Mortality and work-related disability as long-term consequences of anxiety and depression: Historical cohort designs based on the HUNT-2 study

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Summary

Objective

Over the last decades, quality epidemiological studies have repeatedly shown that the prevalence of mental illness is substantial, but still largely under-recognised and under-treated. Under-recognition in general health care might also explain the modest attention to possible detrimental effects of such illness in terms of disability and mortality, and the mechanisms it operates through, compared to similar issues in other important fields of public health.

This thesis is based on three papers, all focusing on grave outcomes of two of the most common mental illnesses; anxiety and depression. First, we investigated empirically the contribution of psychiatric morbidity to the award of disability pensions. With the purpose of finding out if anxiety and depression are under-recognized as risk factors for disability pension award, we examined if they had an effect independent of awards for physical diagnoses. Effects of mental disorders on disability pension award are generally estimated by aggregation of diagnoses reported in medical certificates underlying applications for disability pension, which is vulnerable for biases including the above mentioned under-recognition of mental disorders.

There are numerous reports of effects of depression on general mortality, and specifically for cardiovascular diseases (CVD) and suicide. The second and third papers address six uncertainties in this literature concerning (i) residual confounding, (ii) dose-response effect of severity of depression, (iii) mechanisms driving the association, (iv) whether there is an effect of mortality beyond CVD and suicide, (v) effect-moderation by gender, and (vi) effect of comorbid anxiety.

Method

For all three papers we used historical cohort designs utilizing unique links between a large epidemiological cohort study and comprehensive national databases of disability pension award and mortality. Baseline information on mental and physical health was gathered from the population-based health study of Nord-Trøndelag County in Norway in 1995-97 (the HUNT-2 study), aiming at including the entire population aged 20 years and older. Addressing mortality, 61 349 individuals were eligible for inclusion, restricted to 45 782 individuals within working age (20-66 years) not already claiming disability pension in analyzing work-related disability. Anxiety and depressive symptoms were ascertained using the Hospital Anxiety and Depression Scale (HADS). Possibly confounding and mediating factors included somatic symptoms and conditions, health-related behaviour, subjective impairment, and socio-economic factors. In the first paper, the outcome was the award of disability pension within a 2 year follow up, as registered by the eliciting ICD-10 diagnoses in the National Insurance Administration. For the second and third paper, general mortality and cause specific mortality registered with ICD-10 diagnoses during 4.4 year follow-up were outcomes, respectively.

Results

From the first paper it is concluded that anxiety and depression are robust predictors of award of disability pensions in general, even when disability pensions awarded for any mental disorder (any F-diagnosis) were excluded. These effects were only partly explained by baseline somatic symptoms and diagnoses. Somatic symptoms accounted for far more awards of disability pensions than somatic diagnoses. The effect of anxiety and depression on disability pension award was equally strong in men and women, but stronger in younger sub-groups than older.

In the second and third paper, (i) depression was found to have an independent effect on general mortality. (ii) We found a dose-response association between severity of depression and mortality within the clinical range of the distribution. (iii) As to underlying mechanisms involved; factors not accounting for the association included body mass index (BMI), cholesterol level, and blood pressure, whereas educational level and health related behaviour accounted for a marginal proportion of the effect. Adjustment for somatic conditions was the strongest single contributor to explain the association, followed by subjective physical impairment and somatic symptoms. (iv) The effect of depression was equally strong on cardiac mortality as on all other causes of mortality combined, and confounding factors were also markedly similar. Depression predicted disease-mortality beyond CVD, and also accidents and mortality with uncertainty as to diagnoses. (v) There was no effect moderation by gender, but the effect of depression on mortality was stronger in younger individuals than older. (vi) Anxiety comorbid with depression was associated with lower mortality than in depression alone. We found no effect of case-level anxiety beyond the effect of comorbid case-level depression. Expanding the analysis beyond case-levels, we found a U-shaped and slightly negative effect of anxiety on mortality.

Conclusions

Anxiety and depression do predict grave outcomes like disability pension and mortality.

The effect of anxiety and depression on disability pension awarded for non-psychiatric diagnoses indicates that the cost of common mental disorders in terms of disability pension expenditure and lost productivity may have been considerably underestimated by official statistics. We suggest this might be due both to over-use of physical diagnoses and under-recognition of common mental disorders in primary care.

The two mortality papers contribute to the existing literature in several ways: (i) We conclude that the effect of depression on mortality is not an artefact from residual confounding. (ii) Contrary to conclusions from reviews and meta analyses, we find a dose-response association between symptom load of depression and mortality within the clinical range of the distribution. (iii) We dismiss some candidate explanations on mechanisms underlying the association (including the biological factors examined). (iv) Our finding of effects of depression beyond CVD mortality and suicide has consequences and should spur generation of new hypotheses on mechanisms underlying the association. (v) The evidence for effect moderation by gender in the association between mortality and depression is weak (but the hypothesis seems long-lived), and our findings indicate that it should be put to rest. (vi) The findings on the effect of anxiety were contrary to our expectations, and needs replications, and further examinations of underlying mechanisms.

