association found with use of antidepressant agents with an OR of almost five. No significant associations with any measure of depression were found for insulin treated diabetes.

For persons aged 40-47 years, all the *a priori* identified potential confounding factors were associated with depression defined as HADS-d ≥8 and/or use of antidepressant agents in the crude model. As the distribution of musculoskeletal pain, smoking and cohabiting did not differ significantly by diabetes status (p-level of 0.05), only BMI, physical activity, alcohol consumption and education were regarded as confounders for the association between diabetes and depression, and included in the final model.

Adjusting for BMI gave the strongest attenuation of the effect with a reduction of OR from 3.79 to 3.16 for orally treated diabetes and from 1.53 to 1.34 for un-medicated diabetes when investigating the associations between antidiabetic treatment and depression among person aged 40-47 years. An almost threefold increased OR of HADS-d ≥8 and/or use of antidepressant agents for persons in their forties with orally treated diabetes were found after adjustment for all identified confounders (OR 2.92 (95% CI: 1.48, 5.77)).

4.3. Paper 3

A total of 124 649 persons (2.7% of the total Norwegian population) received minimum one dispension of prescriptions of antidiabetic agents in 2006. Oral antidiabetic agents were prescribed to 91 934 persons (2.0%), of these, 76 526 persons (1.6%) used oral antidiabetic agents in monotherapy, while 15408 persons (0.3%) used the combination of insulin and oral antidiabetic agents. Insulin in monotherapy was prescribed to 32 715 (0.7%), migraine agents to 81 225 persons (1.8%). No major differences in prevalence of dispensions of antidiabetic agents according to gender were found, however, whereas almost 4 times more women than men were prescribed migraine agents (men 16746 (0.7% of the male population), women 64479 (2.8% of the female population)). While the prevalence of dispensions of all 3 groups of antidiabetic agents increased with age, the prevalence of dispensions of migraine agents reached a peak in age group 40-49 years**.**

A total of 1.2% (n= 1460) of persons using antidiabetic agents also used migraine agents, compared to 1.8% (79 765) in the rest of the population, giving an age and gender adjusted OR of 0.72 (95% CI: 0.68, 0.75). Relative to persons not using the

particular agents, OR of using migraine agents for persons receiving insulin in monotherapy, oral antidiabetic agents in monotherapy and the combination of insulin and oral antidiabetic agents were 0.61 (95% CI: 0.55, 0.68), 0.76 (95% CI: 0.71, 0.81) and 0.78 (95% CI: 0.68, 0.89) respectively. Women using antidiabetic agents had a higher risk of using migraine agents relative to men using antidiabetic agents, reflecting the sex-difference in the general population, but stratified analysis on gender revealed no sex specific differences in risk (OR men 0.71 (95% CI: 0.64, 0.79), OR women 0.72 (95% CI: 0.68, 0.76). A formal test of interaction gave a p-value of 0.48 (not reported in the paper).

Relative to the population not using antidiabetic agents, risk of receiving migraine agents decreased with increasing age for all types of diabetic treatment. Persons using oral antidiabetic medication, either in monotherapy or in combination with insulin, had in fact an increased risk of using migraine agents before age 40 years, whereas the risk was decreased from 50 years and above. Similarly, persons using insulin in monotherapy had an increased risk of using migraine agents up to 20 years; those aged 20-29 years had the same risk as persons no using antidiabetic agents, while a further reduction in risk was evident with increasing age. The variation in risk by age for overall antidiabetic drug treatment was significant when evaluated by interaction terms in the logistic regression model ($p<0.0001$). Similarly, using interaction terms in the logistic regression model confirmed significant variation in risk according to age for the three groups of antidiabetic treatments (p insulin monotherapy <0.0001, p oral antidiabtic agents monotherapy <0.0001, p combination insulin and oral antidiabetic agents <0.0001) (last three p-values not reported in the paper).

Repeating the analysis excluding 2898 women and 716 men aged 20-39 years using metformin in monotherapy gave minor changes in the risk estimates (data not shown).

5.0. Discussion

5.1. Methodological considerations

5.1.1. The material

Using data on dispensions of prescriptions from the nationwide, official NorPD as a proxy for disease in paper 1 and 3 limits the risk of *selection* and *recall bias*. While selection bias refers to systematic errors introduced when the participants included in a study are different with regard to exposure or outcome than the non-participants (50) (p 255), recall bias is a systematic error operating if differences in accuracy to remember and report exist with respect to the exposure or outcome (50) (p 208). As all inhabitants in Norway have uniform access to reimbursement, one can argue that the risk of selection bias due to economic reasons for not buying the prescribed medication is low. Nonetheless, we misclassify persons who either do not seek help from a physician and those who do not purchase the medication they prescribed as non-exposed. Further, if persons permanently residing in nursing homes in which use of medication is not registered at personal level have higher risk of the outcome than the persons not residing in nursing homes, our effect estimates might be an underestimation of the association for the whole population in the highest age groups. For example, if persons with diabetes permanently staying in nursing homes have equal prevalence of depression as persons with diabetes in the same age-group not living in institutions, our estimates of the association between diabetes and depression in this age-group are likely not biased due to lack of information on dispensed prescriptions at personal level. However, if persons with diabetes at institutions have higher prevalence of depression than persons with diabetes in the same age-group not residing in institutions, our estimates are likely an underestimation of the association in the total population. The impact of this bias is however likely limited, as the total number of long term beds in nursing homes in Norway equals about 34 000, corresponding to under 7% of the population aged 70 years and above in our study (179)**.** Finally, an obvious strength of using data from national registries is the large

sample size yielding high precision, reflected in the narrow confidence intervals of the effect estimates, as well as no bias introduced by missing values.

The strength of using data from HUSK lies in the extensive data collection from participants requited from a predefined, geographical area. A range of information on various aspects of health was obtained from each participant, thus enabling to control for potential *confounders*. Derived from the Greek word "*confundere"* translated as "mix together", confounding occurs when part or all of the association between exposure and outcome is accounted for by another factor. More formally, a confounder must be associated with both the exposure and outcome under study, and further not be expected to lie on the causal pathway between exposure and outcome (50) (p 49). Based on previous knowledge, we *a priori* selected possible covariates that could act as confounders for the association between diabetes and depression in paper 2, and if formally testing showed associations with both diabetes and depression, they were adjusted for in the final model. In contrast to a confounder, *a mediator* is expected to be an intermediate step on the pathway from exposure to outcome, and should not be adjusted for, as this can result in underestimation of the true association (50) (p 131). Consequently, we regarded cardio vascular diseases as a mediator, as we find it more likely that diabetes precedes cardio vascular diseases than the other way around. Nevertheless, we cannot exclude bias due to residual confounding, understood as confounding persisting after adjustments due to unmeasured or poorly measured confounding factors (50) (p216).

Despite a sample size of almost 22 000 participants in paper 2, the total number of persons reporting diabetes was limited to approximately 350, reflecting that the majority of participants were in an age-group with rather low expected prevalence of the disease. This implies a greater risk of *type 2 error* than in paper 1 and 3, understood as the error of failing to reject a false null hypothesis (50) (p 85). The finding of no statistical significant differences between type of antidiabetic treatment and risk of depression in paper 2 might be a result of such a type 2 error. The finding of fairly similar risk estimates for depression according to type of antidiabetic treatment for persons in their forties in paper 1 and 2, as well as significant differences

according to type of treatment in paper 1 further supports the assumption that type 2 error due to small sample size is operating in paper 2 .

Missing data on variables in surveys bias the result, and must be handled to reduce the impact of these biases. The 220 persons (0.1%) with missing on the item assessing diabetes were defined as non-exposed, since we found that may participants solely filled in the positive responses when browsing the data. A similar pragmatic approach was applied when handling missing on the covariates; however, we acknowledge that using "missing imputation" also could have been appropriate.

Finally, a modest overall participation rate of 66% might have introduced selection bias, threatening the *generalizability* of the study. Generalizability is referred to as the degree to which the results of a study may apply or be relevant to populations that did not participate in the study (50) (p 101). Persons receiving disability pension for mood and endocrine disorders had an increased risk of nonparticipation in HUSK relative to persons not receiving disability pension (180), while nonparticipants in HUNT 3 had higher prevalence of both diabetes and psychiatric disorders relative to the participants (181). If the nonparticipants with diabetes had the same prevalence of depression as participants with diabetes, our estimate of the association between diabetes and depression probably reflects the "true" value. However, possibly more likely, if the nonparticipants with diabetes had a higher prevalence of depression than the participants with diabetes, we have underestimated the strength of the association in the total population.

5.1.2. The validity of measures

Measurement validity can be defined as the degree to which a measurement measures what it sets out to measure(50) (p 251). We argue that in addition to self-reported measures, use of prescribed medication is in general a valid proxy for disease as the initiation of treatment with both antidiabetic, antidepressant and migraine agents requires personal examination by a physician. Nevertheless, the weaknesses with these measures of disease and possible impact of these limitations are addressed in the following sections.