Abbreviations

AUC	Area Under the Curve
BDI	Beck Depression Inventory
BMI	Body Mass Index
CAGE	Abbreviation for four questions concerning alcohol problems: thought of Cutting down, Annoyed by others' criticism of drinking, Guilt of your drinking, and morning Eye opener
CBT	Cognitive Behavioural Therapy
CES-D	Centre for Epidemiological Studies – Depression
CGI-S	Clinical Global Impression – Severity
CRN	Cancer Registry of Norway
CVD	Cardio Vascular Disease
DALY	Disability Adjusted Life Years
DIS	The Diagnostic Interview Schedule
DSM-III	Diagnostic and Statistical Manual of Mental Disorders. Third edition.
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders. Third edition, revised.
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders. Fourth edition.
DSQ	Depression Screening Questionnaire
ECA	Epidemiological Catchment Area study
EUPHA	European Association of Public Health
F-diagnosis	Mental diagnoses as encoded in ICD-10
GAD	Generalized Anxiety Disorder

GAS-Q	Generalized Anxiety Questionnaire
GDP	Gross Domestic Product
GHQ	General Health Questionnaire
GP	General Practitioner
HADS	The Hospital Anxiety and Depression Scale
HEMIL	Research Centre for Health Promotion, University of Bergen, Norway
HPA	Hypothalamic Pituitary Adrenal (axis)
HRV	Heart Rate Variability
HUNT	The Health Study of Nord-Trøndelag County
HUNT-1	The first Health Study of Nord-Trøndelag County in 1984-86
HUNT-2	The second Health Study of Nord-Trøndelag County in 1995-97
HUNT-3	The third Health Study of Nord-Trøndelag County, planned for 2007
ICD-10	The International Classification of Diseases, 10th edition
IoP	The Institute of Psychiatry, Kings College London, UK
LEAD	Longitudinal observations made by clinical experts who have all relevant data for deciding on a diagnosis
MADRS	Montgomery-Åsberg Depression Rating Scale
MD	Medical Doctor
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
NCS	National Comorbidity Study
NCS-R	Replication of the National Comorbidity Study
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NOK	Norwegian Kroner
NTNU	Norwegian University of Science and Technology, Trondheim, Norway

OECD	Organization of Economic Cooperation and Development
OR	Odds Ratio
PAF	Population Attributable Fraction
ROC	Receiver Operator Curve
SES	Socio Economic Status
SGA	Small for Gestational Age
SSRI	Selective Serotonin Reuptake Inhibitors
UK	United Kingdom
USA, US	United States of America

List of papers

1. Mykletun A, Overland S, Dahl AA, Krokstad S, Bjerkeset O, Glozier N, Aaro LE, Prince M. A population-based cohort study of the effect of common mental disorder on disability pension awards. Am J Psychiatry 2006; 163:1412-1418.

2. Mykletun A, Bjerkeset O, Stewart R, Dewey M, Aaro LE, Overland S, Prince M. Anxiety, depression mortality. The HUNT study. Am J Psychiatry (re-submitted after review).

3. Mykletun A, Bjerkeset O, Dewey M, Prince M, Overland S, Stewart R. Anxiety, depression and cause specific mortality. The HUNT study. Psychosomatic Medicine 2006 (re-submitted after review).

1 Background

Health screenings for the major health problems tuberculosis and cardiovascular diseases in the general population have a long tradition in Norway. The initial aim of these studies was to screen for individuals who needed medical treatment, but the primary aim has in later days shifted towards research purposes. During the last decades, mental health problems have gradually received a more prominent status as a major health problem, and measures of symptoms on common mental disorders were therefore included in the surveys (1).

The present dissertation explores hypothesized effects of two of the most common mental disorders; anxiety and depression on mortality and work-related disability and possible mechanisms in this relation. The base-line measures were collected from the largest general health survey in Norway, the HUNT-2 study, where approximately 62 000 individuals aged 20 years and older participated. Dependent variables were identified in national registries, and the data resources were merged by the national personal identification number.

The background is organized in five sub-chapters: First, the epidemiology of the exposures (anxiety and depression) will be presented. Second, a three-dimensional model for measuring health including mental health, physical health, and somatic symptoms will be presented. Third, the outcomes of the studies; disability pension award and mortality will be described, and finally the aims of the studies will be presented in detail.

1.1 The descriptive epidemiology of mental health

1.1.1 Prevalence of mental disorders

Anxiety and depression are common disorders in the general population. In the U.S. Epidemiological Catchment Area (ECA) study in the early 1980s, the 12-month prevalence of

any diagnosable DSM-III disorder was 29.4% (2). The Diagnostic Interview Schedule (DIS) which was used in the ECA, was developed by the National Institute of Mental Health for the purpose of screening for mental disorders by interviewers who not necessarily had to be trained psychiatrists or psychologists (3).

The probably best study of prevalences of mental disorders is the National Comorbidity Survey (NCS) (4) was conducted by Ronald Kessler and collaborators in the late 1980s. This study included an evaluation of parental psychopathology, family problems, social networks, and external stress, and was based on a random sample of 8,090 subjects between 15 and 54 years, excluding institutionalized individuals. The response rate was 82.6% (5). In the NCS, mental disorders were screened with a modified version of the Composite International Diagnostic Interview (6). This is a structured instrument combining aspects of the DIS and the Present State Examination, and was designed for use by trained lay interviewers (7). Through use of the DSM-III-R criteria, the 12-month prevalence of any mental disorder in this study was 29.4% in men and 32.3% in women, whereas the lifetime prevalence was 51.2% and 48.5% respectively. Both affective disorders and anxiety disorders were found to be more prevalent among women, whereas addictions were more prevalent among men. The 12-month prevalence of anxiety disorders was 24.7% in women and 13.4% in men, and affective disorders were found among 14.1% of women and 8.5% of men. Addiction was found among 6.6% of women and 16.1% of men (8).

A Norwegian study, modelling the NCS was carried out by Kringlen and collaborators in Oslo in 1994-97 (7). The prevalence of mental disorders, and also the gender ratios, was in Norway found to be very similar to those found in the NCS, the exception being the prevalence of addiction, which was less prevalent in the Oslo sample.

The NCS prevalence estimates of mental disorders in the U.S. population (8) have been questioned for being too high, and thus being of little clinical relevance (9). Other

prevalence estimates have been proposed also including clinical significance criteria of mental disorders; self-reported use of health services, medication, or impairment (10). By employing such approaches, the prevalence estimates were, not surprisingly, lower with a 12-month prevalence of anxiety or depression at 14.9%. The 12-month prevalence of any anxiety disorder was 11.8% and of major depressive episode 4.5%. Phobias (4.3%) were the most prevalent within the anxiety disorders, followed by posttraumatic stress disorder (3.6%), social phobia (3.2%), generalized anxiety disorder (2.8%), agoraphobia (2.1%), obsessive-compulsive disorder (2.1%), and panic disorder (1.4%). These suggestions for revisions of definitions of mental disorders (and consequently lower prevalences) have later been abandoned (11).