- **Self-reported information on diabetes as a measure of diabetes**

Presence of diabetes was assessed by self-report in paper 2. A Dutch study comparing self-reported information on cardiovascular diseases and their risk factors with information in medical records, considered the "gold standard", concluded that self-reported diagnosis of diabetes is a valid measure of disease (182). On the other hand, the sensitivity of a self-reported diagnosis of diabetes has been found to be modest, ranging from 60-70% (183). If misclassification of persons with diabetes as non-diabetics is independent of caseness of depression, we likely underestimate the true associations between diabetes and depression. An underestimation of the association would also be the result if persons with diabetes reporting depression are more likely to be misclassified as non-diabetics compared to participants with diabetes and no depression.

- **Antidiabetic agents as a measure of diabetes**

The strength of using dispensions of prescriptions of antidiabetc agents registered in NorPD as a proxy for diabetes has been acknowledged by several authors (26, 184). As shown in table 1 in paper 3, the majority of persons using antidiabetic agents in Norway received 4 or more prescriptions in 2006, suggesting a reliable measure of disease over time. The main limitation is the lack of information on diagnoses, making it difficult to draw firm conclusions on whether a person suffers from diabetes type 1 or 2. Still, we argue that persons using oral antidiabetic agents most likely are diagnosed with diabetes type 2, and that younger persons using insulin in monotherapy are expected to suffer from diabetes type 1. It is more difficult to infer any diagnostic information on type of diabetes for those using insulin in monotherapy aged 40 to 50 years and above. They might have been diagnosed with type 1 diabetes earlier in life, or they could suffer from type 2 diabetes responding best to insulin.

Although not a formal indication in Norway, metformin in monotherapy can be used in treatment of polycystic ovarian syndrome (PCOS). To avoid misclassification of these persons as diabetics, we performed sensitivity analysis excluding both men and women using metformin as the only antidiabetic agent in age group 20-39. While the

result of this sensitivity analysis did not differ substantially from the main analysis in paper 3, the higher risk of using antidepressant agents found for men aged 20-29 years compared to women in paper 1 were no longer evident when excluding those using metformin in monotherapy from the analysis. This suggests that women aged 20-29 years using metformin in monotherapy had a lower risk of using antidepressant agents compared to men using antidiabetic agents, and further supports the assumption that they suffer from another condition with lower expected prevalence of depression than diabetes.

Even though our prevalence estimates of diabetes presented in paper 1 and 3 from 2006 are in line with estimates from HUNT 2 undertaken in 1997-1999 (2), we clearly misclassify persons with lifestyle regulated diabetes as non-diabetics. Unpublished data from HUNT 3 (2006-2008) estimates the prevalence of known diabetes to 4.1% from 20 years and upwards (32), while we estimated the prevalence of medically treated diabetes to 3.5% in the same age-groups in 2006. The Norwegian Diabetes association recons that about 30% of persons with type 2 diabetes use no antidiabetic treatment (185), an estimate based on a study of about 5800 patients with diabetes requited from Norwegian general practice in 2006-2007 (186). If patients with lifestyle regulated diabetes have the same prevalence of migraine as the non-diabetic population in paper 3, it can be calculated that our misclassification of about 30% of patients with type 2 diabetes as non-diabetics would lead to an underestimation of the risk of migraine among persons with diabetes, changing the crude OR of migraine from 0.69 to 0.78. On the other hand, if we postulate that patients with lifestyle-regulated diabetes have the same prevalence of migraine as those treated with antidiabetic agents, our misclassification would give only a slight underestimation of the OR in the total diabetic population. Persons with un-medicated diabetes had a non-significantly increased risk of depression compared to the non-diabetic population in paper 2, suggesting that the bias introduced in paper 1 due to misclassification did not affect the overall effect estimate for the association between diabetes and depression to a large extent. However, if the persons with un-medicated diabetes in paper 1 had the same risk of depression as the persons using antidiabetic agents, this misclassification would lead to an underestimation of the true association. Finally, we obviously also

misclassify persons with undiagnosed diabetes in all three studies. Most likely, this has not biased the estimates in paper 1 and 2, as a recent meta-analysis showed no increased risk of depression for persons with undiagnosed diabetes relative to the persons with normal glucose metabolism (187).

- **Antidepressant agents as a measure of depression**

Using antidepressant agents as a proxy for depression has important limitations, and further illustrates the challenges when attempting to measure psychiatric disorders in the general population. Persons with depression do not necessarily receive antidepressant drugs. We therefore misclassify persons with depression who do not recognize their illness, those who do not agree with the diagnosis or refuse to purchase agents even if prescribed, and persons solely receiving psychological treatment. This implies a reduced sensitivity of our measure of depression. Further, if the physician decides that a psychological intervention is most likely too demanding in addition to treatment of the diabetes, one could further speculate that persons with diabetes could be more likely than non-diabetics to be prescribed antidepressant agents as the same level of "depressive symptom load". Such possible differential misclassification could imply that our estimates of the association between diabetes and depression in paper 1 are likely higher than the true association. Antidepressant agents are indicated in treatment of chronic neuropathic pain, anxiety disorders, post-traumatic stress and bulimia, reducing the specificity of our measure of depression. However, many of these disorders are often comorbid to depression (53, 188). To lessen the impact of this reduced specificity and sensitivity, we included persons from 20 years and above, as it is generally recommended to be particularly restrictive with pharmacological treatment of depression in children and adolescents (189). In spite the limitations when using antidepressant agents as a proxy for depression, our prevalence estimates of depression of 7.4 % in 2006 is in line with estimates 12 months prevalence of major depression of 7.3% in the largest psychiatric epidemiological study of adults in Norway undertaken in 1994-1997 (55). Finally, more than 80% of the persons using antidepressant agents in our study received more than one dispension during 2006, suggesting a reliable measure over time (data not reported in the paper).

- **HADS-d as a measure of depression**

A recent systematic review on screening tools for depression among persons with diabetes found that HADS-d was frequently used in screening for depressive symptoms in diabetes (190). The authors argued that due to the exclusions of items that could be confounded with symptoms of poorly regulated diabetes, HADS-d was likely more valid in diabetic populations than other commonly used screening tools for depression. Nevertheless, HADS is not a diagnostic interview, and use of HADS-d with cutoff ≥8 can only indicate possible cases of depression. In general, screening tools measuring symptoms of depression tend to give a high rate of "false positive" cases, overestimating the prevalence of depression in the population under study (190). This would only bias our estimates in paper 2 if persons with diabetes are more likely than persons without diabetes to be misclassified as depressed. To reduce the likelihood of such bias, we performed additional analyses using HADS-d with cutoff ≥11, however, the number of persons in each subgroup were too small to give meaningful and precise effect estimates (data not shown). Further, we performed an analysis with the outcome depression defined as mutually exclusive groups in 1) HADS-d ≥8 and no antidepressant agents, 2) antidepressant agents and HADS-d <8, 3) HADS-d ≥8 and antidepressant agents. Again, the number of persons in each group was too small to give meaningful and precise effect estimates (data not shown)**.** To reduce the risk of misclassifying persons with depression in remission due to medical treatment at the time of participation, we defined the dependent variable in the final regression analysis as HADS-d ≥8 and/or use of antidepressant agents. However, we could not avoid misclassifying persons with depression now in remission due to psychotherapeutic treatment.

As discussed under the section *"3.3.2. Measures/depression"* in this thesis, HADS-d has been found to have good case finding properties for depression among both psychiatric, somatic and primary care patients, as well as in the general population (175). Nevertheless, we are not aware of studies of measurement validity in populations with solely elderly persons, and the assumption of sensitivity and specificity of 0.8 each for caseness of depression in the general, adult population might

not be justified in our sub sample of persons aged 70-72 years. An investigation of factor structure, item analyses and internal consistency of HADS using data from about 50 000 participants HUNT 2 found that the internal consistency of the depression subscale measured by Cronbach's α was fairly equal across different groups of age (whole sample: 0.76, age 60-79: 0.75, 80+: 0.73) (191). Importantly, as the Cronbach's α is a measure of the correlation between items in the scale, these results only suggest that the correlation between items are fairly consistent across age groups, and not necessarily that the scale measure what it sets out to measure also in an elderly population.

- **Migraine agents as a measure of migraine**

Similarly, the assumption that use of migraine agents can be used as a proxy for migraine in paper 3 must be considered with caution. Persons receiving migraine agents most likely suffer from migraine, and 65% of the persons using migraine agents in 2006 received more than one dispensed prescription (table 1, paper 3), arguing against low disease activity among our "cases" of migraine. Even though ergotamine and triptans also are indicated in treatment of cluster headache, the prevalence of cluster headache in the Norwegian population is low at approximately 0.1% (79) (p 209). Theoretically, this can reduce the specificity of our measure. Clearly, we misclassify persons with migraine who can control the headache sufficiently with "over the counter" medication or those who successfully use prophylactic treatment. According to a population based study on prevalence of migraine in the US in the late 1990s, about 50% of the migraine suffers reported to use medications that required a prescription to terminate the migraine attack (192). Obviously, this reduced sensitivity of our measure of disease results in an underestimation of the prevalence of "overall" migraine in the population.

Of possibly greater concern is that the finding of an inverse association between migraine and antidiabetic agents could be a result of *confounding by indication,* defined as a type of confounding that occurs when a symptom or sign of a disease is judged as an indication or contraindication for a given therapy, and is therefore

associated both with the intake of the drug and a higher probability of an outcome (50) (p 50). Cardiovascular diseases and age ≥65 are relative contraindication for use of triptans. As it is reasonable to assume that persons with diabetes have a higher risk of cardiovascular diseases relative to persons without diabetes, the finding of an inverse association, particularly with increasing age, between use of migraine and antidiabetic agents could be a result of confounding. The majority of persons using migraine agents in the study in paper 3 used triptans, and only approximately 5% of the persons receiving migraine agents in this study used ergotamine as the only migraine agent (data not shown in the paper). However, when conducting a sensitivity analysis repeating the analysis presented in table 2 in paper 3 with ergotamine in monotherapy as outcome, we found a similar trend with a reduced risk with increasing age, as well as a significantly reduced risk of use of ergotamine for persons using insulin in monotherapy, oral antidiabetic agents in monotherapy and the combination therapy among persons aged 60-69 years relative to persons not using the specific agents (data not shown). We therefore argue that it is less likely that the finding of an inverse association between antidiabetic and migraine agents is a result of confounding by indication.

5.1.3. The design and analyses

Diabetes was chosen as the exposure in all three studies as it is a systemic disease manifesting in a range of organs systems. Nevertheless, defining depression and migraine, respectively, as the exposure would not markedly have changed the interpretation of the results due to the cross-sectional design. Studies with population based cross-sectional designs are useful to investigate the prevalence of conditions, as well as associations between conditions. Though, as the exposure and outcome under study are measured at the same point of time, this design is not suitable to determine the temporal sequence between the exposure and outcome. Further, if persons with diabetes are more often seen by physicians than the non-diabetic population, they might have a higher risk of being diagnosed with other conditions, such as depression and/or migraine. Such possible differential misclassification could imply that our estimates of the associations are higher than the true associations.

In studies with prevalent outcomes, defined as a prevalence of outcome in the unexposed group exceeding 10%, the OR can be problematic to use as a measure of risk, as the OR tends to overestimate the RR (193). This represents a limitation of the interpretation of the results in paper 2, as a total of 11.7% of the non-diabetic population in this study had HADS-d ≥8 and/or use of antidepressant agents (table 1, paper 2).

5.2. Discussion of the specific results

5.2.1. Risk of depression and migraine in diabetes by sex

Even though women with diabetes had in general a higher risk of receiving both antidepressant (paper 1) and migraine agents (paper 3) compared to men with diabetes, stratified analysis on gender revealed no sex specific differences in risk of depression and migraine, respectively. This finding was also evident in paper 2 (data not shown in the paper). Only one of the identified studies on the association between diabetes and migraine presented gender stratified estimates, suggesting that the increased risk of diabetes among persons with migraine possibly was higher in men than in women (166). Conflicting results regarding risk according to gender were found when reviewing the literature on diabetes and depression. The meta-analysis from 2000 by Anderson et al found that the odds of depression in a mixed sample of both type 1 and 2 diabetes were equally increased in men and women compared to the non-diabetic population (146), while an association between diabetes type 2 and depression was only evident among women in a more recent study by Adriaanse (136). The meta-analysis by Ali et al estimating risk of depression among persons with type 2 diabetes relative to the non-diabetic population found higher estimates among men than women (147), however, the authors advised these results to be interpreted with caution as they were based on a subsample of only 4 studies. We found no sex specific differences in risk of depression when stratifying on type of antidiabetic treatment (insulin monotherapy, oral antidiabetic agents monotherapy and the combination of insulin and oral antidiabetic agents) (results not reported in the paper), suggesting that the conflicting results in the literature was not a result of different types of diabetes

included. Given the methodological limitations of our studies, we find it reasonable to conclude that existence of sex specific differences in risk of depression and migraine among persons with diabetes relative to the non-diabetic population is minor.

5.2.2. Risk of depression in diabetes by presence and type of antidiabetic treatment

As discussed in section *5.1.2 Methodological considerations/ The validity of measures*, a clear limitation of all three studies in this thesis is the lack of diagnostic information on type of diabetes, and the assumption on type of diabetes based on type of antidiabetic treatment must be made with caution. For example, in paper 2, we assume that persons with self-reported diabetes who do not disclose using antidiabetic agents yesterday have un-medicated diabetes, understood as a type 2 diabetes sufficiently regulated with lifestyle interventions (termed lifestyle regulated diabetes in paper 1 and 3). Studies investigating the association between depression and un-medicated diabetes have yielded conflicting results. Though a prospective study using diagnostic codes from a national health insurance database found increased risk of affective disorders for persons with un-medicated diabetes relative to those using antidiabetic agents (194), results from both the prospective Nurses' Health Study (130) and the cross-sectional Pathways Epidemiologic Study (109) suggested a fairly equally increased risk of depression for persons with dietary or orally treated diabetes. Further, cross-sectional analyses in the Multiethnic Study of Atherosclerosis found no association between depression and un-medicated diabetes (126), a result in line with our finding of a non-significantly increased risk of depression for persons with un-medicated diabetes when compared with the non-diabetic population (OR 1.53 (95% CI: 0.89, 1.61)). A further weakness of our results in paper 2 is caused by the utilization of relatively old data. The indications for timing of treatment with different antidiabetic agents might have changed the last 15 years. As much as 55% of persons with diabetes included in paper 2 did not use antidiabetic agents, in contrast to the estimated 30 % by the National Diabetes Association, suggesting that in particular the results regarding risk of depression in un-medicated diabetes are not necessarily valid today.

Relatively few studies have investigated a possible association between diabetes type 1and depression. The systematic review by Barnard et al from 2006 did not show a significantly increased risk of depression in persons with type 1 diabetes compared to the non-diabetic population, although the overall OR was estimated to 2.4 (148). Later, an approximately 50 % increased risk of depression defined as HADS-d ≥8 among persons with type 1 diabetes has been shown by Engum using cross-sectional data from HUNT 2 (115), while a doubled risk of using antidepressant agents and a more than three times increased risk of clinically significant depressive symptoms defined as Beck Depression Inventory score above 14 was found in the study by Gendelman (142). Though not significant, the finding of a gender adjusted OR of 1.26 for depression in persons with insulin treated diabetes relative to the non-diabetic population aged 40 years in paper 2 is in fairly in line with the findings from paper 1, with a gender adjusted OR of depression for persons treated with insulin in their forties of 1.55. It must be noted that in paper 1, we estimated the risk of depression for persons exposed to the specific agents, such as insulin, compared to those who were not exposed to that specific agents, and not relative to persons exposed to no antidiabetic agents. If we had compared the risk of depression among persons using insulin in monotherapy relative to persons not using antidiabetic agents in paper 1, the effect estimates would have been slightly lower.

We found the highest risk of depression among persons using oral antidiabetic agents. Persons in their forties using oral antidiabetic agents irrespective of use of insulin had the highest risk with a gender adjusted OR of 3.79 in paper 2, whereas those using the combination of insulin and oral antidiabetic agents in paper 1 had the highest age and gender adjusted OR of 1.82 as well as a gender adjusted OR of 3.41 in age-group 40-49 years. If we assume that in general, persons using oral antidiabetic agents suffer from diabetes type 2, the age and gender adjusted OR of 1.44 for persons using oral antidiabetic agents in monotherapy and 1.82 for persons using both insulin and oral antidiabetic agents presented in the first paper are in agreement with the most recent systematic review and meta-analysis on risk of depression among persons with type 2 diabetes (OR: 1.6 (95% CI: 1.2, 2.0) (147).

Theoretically, persons using antidiabetic agents might have increased risk of depression due to effect of the antidiabetic agent itself. However, we find not support for this hypothesis in the literature and find it further no evidence that such effect would act markedly different according to different age groups. Severity of the disease might be more plausible explanation of our finding of a "gradient" in risk of depression according to type of treatment. Persons with un-medicated diabetes might be considered having a "mild" type of disease, and had no statistically significant increased risk of depression in age-group 40 years in paper 2. Further, one could argue that younger persons using the combination of insulin and oral antidiabetic agents (paper 1) suffer from a more "severe" form of diabetes, explaining the highest OR in this group.