A replication of the NCS (NCS-R) was conducted from 2001 through 2003. It was, like the first one, organized as a face-to-face interview, and diagnoses were coded according to DSM-IV. The 12-month prevalence of any mental disorder was 26.2%. In detail, the 12-month prevalence for anxiety was 18.1%, 9.5% mood disorder, 8.9% impulse control, and 3.8% substance abuse. Of the cases in the study, 22.3% were classified as serious; 37.3% moderate; and 40.4% as mild. Fifty-five percent carried only a single diagnosis; 22% 2 diagnoses, and 23% carried 3 or more diagnoses. The authors concluded that although mental disorders are widespread, serious cases are concentrated among a relatively small proportion of cases where comorbidity between disorders is common (12). The lifetime prevalence of any DSM-IV disorder was 46.4%, mainly distributed as anxiety disorders 28.8%, mood disorders 20.8%, impulse-control disorders 24.8% and substance use disorders 14.6%. Median age of onset was lower in anxiety and impulse control disorders (both 11 years) than for substance use (20 years) and mood (30 years) disorders. Half of lifetime cases of mental disorders started by age 14 and three fourths by age 24 (13). Consequently, the authors

concluded that interventions aimed at prevention or early treatment must be focused on adolescents.

1.1.2 Anxiety and depression have severe consequences for both the society and for the individual

Mental illnesses commonly have a long-lasting or chronic course with recoveries and relapses, and have serious consequences for both the society and for the individual. The Global Burden of Disease Study concluded that depression is the single diagnosis that causes the highest number of lost *healthy* years in the western world (14). Worldwide, depression was ranked as the fourth most important specific cause of global disability-adjusted life years (DALY, sum of life years lost due to premature mortality, and years lived with disability adjusted for severity) (15), and was predicted to advance to the second most important cause by year 2020 (16). These estimates have been much debated as to methodology in general, and the epidemiological knowledge underlying the estimates (17). It has been suggested that the impact of major depression and substance disorder are overestimated at the expense of anxiety disorders (18).

Depression is also reported to increase general mortality (19), CVD mortality (20-23), suicide (24), and other non-illness causes of death (25-27). In addition to individual consequences, depression in mothers has consequences for development among children, especially when children are young (28), and mental disorders, and depression in particular, is a risk factor for divorce (29). It has societal consequences in that mental disorders, most often depression, is the primary medical diagnosis in 30% of awards of disability pension (30), depression causes considerable economic loss for employers, and the cost in terms of lowered productivity accounts for more economically than sickness absence (31, 32).

For the anxiety disorders, corresponding figures or estimates are scarce. In addition to depression, all common physical diagnoses were included in the rankings in the Global Burden of Disease Study (14), but anxiety disorders were not included. However, analyses from the NCS suggest the annual costs of anxiety disorders similar to the total costs of affective disorders (33).

1.1.3 Dimensional and discrete approaches to measurement of anxiety and depression

In mental health research, anxiety and depression are represented both by continuous and discrete measures. In clinical practice, the discrete approach has been the most influential, largely because it is a premise of the commonly accepted diagnostic manuals DSM-IV (34) and ICD-10 (35). For research purposes, the discrete approach can be compelling as it eases the transition from research to applied knowledge amongst clinicians. But for both clinical- and research purposes it is important to keep in mind the limitations of the categorical models:

Diagnostic classifications are reached by consensus in expert panels, and the diagnostic entities are continuously subjects to change and revision. These diagnostic instruments must be regarded as social constructions rather than true descriptions of aspects of reality. The discontinuity model may be useful in clinical settings and even serve important purposes in research, but over time, present cut-offs and demarcations may appear arbitrary. It is important to be aware of the limitations of the diagnostic systems.

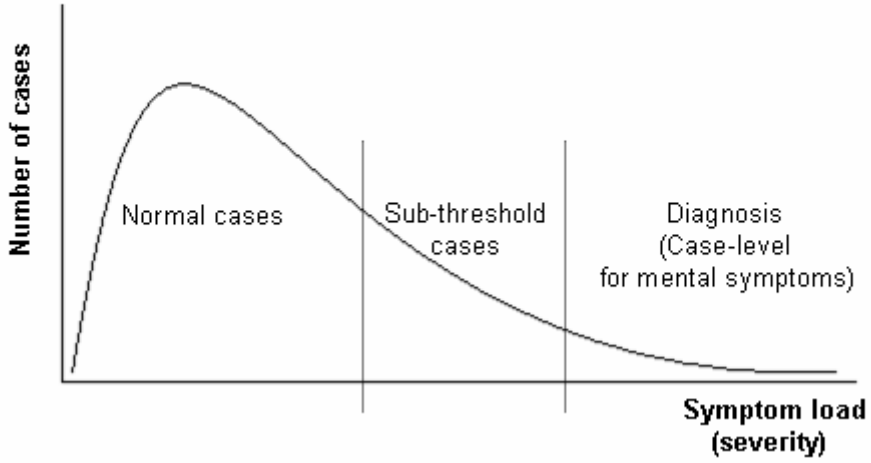
Furthermore, mental disorders are dimensional rather than discrete by nature. The actual distribution of symptoms of anxiety and depression in the general population are best represented as a continuum from low to high symptom load (that is, from every degree of good mental health to different levels of psychopathology) with corresponding lower prevalences in the general population (Figure 1). There is a dose-response relationship

between the number of symptoms of depression, the frequency and the duration of depressive episodes, and indicators of diagnostically acknowledged depression (36). In the dominant diagnostic manuals, a mental disorder is simply a mental symptom load above a certain threshold, although in ICD-10 and DSM-IV, symptoms are weighted such that some criteria are obligatory and others additional. Still, the number of additional criteria needed for a diagnosis applies a cut-off on a continuum, and the weighting system may be subject to revision in future diagnostic manuals. The thresholds for case-levels might not only be only arbitrary, but sub-threshold "conditions" (defined as individuals with a defined symptom-range immediately *below* case-level for a mental diagnosis) have repeatedly been found to have significant clinical impact in terms of for example functional work-related impairment (37). Among elderly with high loads of depressive symptoms, few fulfil DSM criteria for affective disorders, but many cases with sub-threshold depression were found to be chronic or fluctuating over a 6-year period in a Dutch prospective community based study (38).

As a property of the distribution, most suggested analyses identify a larger group of individuals within the sub-threshold range than on clinical levels. As a consequence, the sub-threshold cases accumulate more adverse outcomes than case-levels, even if the risk associated with sub-threshold case-levels commonly are lower than for case-levels (37). Individuals with symptom loads within the sub-threshold level of psychiatric morbidity are also reported to be in need of mental health care (39). Simply lowering the diagnostic threshold does not solve the problem of categorization (40), and the suggestion that anxiety and depression are dimensional phenomena with no thresholds between pathology and normality (41) is plausible, and the use of continuous symptom scores is suggested as an alternative to discrete measures in measuring and describing mental symptoms (42). Recent evidence, mainly provided by Jim van Os' group, suggests this continuum model for mental disorders also applies to schizophrenia (43, 44). The perhaps most convincing argument

offered by this group is that common symptoms in schizophrenia, for example hallucinations, also occur in healthy individuals and individuals with anxiety and depression (43).

Figure 1. Distribution of symptoms of mental disorders



The use of discrete diagnostic entities with cut-offs for case-levels in diagnostic manuals are motivated by ideals from bio-medical models. It can be argued that discrete diagnostic entities are useful for decision-making in clinical practice (in offering indications for treatment), and also on a policy level (in planning and establishing services). This argument is, however, precluded by that most individuals who fulfil diagnostic criteria for a mental disorder will not seek treatment (45). There is a large discrepancy between the prevalence of mental disorders and treatments for them in the general population, but this does not imply that everybody with a mental disorder is in need of treatment (46). The perhaps best argument for employing discrete measures of mental symptoms based on ICD-10 and DSM-IV for clinical purposes and research is that a common terminology can stimulate communication, recognition, research and development: It can be held that it is easier to communicate a prevalence of a mental disorder than a left-skewed normal-distribution of mental symptoms, and relative risks

between two groups compared to a standardized regression coefficient of continuous measures (perhaps even based on log-transformed variables).

Finally, use of discrete measures in describing mental disorders relate to the problem of comorbidity. Most mental symptoms are co-occurring, anxiety and depression in particular (5). Commonly, individuals have sub-threshold levels of both anxiety and depression, resulting in a high total symptom-load, despite being below the diagnostic levels of both diagnoses (41).

1.1.4 Comorbidity between anxiety and depression

As mentioned above, most mental disorders are associated, and this also applies to anxiety disorders and depression (5, 47). Embedded in the term "comorbidity" is use of a discrete diagnostic system. Alternatively, the term co-dimensionality has been suggested to describe this within a dimensional approach (41). Comorbidity between any two diagnoses is present if their co-occurrence is more frequent than by chance (48). It can be objected that the comorbiditiy between mental disorders simply are artefacts of separating what essentially is nosological entities (41). The comorbidity between anxiety and depression can be described both as *diagnostic comorbidity*, that is some diagnostic criteria are shared, and *pathogenic comorbidity*, e.g. that depression commonly follows anxiety (41).

In the previously described NCS-study, the comorbidity between 12-month prevalence of any anxiety disorder and major depressive disorder (MDD) was 51% (47), but estimates across studies vary. The association between mental symptoms has also been described as correlations between continuous measures. Employing HADS (49) in the HUNT study, anxiety and depression was reported to share 30% of the variance, which is within the range of correlations with this instrument (24-40%) previously reported (50).

Several publications have addressed properties of the comorbidity between anxiety disorders and depression. Comorbid anxiety and depression implies poorer treatment response to antidepressive medication (51), lower rate of recovery from depression, increased time from debut till recovery, decreased time from remission to relapse (52, 53), and increases risk of suicide (54) than when anxiety disorders or depression occur alone. As comorbid anxiety and depression in the discrete approach implies having two mental disorders rather than one, comorbid conditions can be expected to entail more adverse outcomes (55). Employing the screening instrument HADS, comorbidity is defined as a score above case-level (56) on both sub-scales (57), and with few exceptions, the association between somatic health problems (e.g. myocardial infarction, diabetes, migraine, fibromyalgia and muscle-skeletal complaints) and comorbid anxiety depression was reported to be stronger than in anxiety or depression alone (57). It can be objected to these findings of worse outcomes in (and correlates to) comorbid anxiety depression than pure cases that they may be driven from the higher symptom-load in comorbidity rather than the qualitative nature of comorbid symptoms alone.

1.1.5 Anxiety and depression – one or two dimensions?

The strong correlation between anxiety and depression that is observed using screening instruments (50), and comorbidity rates between anxiety disorders and major depression in surveys like NCS (5) and the Oslo study (7) may indicate that anxiety and depression should be considered a uni-dimensional scale rather than two separate dimensions. The screening instrument HADS is appropriate for examining this hypothesis as it contains symptoms of both anxiety and depression, and multiple factor analyses have been performed both in clinical samples and samples from the general population. Support for a uni-dimensional model for both anxiety and depression was reported from a Belgian cancer population (58), whereas Moorey et al suggested a two-dimensional model after analyses of a sample of

British cancer patients (59). The two-factor solution is also confirmed in the Norwegian translation (50). Objections to this two-factor solution were after this publication proposed by authors examining the factor structure in a sample of inpatients (60), but this and other deviations from the original two-factor solutions are probably due to restraints of the variance in either (or both) sub-scales resulting from inclusion of severely mentally ill patients in the samples examined only (61). The debate whether anxiety and depression are one or two dimensions by nature will probably continue.