5.2.3. Risk of depression and migraine in diabetes by age

In all three papers in this thesis, the risk of depression and migraine among persons with diabetes varied considerably by age. Although the differences in the OR's between the age group 40-47 and 70-72 years did not reach statistical significance when evaluated by interaction terms in the logistic regression model in paper 2, we found a higher risk of both depression (paper 1 and 2) and migraine (paper 3) among younger persons with diabetes relative to the older persons with diabetes. This finding underscores the importance of estimating age-specific estimates when investigating the associations under study. It is tempting to suggest that the previously conflicting results presented in the literature review on the risk of migraine among persons with diabetes could be a result of different age-groups included and/or not presenting age stratified estimates. For example, both studies in this review including persons from early adulthood and providing age-stratified estimates found a trend with increased strength of the association in lower age groups and weaker associations at higher age (157, 166). Similarly, the differences in risk according to age could at least partly be expected to explain the variation in strength of the association between diabetes and depression evident in the literature review. However, this variation could also be a result of different methods of assessment of both diabetes and depression. Anyhow, it is interesting that the highest estimate for this association was found in a study

including persons with type 2 diabetes in their thirties and forties with an OR of about 3.4 (143).

One can only speculate why the risk of depression and migraine among persons with diabetes varies by age. The finding of weaker associations in higher age groups could be a result of selective mortality, suggesting that individuals with both diabetes and depression/migraine have higher mortality than persons with diabetes only. An argument against this is that persons with depression clearly have increased mortality relative to the non-depressed population (114), effect sizes in range with the increased mortality shown for persons with diabetes and depression when compared with persons with diabetes only (111-113). Further, we find it less likely that selective mortality can explain the finding of a reduced risk of migraine among older persons with migraine, as a recent meta-analysis concluded that presence of migraine was not associated with either all cause, cardiovascular or coronary mortality (195).

Alternatively, one could speculate if an influence of diabetes on the sensation of migraine pain could, at least to some extent, explain our finding of an overall invers association between diabetes and migraine as well as an age stratified inverse association from about 50 years. As illustrated in Figure 2 in section *1.2.1. Diabetes* in the background of this thesis, neuropathy is a well-known microvascular complication to diabetes. Although the distal symmetrical polyneuropathy often associated with pain is the most frequent neuropathy among persons with diabetes, involvement of the central nervous system in diabetic neuropathy has also been suggested (196), possibly reducing the perception of pain as well as cerebrovascular reactivity. As poorly controlled diabetes increases the risk of complications (197), the finding from the cross-sectional study by Aamodt in which high HbA1c was associated with reduced risk of migraine among participants with diabetes is in line with this hypothesis (157). Interestingly, there is also evidence of an inverse association between various measures of blood pressure and migraine (198), often ascribed to a phenomenon called hypertension-associated hypalgesia. According to this phenomenon, stimulation of the baroreflex arch by high blood pressure can inhibit transmission of pain at several levels, such as the brainstem and peripheral baroreceptors (199). Finally, as the risk of

migraine in the general population decreases with increasing age, our finding of a further decreased risk of migraine among persons with diabetes from about 50 years of age could lead to speculations whether presence of diabetes somehow is associated with acceleration of the general aging process.

One could further hypothesize that the higher risk of both depression and migraine among younger and middle aged persons with diabetes relative to the non-diabetic population could be explained by the known comorbidity between depression and migraine (85, 86, 88). This scenario corresponds to "association" nr 3 under "true associations" presented in Figure 1 in the background of this thesis under *1.1. Comorbidity*, picturing "X" as diabetes and "A" and "B" as depression and migraine, respectively. We have previously shown that the increased risk of using migraine agents for persons using oral antidiabetic agents aged 20-39 years was fairly equal when stratifying on additional use of antidepressant agents, arguing against the hypothesis that the increased risk of migraine in young persons treated with oral antidiabetic agents could be explained by comorbid depression (200).

Instead, one could speculate if shared etiology could explain the findings of positive associations in the general population up to 50 years of age between both diabetes and migraine and diabetes and depression, the latter association even after adjustments for identified confounders. A possible example of such shared etiology is exposure to "stress" in childhood and adolescence, defined in a broad sense as "a stimulus judged to be a threat which is unmanageable", often considered to be forms of parental maltreatment and socioeconomic disadvantage (201). Persons exposed to various forms of stressors early in in life have been found to be more prone to develop chronic diseases, such as diabetes (202, 203). Similarly, as reviewed in the background of this thesis, adverse childhood advents, experiences of loss and low socioeconomic status are regarded risk factors for depression (46, 57), while low socioeconomic status and no vocal education has been associated with increased risk of incident migraine (78, 81). Further, prospective studies on the association between depression and incident migraine has suggested that the association to a large extent can be explained by stress (89, 204), supporting the hypothesis of stress acting as common etiologic factor.

Another example of a factor possibly representing shared etiology is obesity, as it is regarded as one of the most important risk factors for development of diabetes type 2 (17)(p 24) (3)(p 23), associated with increased risk of depression in prospective studies (18), and further associated with migraine in cross-sectional studies of middle-aged adults (82, 83). Hypothesizing that shared etiology to some extent could explain the finding of increased risk of both migraine and depression among younger and middle aged persons with diabetes relative to the non-diabetic population resembles, with some modifications, "association" nr 4 under "true associations" presented in Figure 1 in the background. If "X" is understood as "stress" or "obesity", "A" as migraine, "B" as depression and "Y" as diabetes, the arrow from "X" to "Y" must be unidirectional, while the arrow from "Y" to "B" should be bidirectional in order to be in line with this hypothesis.

5.2.4. Issues on causality

Are diabetes and depression causally associated, e.g. does diabetes *cause* depression? And similarly, does diabetes have a *protective* effect on migraine, as suggested in the title of paper 3? These questions can obviously not be addressed by our studies with cross-sectional designs. However, the literature illuminating various aspects of the association between diabetes type 2 and depression are extensive, and some of it relevant in this regard. On the contrary, the literature on the association between diabetes and migraine, and more specific, diabetes type 1 and depression are sparser, limiting the discussion on causality for these associations. In 1965, Sir Bradford Hill suggested a list of considerations which could be useful in determining whether an association is observed due to causation, concerning amongst others *consistency, strength, specificity, dose-response relationship, temporal relationship and biological plausibility* (205), often referred to as *Bradford-Hills criteria of causation* (50) (p116).

Two recent meta-analyses have investigated whether presence of diabetes type 2 increases the risk of depression in a prospective design (15, 131). Even though the *strength* of this association is not very large, they suggest fairly *consistent* results with an OR of 1.24 and 1.29, respectively, for incident depression among persons with

diabetes type 2 relative to persons without diabetes. No association between type 1 diabetes at baseline and incident depression was found in a prospective study using data from HUNT (177), while the results from this study regarding the positive associations with type 2 diabetes are included in both of the meta-analyses (15, 131). Interestingly, the association between diabetes type 2 and depression is considered to be bidirectional, as suggested by at least 3 additional meta-analyses (16, 127, 132). Furthermore, a recent systematic review and an additional meta-analysis suggest that use of antidepressant agents per se is associated with increased risk of developing type 2 diabetes (206, 207).This bidirectionality is not necessarily an argument against a *temporal relationship* for the association between diabetes and incident depression. However, due to the often naturally fluctuating course of depression challenging the measurement of the disease as described in the background of this thesis, it can be difficult to determine the onset of the first episode, possibly threatening the validity of the assessment of onset of the diseases and therefore also the temporal relationship between them.

Unfavorable lifestyle factors such as obesity and low physical activity associated with diabetes might, at least in part, account for some of the increased risk of incident depression. Nevertheless, the two meta-analyses presenting "most-adjusted" estimates both found a significant increased risk in these models (15, 127), arguing against these factors fully explaining the association. Further, some *biological plausible* hypotheses have been suggested to explain the association. In brief, increased activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) as well as the inflammatory systems has been demonstrated both among persons with diabetes and depression (208). It must be emphasized that these biological alterations cannot be regarded as *specific* for diabetes and depression, but most likely rather represents a measure of general disease activity or "stress".

If a *dose-response relationship* existed between the glucose disturbances *per se* and depression, one should expect an increasing risk of depression and/or more severe symptoms of depression with increasing levels of serum glucose. Although a recent meta-analysis found a weak, but significant association between depression and insulin

resistance (209), this study has been criticized for large heterogeneity and for including single studies with subjects with type 2 diabetes, possibly contributing to, or even explaining the association found (210). Further, a recent meta-analysis suggested no increased risk of depression in persons with undiagnosed diabetes and impaired glucose metabolism compared to persons with normal glucose metabolism (187), while others have found no increased risk of depression among persons with diabetes after adjusting for number of comorbid conditions (115, 139, 140). As the risk of depression additionally was found to increase with number of diabetes-specific complications in a clinical sample of persons with type 2 diabetes attending a specialized outpatient clinic (211), it might be more likely that the increased risk of depression found for persons with diabetes is not *specific* to diabetes, but rather indicates an increased risk of depression associated with some measure of severity of disease.