1.1.6 Is the prevalence of mental disorders increasing?

An increase in the prevalence of common mental disorders among adults is commonly hypothesized, perhaps justified by an increasing attention to mental disorders in the media and in the public, as well as a strong increase in use of psychotropic medication for depression in USA, which was reported to triple from 1987 to 1997 (62). There was, however, no increase in outpatient psychotherapy use (63).

For several reasons, trends in the prevalence of mental disorders are difficult to address empirically: The history of measuring common mental disorders, both through dimensional screening instruments or discrete diagnostic measures, is short. Due to differences in measurements, it is difficult to compare prevalence estimates of mental disorders further back in history than the introduction of DSM-III-R. Even if instruments were corresponding, the meaning of words and phrases might change over time from changes in culture and language. Lastly, psychiatric epidemiology is a relatively novel discipline, and there are few empirical studies on prevalences of mental disorders to be replicated in modern time for comparison.

The ECA and NCS studies are probably the best empirical basis for evaluation of trends in prevalence of mental disorders. As mentioned above, the 12-month prevalence of

any DSM-III disorder in the ECA was 29.4% in the 1980s (2). A decade later, the 12-month prevalence of any DSM-III-R disorder was 30.5% (5) among people 15 to 54 years of age. The NCS replication conducted in 2001 through 2003 found a 12-month prevalence of 30.5% of any DSM-IV diagnosis, which compares to 29.4% in the NCS in 1990-92 (p=.052) (numbers are NCS estimations recalculated from DSM-III-R to DSM-IV for the purpose of comparison) (11). Further, there was no significant change in the prevalence of serious disorders (5.3% vs. 6.3%, p=.027), moderate disorders (12.3% vs. 13.5%, p=.030), and mild disorders (11.8% vs. 10.8%, p=.037), and there was no statistically significant interaction between time and any socio-demographic characteristic in the prediction of prevalence (11).

In conclusion, there is no evidence for any increase in the prevalence of mental disorders in the USA from the 1980s. Any changes from longer back cannot be ruled out. Whether these US findings can be generalized to European or Norwegian populations can obviously be questioned.

1.2 Three main dimensions in the measurement of health: Mental health, physical conditions[1], and somatic symptoms

The relationship between mental and physical health is complex: Mental health problems might cause somatic disease, e.g. depression being a risk factor for CVD (64), somatic diseases may cause or aggravate the mental health (65), a mental health problem can be prodrome of a physical disorder not yet diagnosed, e.g. depression being a prodrome of dementia (66). Furthermore, there may also be some common pathophysiological mechanisms underlying both mental disorders and somatic disease (65) and reciprocal relationships between depression and somatic health problems are reported (67).

[1] The terms *physical conditions*, *somatic conditions*, *somatic diagnoses* and *somatic diseases* are used as synonyms throughout the text.

Increased prevalence of anxiety and depression is reported in almost all physical diseases. This is demonstrated in studies based on the general population (5, 57, 68), among patients in general practice, and in numerous studies of specific physical disorders, like CVD, which is one of the physical conditions most frequently reported to be associated with mental disorders in general, and depression in particular (41).

Associations between physical health and depressive symptoms in later life are found to be consistent across Western Europe (69).

The HUNT study is suitable for examining these hypotheses as it is based on the general population, and includes multiple variables on physical conditions in addition to measures of anxiety and depression. Examples of studies reporting increased prevalences of anxiety and depression in somatic conditions are numerous, and include the HUNT studies of e.g. myocardial infarction (70) and migraine (71). Reports of absent associations between anxiety or depression and physical diseases are uncommon in well-powered studies, and do from the HUNT study include studies of thyroid dysfunction (72, 73) and Type-2 diabetes (adjusted for comorbid physical conditions and complaints) (74). The latter finding is also reported in a Dutch community-based study (75). Increasing prevalence of physical symptoms and conditions with age (76) is in the HUNT study reported to account for some of the increase in depression by age (77).

The more complex issue, however, is the area of somatic symptoms without any known organic aetiology, labelled somatization, somatoform disorders, medically unexplained symptoms, or functional somatic symptoms (78). Such symptoms might be related both to physical conditions as described for mental disorders above, and are also related to mental disorders, partly as vegetative symptoms that define mental disorders like depression (35), but also co-occurring more frequent than by chance. From the HUNT study, comorbidity with anxiety and/ or depression is reported for gastrointestinal complaints (79, 80), for

psychosomatic symptoms in general (81), and to subjective impairment attributed to physical conditions (57).

There exists a more or less subtle conflict between the mental and somatic health professions as to how somatic symptoms shall be interpreted. From a mental health perspective, somatic symptoms with unclear or absent organic aetiology can be interpreted as somatic symptoms in e.g. depression. If symptoms are spread over multiple organ systems, persist over time, and proper examinations have revealed no organic aetiology, the diagnosis somatization disorder (ICD-10 diagnosis F45.0) might be relevant.

Patients with common psychiatric disorders such as anxiety and depression frequently present to their doctors with medically unexplained physical symptoms (82), which in cases without organic aetiology have been labelled "somatization". However, patients with medically unexplained somatic symptoms do often not have psychiatric disorders, and the symptoms might rather indicate minor pathological change, physiological perceptions, and other factors including previous experience of illness (83). Comparing physicians' initial assessment of the nature of symptoms and their final diagnosis, Nimnuan et. al. concluded that physicians were more likely to error on the side of diagnosing the symptoms as medically explained rather than unexplained (83). Further, when physicians perceived the interaction with the patient to be positive, they were more likely to make provisional diagnosis that an explanation of the symptoms were identified, and conversely, negative perceptions of interactions more often increased likelihood of viewing symptoms as medically unexplained.

The proportion of medically unexplained symptoms presented in both general practice and in various specialist disciplines are perhaps surprisingly high given their strong focus on biomedical models. In one study, the proportion of consultations where organic aetiology was concluded ranged between 10 and 25% across symptoms (chest pain 12%, fatigue 17%, dizziness 19%, headache 11%, back pain 10%, dyspnoea 25%, abdominal pain 10%, and

numbness 20%) (84). The proportion of patients with medically unexplained symptoms in medical specialised clinics is also high, overall as high as 56% (95% confidence interval 52-60), and varying in one study from 49% (95% confidence interval 37-61) in dental clinics to 60% (95% confidence interval 45-73) in gastroenterology (85). The authors concluded that medically unexplained symptoms are common across general and internal medicine, and represent the most common diagnosis in some specialities. They further found that psychiatric morbidity was not per se associated with the presence of medically unexplained symptoms, but was more likely in those complaining of multiple symptoms. In this epidemiological study, patients with medically unexplained symptoms were more likely to attribute their illness to physical causes than lifestyle factors.

Medically unexplained somatic symptoms have serious consequences (78). In UK primary care they account for 35% of all consultations in primary care (medically unexplained symptoms being *main* clinical problem) (86). Chronic fatigue syndrome is associated with worse disability than conditions such as heart failure (87). The prevalence of emotional disorders is higher in patients with functional syndromes than in patients with comparable medical conditions (88).

From the perspective of psychiatry, the development and marketing of e.g. the diagnosis chronic fatigue syndrome is suspected to be “old wine in new bottles”. Both chronic fatigue and chronic fatigue syndrome are common among primary care patients and represent a considerable public health challenge (89). Most subjects with chronic fatigue or chronic fatigue syndrome in primary care also meet criteria for current psychiatric disorders, and both are associated with previous psychiatric morbidity. The symptoms are thought to represent a specific process in chronic fatigue syndrome that may be related to the joint experience of somatic and psychological distress (90).

Disputes around the medically unexplained symptoms are indeed an issue where not only mental and somatic specialities struggle; also medical specialities beyond psychiatry have their own claims of understanding these patients. It is even suggested that patients with medically unexplained symptoms are given diagnoses dependent upon the particular medical speciality consulted (91, 92). One suggested list of syndromes by speciality includes irritable bowel syndrome (or non-ulcer dyspepsia) in gastroenterology, premenstrual syndrome or chronic pelvic pain in gynaecology, fibromyalgia in rheumatology, atypical or non-cardiac chest pain in cardiology, hyperventilation syndrome in respiratory medicine, chronic (postviral) fatigue syndrome in infectious diseases, tension headache in neurology, temporomandibular joint dysfunction and atypical facial pain in dentistry, globus syndrome among ear, nose, and throat specialists, and multiple chemical sensitivity in allergy (78). Factor analyses of symptoms presented by consecutive new patients across seven outpatient clinics suggested that the existence of distinct functional somatic syndromes as defined clinically in medicine should be reconsidered (91).

Wessely and collaborators argue that the existence of specific somatic syndromes is largely an artefact of medical specialization (78), after having found overlap in case definitions across specific syndromes and that the patients with one functional syndrome frequently met diagnostic criteria for other functional syndromes. Furthermore, they found that different functional syndromes frequently shared non-symptom characteristics, and that different functional syndromes responded to the same therapies. It is concluded that existing definitions that claim these symptoms to point to specific syndromes is of limited value, and could be replaced with a dimensional classification (78).

The debate on ways to define unexplained somatic symptoms (either they are labelled as functional disorders or not) is relevant for psychiatric epidemiology in several respects: Somatic symptoms are legitimate symptoms of both mental and physical diagnoses (not

including the functional ones). For the case of depression, employment of standard diagnostic tools for mental disorders like ICD-10 (35) or screening instruments like Centre for Epidemiological Studies – Depression (CES-D) (93) or Beck Depression Inventory (BDI) (94) might bias the measurements in direction of false positive cases in individuals suffering from physical conditions. This because most instruments measuring depression include items on poor appetite, disturbed sleep, somatic preoccupation, or weight loss, which are not only sensitive to depression, but also a whole range of physical disorders in addition to unexplained medical symptoms. Often statistical strategies are applied to avoid this bias in models both where mental health is a dependent or an independent variable. Such strategies include adjustments for the presence of possible physical diseases and somatic symptoms. A different approach is evident employing the HADS that does not include somatic items to in this vein attempt to avoid false positive cases from co-occurring somatic conditions (49). As the name implies, the instrument was originally developed for use in a setting where such somatic symptoms are abundant. This last strategy does, however, bias the results in the opposite direction; in under-estimating the correlate to mental disorders of interest. Among the two possible biases described here, the latter seems to be the most acceptable in the scientific medical community and journals in general, and also in psychiatry, perhaps a reflection of the balance of power between mental and physical health professions?

It might be fair to claim there is a hierarchy from somatic conditions on top via somatic symptoms till mental disorders. This is illustrated by echoing Eaton (95, referred in 96): "Epidemiology is a branch of medicine, and thus the assumptions of the medical model of disease are implicit. The most important assumption is that the disease under study actually exists […] In psychiatry this assumption is assured more tenuous than in other areas of medicine, because psychiatric diseases tend to be defined by failure to locate a physical cause …"

1.3 Disability pension

In Norway in the 1990s and up to 2004, disability pension is awarded to any individual within working age whose workability is permanently deteriorated, and where the cause is a medical diagnosable condition (mental or physical). The arrangements differ across countries, but most countries within the Organization of Economic Cooperation and Development (OECD) have arrangements for long-term or permanent occupational disability (97). For ease of international comparison, disability pension can be regarded as a kind of long-term sickness absence.