Increasing risk of depression with increasing number of comorbid somatic diseases relative to the population without the somatic disorders has been shown in a cross-sectional epidemiological study including patients with cancer, musculoskeletal, cardiovascular and respiratory tract diseases (212). Likewise, using data from the HUNT 2 study, cross-sectional associations between self-reported somatic disorders and depression were found for a range of conditions, such as musculoskeletal and cardio vascular disorders, stroke and migraine (213). Interestingly, the only somatic disorder not being associated with depression in this study was diabetes, however, an association with comorbid depression and anxiety was found. Furthermore, similar to the association between diabetes and depression, there is evidence that a bidirectional association between depression and somatic disorders also exist in prospective studies. A study from Canada showed an increased risk of depression at 2 year of follow up among persons with long term medical conditions relative to those without (214), whereas both mental illness and more specifically, major depression, has been associated with increased risk of incident somatic diseases at 10 and 8 years of follow up, respectively (215, 216).

5.2.5. Future perspectives

Regardless of the distinction between psychiatric and somatic disorders, if the presence of one disease increases the risk of falling ill from a second disease, our finding of an overall inverse association between diabetes and migraine is particularly interesting. One step further in order to determine whether diabetes has a protective effect on migraine would be to investigate a possible *temporal relationship* in a prospective design. If preliminary analysis showed sufficiently statistical power, one could compare incident cases of migraine among persons with diabetes relative to incident cases of migraine among persons without diabetes in a prospective design between HUNT 2 and 3, as this survey probably have one of the most valid measures of both diabetes and migraine in a large cohort. Ideally, if sufficient power, the effect estimate should be stratified on age groups, however, overall estimates adjusted for age and gender should also be presented, in addition to adjustment for some measure of socioeconomic status. To investigate whether the possible inverse association could be due to higher blood pressure among persons with diabetes relative to the non-diabetic population, additional analyses adjusting for measures of blood pressure should be performed. Finally, it would be interesting to study if a possible invers *dose-response relationship* existed between HbA1c and incident migraine among persons with diabetes at HUNT 2, as a further argument for possible causality.

As illustrated in this thesis, the association between depression and diabetes type 2 is extensively studied, both in cross-sectional and prospective designs, while considerably fewer studies have investigated the association between depression and diabetes type 1. Associations between baseline diabetes type 1 and incident depression in a prospective design has, to our best knowledge, only been studied in data from HUNT 1 and 2, finding a non-significantly increased risk of incident depression among participants with diabetes type 1 relative to the non-diabetic participants (OR crude model 1.75 (95% CI: 0.83, 3.67)) (177). In order to determine whether this non-significant finding is due to *type 2 error*, one could conduct a prospective cohort study with data from NorPD to investigate incident dispensions of antidepressant agents among persons using insulin in monotherapy at a defined baseline (such as one or two

years after the establishment of the registry in 2004), relative to persons not using insulin in the same period.

6.0. Conclusion and implications

Using cross-sectional data from the Norwegian Prescription Registry and Helseundersøkelen i Hordaland, we have shown that persons with diabetes have an increased risk of depression and a decreased risk of migraine treated with migraine agents relative to persons without diabetes. Paper 1 demonstrated that persons using antidiabetic agents had overall age and gender adjusted OR of about 1.5 of using antidepressant agents relative to persons not using antidiabetic agents. While the highest risk of using antidepressant agents was found for persons in their thirties using oral antidiabetic agents with an OR of about 4.5, this increased risk decreased with increasing age to about 1.5 among persons aged 70 years and upwards. Persons using insulin in monotherapy had less variation in risk according to age, OR ranging from 1.7 for persons in their fifties to 1.3 among persons aged 70 years and upwards. This finding of a high risk of depression among middle aged persons with diabetes relative to the non-diabetic population was confirmed in paper 2. After adjustments for gender, BMI, physical activity, alcohol consumption and education, persons with diabetes in their forties using oral antidiabetic agents still had an OR of 2.9 for depression defined as symptoms and/or antidepressant treatment of depression. No significant associations between depression and un-medicated diabetes or insulin treated diabetes were found.

We did not find support for the hypothesis of an overall positive association between diabetes and migraine. A positive association between migraine treated with migraine agents and medically treated diabetes was only found for persons using insulin in monotherapy under 20 years of age and for persons using oral antidiabetic agents up to 40 years in paper 3. In contrast, persons with medically treated diabetes had an overall reduced risk of migraine treated with migraine agents relative to the non-diabetic population (age and gender adjusted OR: 0.72). Stratifying on age-group and type of antidiabetic agents, we found that the risk decreased with increasing age to about the same reduced risk (OR: 0.4-0.6) for persons aged 60-69 years using insulin monotherapy, oral antidiabetic agents monotherapy and the combination of insulin and oral antidiabetc agents.

No sex-specific differences in risk were found in either paper 1 or 3, while the finding of a substantial variation in risk of both depression and migraine treated with migraine agents by age shown in all three papers was not expected. One could speculate if the finding of the highest risk of the outcome among middle-aged persons with diabetes could, to some extent, be explained by shared etiology. Even though the literature argues against selective mortality explaining our finding of a lower risk of the outcome among older persons with diabetes, we cannot exclude this effect, at least partly, explaining the differences in risk according to age.

Additionally, an overall inverse association between diabetes and migraine as well as a decreasing risk with increasing age could reflect an effect of presence of diabetes over time, inferring with the sensation of pain. If this finding is confirmed in prospective studies, it might provide clues on a possible relation between migraine and neuropathy. Nevertheless, regardless of possible explanations, we believe that our findings of variations in risk of depression and migraine among persons with diabetes according to age can be valuable for clinicians, as a supplement to other factors known to be associated with risk of depression and migraine in the general population. Given the anticipated increasing life expectancy, it is further interesting to find the highest risk of comorbidity between these prevalent and disabling diseases among middle-aged adults. If possible preventive strategies to reduce the prevalence and impact of depression comorbid to diabetes are considered in the general population, one should first consider targeting middle-aged adults with diabetes type 2.

7.0. Errata

Paper 1: Page 512: “Only 4% of those receiving oral antidiabetic agent in our study used metformin in monotherapy”. Correct number should be 47%. In age-group 20-39 the corresponding number is 76%.

Paper 3: Page 129:” As low prevalence of migraine in this later study was also associated with poorly regulated and long-lasting diabetes”, should be replaced with “As low prevalence of migraine in this later study was also associated with poorly regulated diabetes,”

Paper 3: Reference 12 “Midthjell K, Kruger O, Holmen J, Tverdal A, Claudi T, Bjorndal A, et al. Rapid changes in the prevalence of obesity and known diabetes in an adult Norwegian population. The Nord-Trondelag Health Surveys: 1984-1986 and 1995-1997. Diabetes care. 1999;22(11):1813-20” (2) should be replaced with “The DECODE Study group: Age and sex specific prevalence of diabetes and impaired glucose regulation in 13 European Cohorts. Diabetes Care 2003, 26, 61-69“ (217).

Throughout paper 1 and 3, we have used the term “prescription(s)” as a synonym for “dispensed prescription(s)”. To solely use the term “prescription” is imprecise, as a person can be prescribed a certain agent without being dispensed the medication from the pharmacy. Therefore, the phrase “dispension of precriptions” was used in the main text of this thesis.

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Tables

Author/Journal/ Year	Materials and study sample	Exposure	Outcome	Results	Other
Kruse Diabetes Care 2003	The German National Health Interview and Examination Survey (GNHIES), including data from a national representative sample of approximately 4200 persons aged 18-65 years.	Self-reported and physician verified diagnosis of diabetes (interviewed regarding medications, symptoms and clinical parameters). N (both type 1 and 2 diabetes)=141	Mental disorders, screening with CID-s. Screen positive and 50% of screen negative underwent CIDI, including affective, anxiety, somatoform and substance abuse/dependence disorders.	Relative to persons without diabetes, crude OR for affective disorders among persons with diabetes was 1.73 (95% CI:1.01, 2.96), while no significant association after adjustment for age, sex, socioeconomic and family status was found.	In the total sample, female gender, increasing age and diabetes and HbA1c <7% (in contrast to diabetes and HbA1c >7%) were associated with affective disorders. No significant crude associations between diabetes and 1) any mental disorder 2) somatoform disorder and 3) substance abuse/dependence.
Egede Diabetes Care 2003	National Health Interview Survey (NHIS), including a random sample of about 31000 nonmilitary and noninstitutionalized persons aged ≥18 years	Self-reported diabetes N (all types of diabetes) =1800	Major depressive disorders, assessed by CIDI-SF	Prevalence of major depressive disorders among persons with diabetes was 9.3% compared to 6.1% among persons without diabetes.	Main aim of the study was to investigate independent factors associated with major depressive disorders in persons with diabetes, which among others was: age <64 years (compared to age ≥65 years) and female sex.
Engum Diabetes Care 2005	The second Nord-Trøndelag Health Study (HUNT 2), including about 60000 persons ≥20 years.	Diabetes initially assessed by self-report. Persons reporting diabetes received a diabetic specific questionnaire and had a fasting blood sample analyzed for glucose, C-peptic, and anti-GAD antibodies. N (type 1 diabetes)=223. N (type 2 diabetes)=958.	Depression, assessed by HADS-d (cut-off ≥8).	Prevalence of depression among persons with type 1 and 2 diabetes were 15.2% and 19.0% respectively, both estimates significantly higher than the prevalence of 10.7% in the non-diabetic population.	Relative to persons without diabetes, crude OR of depression among persons with a) type 1 diabetes and chronic somatic diseases (CSD) b) type 2 diabetes with CSD and c) type 2 diabetes without CSD were 2.21 (95% CI: 1.41, 4.36), 2.93 (95% CI: 2.44, 3.52) and 1.47 (95% CI: 1.00, 2.16) respectively. Adjusted for age, sex, marital status, education, smoking, physical activity, BMI, somatic complaints and physical impairment, only persons with type 2 diabetes and CSD had increased OR of depression (OR 1.38 (95% CI: 1.10, 1.74)) compared to persons without diabetes.
Das-Munshi Psychosomatic Medicine 2007	The National Psychiatric Morbidity Survey in Great Britain (UK NPMS), including about 8600 persons aged 16-74 years	Self-reported information on diabetes obtained at interview, and/or self-reported use of antidiabetic mediciation. N (all types of diabetes) =249	Common mental disorders (CMD) assessed by CIS: 4 mutually exclusive categories of depression, anxiety, comorbid anxiety and depression and mixed anxiety and depression (MADD)(i.e.: symptoms of both anxiety and depression is present, but neither set of symptoms considered separately is sufficient severe to justify a diagnosis).	No significant association between diabetes and depression. Relative to persons without diabetes, increased odds of MADD (OR 1.8 (95% CI: 1.1, 1.26)) and CMD (OR 1.5 (95% CI: 1.1, 2.2) were found after adjustments for age, gender, ethnicity and socioeconomic status. These associations were no longer significant after adjustments for impairment in activities of daily living.	Among persons with diabetes, female gender was associated with CMD (2.1 (95% CI: 1.1, 4.3), while no significant differences according to age were found. No differences in risk of CMD according to type antidiabeti c treatment (insulin, oral antidiabetic agents or unmedicated).
Knol Psychosomatic Medicine 2007	The Utrecht Health Project (UHP), including about 5000 persons ≥18 years.	Persons reporting a physician diagnosis of diabetes were defined as "diagnosed diabetes" (N=102). The remaining participants were categorized according to their fasting plasma glucose (FPG) concentration in 1) normal FPG (<5.6 mmol/l) 2) impaired FPG (5.6-7.0 mmol/l, n=671) and 3) undiagnosed diabetes (≥7.0 mmol/l, n=55). Excluding persons using insulin and no oral antidiabetic agents, regarded as type 1 diabetes (n=14).	Symptoms of depression assessed by SCL-90, subscale depression (cut-off ≥ 25), and/ use of antidepressant agents (irrespective of depressive symptom score).	Relative to persons with normal FPG, persons with diagnosed diabetes had a crude OR of 1.79 (95% CI: 1.17, 2.75) for depression. This association persisted after adjustment for gender, age, education, BMI, smoking, alcohol consumption and physical activity. After adjustment for chronic diseases, no association was found.	Relative to persons with normal FGP, persons with impaired FPG and undiagnosed diabetes had no increased risk of depression.
Lin Journal of Psychosomatic Research 2008	The World Mental Health Surveys, including about 85 000 persons from 17 countries in all continents, age ≥18 years.	Self-reported information on diagnosis of diabetes given by a doctor or health professional (all types) Weighted sample, number of persons with diabetes not reported.	1) Anxiety disorders, 2) Mood disorders and 3) Alcohol abuse or dependence assessed by WHO CIDI.	Relative to the non-diabetic population, persons with diabetes had a pooled OR of 1.38 (95% CI: 1.15, 1.66) for depression after adjustment for age and gender, while OR of anxiety was 1.20 (95% CI: 1.01, 1.42). No association between diabetes and substance abuse or dependence was found.	The pooled estimate for the association between diabetes and depression was significant, although only the surveys with participants from Germany and Mexico had a significant OR ≥1.
Icks Diabetic Medicine 2008	The Heinz Nixdorf Recall Study, including about 4600 persons aged 45-75.	Diabetes defined as interview reported diagnosis of diabetes and/or use of antidiabetic agents. Undetected diabetes defined as no reported diabetes /use of antidiabetic agents and either fasting blood glucose ≥7.0 mmol/l or random s-glucose ≥11.1 mmol/l. Type 1 diabetes excluded. N (known type 2 diabetes)=352. N (undetected diabetes)=428.	Symptoms of depression assessed by CES-D short form (cut-off ≥15).	Relative to the non-diabetic population, both women and men with known diabetes and women with undetected diabetes had no increased risk of depressive symptoms (crude and adjusted models). Men with undiagnosed diabetes had a age adjusted reduced risk (OR 0.30 (95% CI: 0.13, 0.70)), persisting even after adjustment for comorbidities, depression-inducing medication (beta blockers, reserpine, immune modulators, corticosteroids), BMI, smoking, activity level, cohabiting and education.	
Adriaanse Diabetic Medicine 2008	Follow up from the population based Horn Studiy, including 550 persons aged 50-75 years.	Diabetes type 2 (DM2) defined as using antidiabetic treatment or fasting s-glucose≥7.0 mmol/l or ≥11.1 mmol/l 2h post oral glucose tolerance test. Impaired glucose metabolism (IGM): fasting s-glucose ≥6.1 mmol/l and ≥7.8 mmol/l 2h post oral glucose test. N (DM2)= 126. N (IGM) =164.	Symptoms of depression assessed by CES-D (cut-off ≥16).	Relative to the non-diabetic female participants, women with DM2 had an increased risk of depression in the all models (adjusted for age, education and either 1) cardiovascular risk factors, 2) cardiovascular diseases or 3) diabetes symptoms, OR crude estimate 3.18 (95% CI: 1.31, 7.74). Women with IGM had increased risk of depression in all models, except nr 3 (adjusting for diabetes symptoms). Relative to non-diabetic male participants, men with DM2 or IGM had no increased risk of depression.	Claims statistically significant effect modification by sex of the associations under study (data not shown).
Gendelman	Case-control study: about 500 participants with	Diabetes type 1 (method of assessment no	Symptoms of depression assessed by the	Relative to the non-diabetic group, person with type 1 diabetes had age	Relative to men without diabetes, men with diabetes had