A recent and thorough literature review of sickness absence and disability pension award (98) concluded that despite the public focus on sickness absence and its major impact on society and the individual, there is limited knowledge about the causes and consequences, and how they can be influenced. Further, the review concluded that the field of sickness absence research is underdeveloped in terms of theory, methodology, and concepts and that several research questions raised today still are very general in nature. As such, current research and the present knowledge base does not provide physicians, insurance officers, employers, labour unions, and politicians with the necessary insight for improved decision-making. The authors of the review list surprisingly few studies on causes and consequences of sick leave and on physicians' sickness certification practices, and only few of these are of high methodological quality (99). For disability pensioning, only 18 studies with sufficient quality for inclusion in a review were identified (100). There is therefore a demand for longitudinal studies of causes of disability pension of good methodological quality (99, 101). A majority of previous studies were undertaken in Finland (e.g. 102, 103, 104), Sweden (e.g. 98, 105), or Great Britain (e.g. 106). American studies are commonly based on either work-place samples (e.g. 31) or for example data from the NCS (e.g. 107). There is also some research in this area

in Norway, in particular studies based on sociological or economic perspectives, but unfortunately, much of it is published in Norwegian only (e.g. 108, 109).

1.3.1 Consequences of disability pensioning for the society

Early age occupational disability is a burden to society, both in terms of expenses from direct costs to disability pensions, but also due to lost productivity and income taxes. At the end of 2004, there were 302,369 permanent disability pensioners in Norway and additional 8515 on time-limited disability pension (according to revised rules for award of disability pension) (30). Disability expenditure accounts for a significant proportion of Gross Domestic Products (GDP) across Europe, varying from about 1% in Ireland to 5% of GDP in Norway (97). The direct expenses to permanent disability pensions were in 2004 Norwegian Kroner (NOK) 41,060,000,000 and accounts for 18% of the total expenses to social security in Norway (30). The increase in direct expenses to permanent disability pensions from year 2000 till 2004 is 25% (both NOK in 2004 values) (30).

The number of individuals on sick leave and disability pension has in the OECD region increased dramatically in recent years, which translates into major economic costs and, and potentially also long-term consequences for the design of welfare state (110). Combined with a change in demographic distribution towards the higher age cohorts and no change in mean age retirement, the proportion of the population working and providing for the rest is decreasing dramatically. An increased rate of disability pension award adds to this financial problem for the society. At the end of year 2004, 12.0% of the total population aged 18 to 67 years were recipients of disability pension (173 012 of 1 437 209 individuals). Return to work from disability pension is uncommon: In 2004, exits from disability pension were due to receipt of other kind of pension (74.4%), mortality (18.4%), and other causes (7.2%) (30), and

the exit from disability pension was less than 1% in Norway in 1995, which is at the very lowest level among OECD countries (97).

1.3.2 Consequences of being on disability pension

It is claimed that sick listing, through processes like isolation, stigma and loss of work-role, may have serious negative individual consequences (111), and that physicians should be more restrictive in issuing sickness certificates. An alternative position suggests that becoming disability pensioner can be an attractive position for the individual, as it may imply relief from work-related strains and burdens, and also relief from financial worry. A recent publication utilizing the British household panel survey revealed increased psychological distress corresponding to transitions from paid employment to unemployment or long term sick leave, and also associations between improvement in psychological distress and moving from non-employed roles into formal employment (112). A review of available literature in English and Scandinavian languages published in 2004 reported a lack of scientific studies in this area, and also that scientific studies seldom were referred in this debate (110). The 3rd pre-conference meeting on sickness absence at the European Association of Public Health Association's (EUPHA) conference in Graz (November 9th 2005) on research on health consequences of sickness absence and disability pension landed on the same conclusion.

1.3.3 The physicians' role in the process of disability pensioning and sick-listing

In Norway and several other European countries, applications for disability pension must be issued by a physician certifying to the presence of a diagnosable sickness or injury that permanently impairs the patient's ability to undertake any feasible work. Over the years, the

certificates have taken various forms, but the key information requested has always been related to the patient's diagnoses and work ability (110).

The physician has six roles in the process of sick-listing (113): (a) Determine if the disease or injury is present according to existing criteria; (b) and if it implies impaired ability to work. Currently, in Norway, more than 50% impairment is necessary for award of disability pension. (c) Further, advantages and disadvantages of sick leave must be considered in dialogue with the patient, (d) the grade and duration of sick leave must be determined (e) as must also need for contact with specialists, the social insurance office, or other parties. (f) Finally, the standard certificate must be completed.

The physicians' role in the process of disability pensioning is a balance between being the patient's advocate and being a gate-keeper restricting the access to public generous (and expensive) welfare systems (113). According to formalities, the physician is supposed to decide on workability and eventual diagnosis based on examinations of the patient. Already in the 1960s, the information imbalance in the patient-doctor dyad was evident: "Examining by the doctor is usually a meaningless formality, since it is the patient who decides when he is fit for work" (114).

Both physicians and patients raise the question of sick leave in consultations, and physicians do almost always issue sick leave certificates when requested by the patient (113, 115). To the best of our knowledge, no such study exists for disability pension. Physicians generally find the issue of assessment of workability difficult (113). Patients and physicians usually agree on the need for sick leave (113), but a Swedish study on young immigrants suggests there is disagreement between physicians and external experts' reviewing decisions, probably due to insufficient objectivity in the assessment (116). Certificates are often inadequately completed by the physicians (113). Physicians differ in their assessment of the need for sick leave, not only at the level of general practitioner (117, 118), but also between

geographic regions (119) and specialists (113, 120). Strong demands from the patient for the need for sick leave increase sick leave certification (120) and when physicians report good knowledge of the patient, the sick-leave increases (121). An explorative Norwegian analysis indicates conflicts between the dual roles of being the patient's advocate and the gate keeper (122). In summary, there exist only few studies on the physicians' role in the process of sick listing patients, and these are of varying quality (113), and the above referenced studies do not specifically address disability pension award.

1.3.4 The *push* and the *pull* models for the transaction from work to disability pension

Models explaining the transaction from work to disability pension award can be sorted into two groups: The *push* model focuses on involuntary processes beyond control of the individual *forcing* the employer out of work and on to disability pension. In opposition, the *pull* model is inspired by rational choice theory (123), and hypothesizes that the individual *chooses* disability pension over continued work having rationally considered issues as economic incentives for continued work versus disability pension over increased leisure time. Health is hardly a variable of interest in the pull model.