Diabetes Care 2009	type 1 diabetes included in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study compared to 500 non-diabetic controls who were friends/spouses/neighbors of the participants. Age 20-55*	reported). N (diabetes type 1)=500.	BDI-II (cut-off >14) and/or use of antidepressant agents.	and sex adjusted OR of 3.66 (95% CI: 2.35, 5.71) for BDI-II>14, and OR of 1.99 (95% CI: 1.39, 2.84) for use of antidepressant agents.	significant higher prevalence of depression defined as 1) BDI-II and 2) BDI-II and/or antidepressant agents. Relative to women without diabetes, women with diabetes had significant higher prevalence of depression defined as 1) use of antidepressant agents, 2) BDI-II and 3) BDI-II and/or antidepressant agents. Among persons with diabetes, women had significant higher prevalence of depression defined as BDI-II and/or antidepressant agents, compared to men.
Aujla Plos One 2009	Participants attending a diabetes screening program recruited from general practitioners in England . Including total 6000 persons aged 25-75 years with no known diagnosis of type 2 diabetes.	Diabetes type 2 (DM2) and impaired glucose regulation (IGR) defined according to the WHO diagnostic criteria (DM2: fasting glucose ≥7.0 mmol/l, and/or 2 h glucose ≥11.1mmol/l, IGR: Impaired fasting glycemia: fasting glucose 6.1-6.9 mmol/l and/or impaired glucose tolerance (2 h glukose 7.8-11.0 mmol/l). N (DM2)= 198. N (IGR)= 855.	Symptoms of depression assessed by WHO-5 Wellbeing Index (cut-off ≤ 13).	Relative to persons which screen normal glucose tolerance, no increased risk of depression was found among persons with newly diagnosed DM2 or IGR in crude models or models adjusted for ethnicity, age, gender, exercise, smoking, BMI, waist circumference and level of deprivation.	
Gale Biological Psychiatry 2010	Random sample of paticipants in The Vietnam Experience Study of about 43000 men, age range from 31-49 years **	Diabetes type 2 defined as fasting glucose ≥7.0 mmol/l, self-reported physician diagnosis of diabetes or use of antidiabetic agents. In non-diabetic participants, impaired fasting glucose (IFG) were defined as fasting glucose between 5.6-6.9 mmol/l. N (diagnosed type 2 diabetes) = 46. N (undiagnosed type 2 diabetes) = 182. N (IFG) = 492.	Depression assessed by DIS and MMPI	Compared to men with normal fasting glucose, men with undiagnosed and a known diagnosis of diabetes scored about 5% (1.7, 8.3) and 11% (4.7, 17.6) higher on the MMPI depression scale after adjustments for age and ethnicity, while no differences in score were found for men with IFG. Compared to men with normal fasting glucose, men with undiagnosed and a known diagnosis of diabetes had higher OR of a diagnosis of depression assessed by DIS of 1.67 (95% CI: 0.99, 2.81) and 3.39 (95% CI: 1.54, 7.43) adjusted for age and ethnicity respectively. No increased risk was found for men with IFG.	
Osborn Annals of Behavioral Medicine 2011	The Southern Community Cohort Study, a population based study including about 66 000 persons aged 40-79 years.	Diabetes assessed by self-report. N (all types of diabetes)= 14279	Symptoms of depression assessed by CES-D, and scores categorized as mild (10-14), moderate (15-19) and severe (≥20) depression.	Relative to the non-diabetic population, persons with diabetes had higher risk of mild (1.15 (95% CI: 1.09, 1.21)), moderate (1.17 (95% CI: 1.10, 1.25)) and severe depression (1.24 (95% CI: 1.14, 1.34)), adjusted for demographic and lifestyle factors, BMI, and use of antidepressant use.	No crude estimates are given.
Reviews/meta-analysis:					
Gavard Diabetes Care 1993 (review)	Identified 20 studies, of which 9 included a non-diabetic control group. Participants requited from both clinical and community settings. Age ≥18 years. N controlled studies approximately 24 000.	Persons with a diagnosis of diabetes categorized as insulin dependent diabetes (IDMM) or non-insulin dependent diabetes (NIDDM). Method of assessment not reported. N (IDDM+NIDDM in controlled studies) = 1434.	Diagnosis or symptoms of depression. Of the 9 controlled studies, 4 used a structured diagnostic interview (DIS-DSM-III, PSE, CIS) while 5 used depression symptom scales (BDI, Zung SC Scale and CES-D (used with different cut-offs in different studies).	Increased prevalence of a diagnosis or symptoms of depression among persons with diabetes compared to controls was found in 8 of 9 studies. Prevalence of a diagnosis of depression in controlled studies ranged from 8.5% to 27.3%, with a mean prevalence of 14.0%.	Due to large variability in method of assessment of depression, no meta-analysis could be performed. One of the controlled studies using a structured diagnostic interview found that women with diabetes had significant higher prevalence of depression than men with diabetes. No estimates of prevalence of depression among persons with diabetes compared with the prevalence of depression in the non-diabetic population stratified by sex.
Anderson Diabetes Care 2001 (meta-analysis)	Identified 42 studies, of which 20 included a non-diabetic control group. Participants requited from both clinical and community settings. Age ≥18 years. N controlled studies approximately 18500.	Persons with a diagnosis of diabetes categorized as type 1 diabetes (N= 261), type 2 diabetes (N=877) and mixed sample (N=1765). Method of assessment not reported.	Diagnosis or symptoms of depression. Of the 20 controlled studies, 7 used a structured diagnostic Interview (PSE, DIS, CIS), while 13 used depression symptom scales (BDI, GDS (geriatric depression scale), Zung, BDI (used in different studies with different cut-offs), CES-D (used in different studies with different cut-offs)	Compared to non-diabetic subjects, persons with diabetes have an OR of 2.0 (95% CI: 1.8, 2.2) for depression. The estimate did not differ according to sex, type of diabetes, where participants were requited from and method of assessment of depression.	Compared to non-diabetic subjects, odds of depression was equally increased in both type 1 (OR 2.9 (95% CI: 1.6, 5.5) and type 2 diabetes (2.9 (95% Ci: 2.3, 3.7)). Seven studies reported effect estimates stratified by gender. The odds of depression among persons with diabetes compared to the non-diabetic population were similarly increased among women (OR: 1.7 (95% CI: 1.4, 2.0) and men (OR: 1.7 (95% CI: 1.4, 2.2).
Ali Diabetic Medicine 2006 (systematic review and meta-analysis)	Identified 10 controlled studies. Persons requited from both clinical and community settings. Age≥18 years. N approximately 51 000.	Persons with a diagnosis of type 2 diabetes. Diabetes defined according to WHO diagnostic criteria, self-report, physician diagnosis or through review of patients medical records. N (diabetes type 2) = 18445.	Diagnosis or symptoms of depression. 6 studies used depression symptom scales (GDS, CES-D, BDI, Zung), 3 studies used diagnostic interview (DIS-DSM-III, DIS-(DSM)-IV, DSM-IV), and one used information from patient notes.	After excluding one study due to heterogeneity, the OR of depression for persons with type 2 diabetes compared to non-diabetics was 1.6 (95% CI: 1.5, 1.7).	Higher prevalence of depression was found among women both with and without diabetes compared to men. The increased risk of depression among persons with diabetes compared to the non-diabetic population was higher in men (OR: 1.9 (95% CI: 1.7, 2.1)) than in women (1.3 (95% CI: 1.2, 1.4)).
Barnard Diabetic Medicine 2006 (systematic review)	Identified 14 studies, of which 4 included a non-diabetic control group. Persons requited from clinical settings. Age ≥18 years. N total controlled studies approximately 2750.	Diabetes type 1, method of assessment not reported. N (diabetes type 1) = 511.	Diagnosis or symptoms of depression. Of the 4 controlled studies, 3 used a diagnostic interview (DIS-DSM-III, PSE, CIDI, DIMD-SF), one used depression symptom scales (BDI)	Weighted mean prevalence of depression in controlled studies was 12.0% among persons with diabetes type 1 compared to 3.2% in the control population. Excluding the study using symptom scale, persons with type 1 diabetes had an OR of 2.36 (95% CI: -0.69, 5.4) compared to the control population.	Concludes that it is not possible to determine if the prevalence of depression is increased in persons with type 1 diabetes compared to the non-diabetic population.

CID-s: Composite International Diagnostic Screener. CIDI-SF: Composite International Diagnostic Interview, short form. CIDI: Composite International Diagnostic Interview. CES-D: Center for Epidemiologic Studies Depression Scale. HADS-d: Hospital Anxiety and Depression Scale, subscale Depression. CIS: Clinical Interview Schedule. SCL-90: Symptom Check List. BDI: Beck Depression Inventory Scale (first version). BDI-II: Beck Depression Inventory (second version). DIS-DSM-III: Diagnostic Interview Schedule for Diagnostic and Statistical Manual of Mental Disorders, third etidition. DIS-(DSM)-IV: Diagnostic Interview Schedule for Diagnostic and Statistical Manual of Mental Disorders, fourth edition. PSE: Present State Examination. CIS: Clinical Interview Schedule. Zung SC Scale: Zung Self-Rating Depression Scale. GDS: Geriatric Depression Scale. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition. DIMD-sf: Diagnostic Interview for Mental Disorders-short form.. WHO-5: World Health Organization-Five Wellbeing Index. MMPI: Minnesota Multiphasic Personality Inventory.

*age range according to http://clinicaltrials.gov/show/NCT00005754

**age range according to Batty et al; IQ in late adolescence/early adulthood, risk factors in middle age and later all-cause mortality in men: the Vietnam Experience Study. Journal of epidemiology and community health, 2008; 62: 522.531.

Table 1: Population based cross-sectional single studies and reviews/meta-analyses on the association between diabetes and depression, with focus on age and gender.

Author/Journal/Year	Materials and study sample	Exposure	Outcome	Results	Other
Sillanpää Functional Neurology 2000	Prospective cohort study of school children from 7 years of age in Finnland. N= 2000.	Migraine, defined according to Vahlquist criteria*	Diabetes, among other comorbid conditions.	Cross-sectional baseline results of children aged 15 years: Compared to adolescents without migraine, adolescents with migraine had a higher risk of diabetes.	No effect estimates on the association between diabetes and migraine are given.
Davey British Journal of General Practice 2002	Matched case-control study with data from General Practice Research Database, a national anonymous database covering about 6% of residents in England and Wales. Including approximately 65 000 pairs, matched on age and sex.	Migraine, defined as physician diagnose and/or prescription of migraine agents. N= 65 000.	Primary outcome: Asthma, chronic obstructive pulmonary disease, respiratory symptoms and hay fever, defined as physician diagnose and/or relevant medical therapy. Secondary outcome (among others): prescription of anti-diabetic agents.	Compared to controls without migraine, persons with migraine had no increased risk of being prescribed anti-diabetic agents (RR: 0.94 (95% CI: 0.87, 1.01)).	With the exception of anti-diabetic agents, persons with migraine had increased risk of being prescribed all other agents included in the study (medication to treat spasms, ulcers, eczema and acne/rosacea as well as diuretic, antidepressant, antiepileptic, antibacterial, antifungal, antiviral medication)
Kurth JAMA 2006	Prospective cohort study of women aged ≥45 years participating in the Women's Health Study. Baseline in 1992-1995, follow up in 2004. N= 278000.	Migraine, assessed by self-reports. N=5125.	CVD, assessed by self-report.	Cross-sectional baseline analysis: No difference in prevalence of diabetes between persons with out without migraine	
Aamodt European Journal of Neurology 2007	Cross-sectional study with data from Head-HUNT. Age ≥20 years. N = 51 000.	Diabetes, initially assessed by self-reports. Persons with self-reported diabetes were given a diabetes specific questionnaire and had a blood-sample analyzed for HbA1c, anti-GAD and c-peptide. (for classification of type 1, LADA or 2 diabetes) N (all types) =1499. N (type 1 diabetes) =179. N (type 2 diabetes) = 870.	Migraine, defined as self-report of diagnosis or meeting 3 criteria: 1) duration of pain: 4-72 hours, 2) minimum one of the following characteristics: pulsating, unilateral, aggravation by physical activity and 3) during attack: nausea, photophobia or phonophobia. Headache not meeting these criteria was classified as non-migraneours headache.	Compared to persons without diabetes, persons with diabetes have a reduced risk of migraine, after adjustments for sex, age and education. OR type 1 diabetes: 0.4 (95% CI: 0.2-0.9), OR type 2 diabetes: 0.7 (95% CI: 0.5, 0.9). Unadjusted prevalence of migraine was lower among persons with diabetes in all age groups except for persons aged 30-39 years. No significant interaction between diabetes and age.	Persons with diabetes and HbA1c ≥6.6% had reduced OR of migraine compared to persons with diabetes and HbA1c ≤6.6
Bensenor Cephalalgia 2010	Cross-sectional study with data from the Sao Paulo Ageing and Health Study (SPAH), age ≥65. N= 1450.	Migraine, information on symptoms assessed by headache questionnaire based on the 2004 IHS criteria. N=165.	Cardiovascular risk factors, including diabetes. Diabetes defined as fasting blood glucose ≥126 mg/dl and/or use of hypoglycemic oral insulin.	Compared to persons without migraine, persons with migraine had no increased risk of diabetes. Crude OR: 1.26 (95% CI: 0.87, 1.83). Adjusted for age, sex, BMI, smoking, alcohol, income; OR: 1.19 (95% CI: 0.81, 1.76).	
Bigal Neurology 2010	Case-control study with data from in the American Migraine Prevalence and Prevention (AMPP) study, a sample representative of the US population. Age ≥18 years. N= 11300.	Migraine, information on symptoms assessed by questionnaire and classified according to the ICHD criteria. N= 6102.	Primary outcome: self-reported medical diagnosis of cardiovascular events (MI, stroke, and claudication). Secondary outcome: risk factors for CVD, including diabetes.	Compared to controls, cases with migraine had an overall increased risk of diabetes (OR: 1.39 (95% CI: 1.23, 1.57).	Compared to controls, both males and females with migraine had increased risk of diabetes (OR males: 1.75 (95% CI: 1.42, 2.16), OR females: 1.28 (95% CI: 1.10, 1.49). OR stratified by groups of age: Possibly trend for increased strength of the association in younger age-groups, decreased in older age-groups, although most likely not significant differences (overlapping CI).
Fernandez-de-las-Penas Journal of Headache and Pain 2010	Cross-sectional study with data from the 2006 Spanish National Health Survey (SNHS). Age ≥16 years. N= 29500.	Migraine, assessed by self-reports. Persons classified as migraineours if they confirmed suffering from migraine the last 12 months and had the diagnosis migraine confirmed by a neurologist. N= 3433.	Diabetes (amongst others), assessed by self-report.	Compared to persons without migraine, persons with migraine have no increased risk of diabetes, crude OR 1.07 (95% CI: 0.88, 1.30).	
Le Cephalalgia 2010	Cross-sectional study with data from Twin Omnibus 2002, including twins born 1931-1982 enrolled in the Danish Twin Registry. Study participants regarded as a random sample from the Danish population. Age ≥20 years. N=32000.	Migraine, assessed by self-report. N= 8044.	30 pre-defined somatic conditions, including diabetes. Assessed by self-report.	Compared to persons without migraine, persons with migraine had no increased risk of diabetes, crude OR: 0.95 (99.9% CI: 0.71, 1.28).	No increased risk of migraine when stratifying on gender. Overall, 21 of 30 conditions were more prevalent among persons with migraine compared to persons without migraine.
Burch Caphalalgia 2012	Prospective cohort study with data from Women's Health Study. Mean follow up 14.6 years. Age ≥45 years. N= 38600.	Migraine (self-reported), stratified in active migraine with aura, active migraine without aura and past history of migraine. Active defined as migraine the last 12 months. N= 7149.	Incident diabetes (self-reported, information validated by physician administred telephone interview or self-administred supplemental questionnaire). Assumption that all incident cases are type 2 diabetes.	Compared to persons without migraine, persons with migraine had no increased (or decreased) risk of incident diabetes. No evidence of effect modification by age.	Cross-sectional multivariable-adjusted** analyses showed an inverse association between any migraine and diabetes (OR 0.79 (0.67, 0.94)). When stratifying on subtype of migraine, the inverse association was only evident among women with active migraine without aura. (0.70, 0.54, 0.91). Discusses that differences in age distributions might explain that the strength of the association varies (in particular in cross-sectional studies) between migraine and diabetes. **Adjusting for: age, lifestyle variables, medications, somatic conditions, family history of diabetes.
Chuang Neuroepidemiology 2013	Prospective case control study with data from the National Health Insurance Research Database (NHIRD) in Taiwan. No information on age range. N=167 000.	Migraine, defined as ICD-9 code 346. N= 33468.	Primary outcome: dementia, defined as ICD-9 code 290, 294.1 and 346. Diabetes (ICD-9 code 250) considered a covariate.	Compared to persons without migraine (7.6%), persons with migraine had significant higher prevalence of diabetes (9.2%).	

*Vahlquist. Migraine in children. Int Arch Allergy 1995:7:348-355

Table 2: Population based studies investigating the association between diabetes and migraine, with focus on age and gender.

A10A Insulins	*A10B Oral antidiabetic agents*	*N06A Antidepressant agents*	*N02C Migraine agents*
A10AB insulins and analogues for injection, fast-acting A10AC insulins and analogues for injection, intermediate acting A10AD insulins and analogues for injection, intermediate or long acting combined with fast-acting A10AE insulins and analogues for injection, long-acting A10AF insulins and analogues for inhalation	A10BA02 metformin A10BB01 glibenklamide A10BB07 glipizide A10BB12 glimepiride A10BD03 metformin and rosiglitazone A10BD04 rosiglitazone and glimepiride A10BD05 metformin and pioglitazone A10BF01akarbose A10BG02 rosiglitazone A10BG03 pioglitazone A10BH01 sitagliptin A10BX02 vildagliptin A10BX03 saxagliptin A10BX04 eksenatide	N06AA04 clomipramine N06AA06 trimipramine N06AA09 amitryptiline N06AA10 nortriptyline N06AA12 doxepine N06AB03 fluoxetine N06AB04 citalopram N06AB05 paroxetine N06AB06 sertaline N06AB08 fluvoxamine N06AB10 ecitalopram N06AG02 moklobemid N06AX03 mianserin N06AX11 mirtazapine N06AX16 venlafaxine N06AX18 reboxetine N06AX21 duloxetine	N02CA72 ergotamine N02CC01 sumatriptan N02CC02 naratriptan N02CC03 zolmitriptan N02CC04 rizatriptan N02CC05 almotriptan N02CC06 eletriptan

Table 3: Agents included as A10A, A10B, N06A and N02C in paper 1 and 3, according to the ATC classification in 2006.

Paper	Material and design	Study sample	Main exposure	Outcome	Covariates	Statistical analyses
1	NorPD Cross-sectional	All persons residing in Norway, January 1st in 2006 aged ≥20 years. N= 3 434 233.	Medically treated diabetes defined as prescription of antdiabetic agents (ATC-code A10A and A10B) during 2006	Medically treated depression defined as any prescription of antidepressant agents (ATC-code N06A) during 2006	Sex Age in 10 year group (categorical)	Descriptive analyses Logistic regression
2	HUSK Cross-sectional	Participants in HUSK with valid responses on HADS-d N=21 845.	Self-reported information on diabetes, classified according to self-reported information on medical treatment	Depression defined as HADS-d ≥8 and/or self-reported use of antidepressant agents yesterday	Sex Age in two groups (40-47 and 70-72 years) Musculoskeletal pain Smoking BMI Physical activity Alcohol consumption Education Cohabiting	Descriptive analyses Logistic regression Test for interaction age-diabetes
3	NorPD Cross-sectional	All persons residing in Norway, January 1st in 2006 N= 4 640 219.	Medically treated diabetes defined as prescription of antdiabetic agents (ATC-code A10A and A10B) during 2006	Migraine treated with migraine agents defined as prescription of migraine agents (ATC-code N02CA and N02CC) during 2006	Sex Age in 10 year group (categorical)	Descriptive analyses Logistic regression Test for interaction age-diabetes

Table 5: Overview of materials and methods employed in the three papers in this thesis.