Arguably the least complex model explaining causes for disability pension award is offered by Insurance Medicine. At the Faculty of Medicine in Oslo, Insurance Medicine is defined as the science of how diagnosis, treatment, and prevention of disease influence, and is influenced by insurance benefits based on medical criteria. It is also the trade of providing the diagnostic, therapeutic, prognostic, and etiological basis for decisions concerning insurance benefits (110). As follows from this definition, the inherent focus is on medically diagnosable disorders as *causes* for disability pension award. In Norway, variables on health according to this tradition are usually based on data from National Insurance Administration, and

tabulations are regularly published describing diagnostic distributions in disability pensions (Table 1). From 1998, all diagnoses for disability pension award were registered by ICD-10 diagnoses. Muscle-skeletal disorders are the most common diagnosis in Norway (main diagnosis among 47.1% of all disability pensioners and 35.8% of new diagnoses), followed by mental disorders (28.0% of population and 21.5% among new awards) (30). This is in line with international studies (124, 125). Awards for mental disorders are prominent and increasing throughout the OECD countries (102, 106).

Table 1. Diagnoses for disability pension in 2004

	Per cent of new awards of disability pension	Per cent of total population of disability pensioners
Muscle-skeletal	35.8	39.1
Mental	21.5	28.0
Circulatory organs	10.2	4.2
Cancer	5.6	2.8
Injuries, poisoning, violence	3.7	3.7
Nervous system	6.4	6.3
Respiratory	3.1	2.5
Temporarily lack of diagnosis	3.8	1.8
Other diagnoses comprised[1]	9.9	11.6

[1] Diagnoses each counting less than 3.0% of the population comprised

Among the empirical studies, only few have used a prospective design to estimate the association between mental health and disability pension award, and they all confirm the strong impact of mental disorders (or symptoms of such) on disability pensioning (103, 104, 126). A recent review identified five studies of associations between psychiatric disorders and sickness absence (125). Based on reimbursements, a US study fond a positive association between depression and sick-leave (127), and the same conclusion was reached in two

Swedish studies of women (128, 129). In contrary, no association between sickness absence and case-level depression was reported in the ECA project, but they did, however, find an effect of sub-threshold depression (37). Associations between any DSM-III-R and sickness absence was reported from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) for men, but not for women (130). As previously noted, studies within this area are few, and the overall quality of most available studies is regarded as low (125).

The Norwegian tradition in insurance medicine administration can be placed within the paradigm of the *push* model as the medical diagnoses and the impairment that follows is involuntary and forced upon the individual. There are several problems with this tradition, whereof some relate to issues of validity of the diagnoses reported in applications for disability pension. First, only ICD-10 diagnoses are accepted, and diagnoses relating to issues like alcoholism and obesity will usually not release disability pension award. There are, however, reports of independent effects of obesity on long-term sick-leave from Norwegian studies, even adjusted for physical and mental health (131). Second, despite being highly prevalent and commonly disabling, vague somatic symptoms without organic aetiology will only partly be covered by ICD-10, hence the discussion of functional disorders above (78, 89, 91, 92). Third, both the physician and applicant (patient) might have preferences for certain diagnoses above others, e.g. for diagnoses with an assumed organic aetiology and somatic conditions rather than e.g. mental disorders. This might explain for example the popularity of chronic fatigue syndrome over depression, despite overlapping diagnostic criteria and effective treatment (90, 132). Physicians have most of their training within somatic medicine rather than in psychiatry, and will perhaps be biased in the direction of physical rather than mental diagnoses when multiple and vague symptoms are presented. It can be argued that the common physician will be more prone to conduct excess investigations to disconfirm potential grave diseases. Incentives in this direction may stem from litigations, and

availability of good routines for referrals, which are less developed within the common psychiatric conditions. Fourth, the tradition offers no explanation as to why it is common to continue work despite of mental and physical illnesses (labelled sickness presence) (133). Finally, there has been an increase in health-related insurance benefits in most OECD countries despite an overall improvement in most key indicators of health in the general population (134), which is more or less incompatible with explaining disability pensioning by medical diagnoses. In summary, medical diagnoses are at best only the last link in a causal chain leading up to disability pension award.

One approach within occupational medicine has focused on work-place characteristics in prediction of morbidity employing the variables demand, control, and social support as descriptions of perception of the work situation (135). The combination of high demand and low control is reported to be associated with mental morbidity, whereas there is less support for a buffer-effect of social support on the work-place (136). Ongoing research is also indicating independent effects of this job demand-control-support model on long-term sickness absence (137). Support from colleagues and supervisors at work are reported to lower the risk of short spells of psychiatric sickness absence in studies based on the Whitehall II data (138, 139). The level of symptoms of mental disorders is varying across occupational groups (140), and farmers seem to be at particular risk (141). These models of causal mechanisms where workplace characteristics increase morbidity, which again increase the risk of disability pensioning, can be described as *health related push factors.*

Push factors can also be related to *economic structures* in the society, for example factory closings (142) and downsizing (111). Economic push factors can be regarded as a consequence of the organization of labour in the society, where demands for profit, effectiveness, and ability for readjustments might exclude individuals from the labour marked. There is empirical support for the hypothesis that disability pension in such cases are used for

early retirement (143). This process of moving structural problems of the labour marked and society onto individuals is commonly known as a *process of medicalization*, as it then becomes a necessity for the expelled individual to obtain a medical diagnosis and demonstrate reduced ability to work to be awarded disability pension (144). It has been suggested that medicalization is politically necessary as large-scale unemployment is incompatible with social democracy (145). Whereas the term *medicalization* indicates a *sick-role* (144), there are also adverse effects of loss of job security on self reported health and minor psychiatric morbidity (146, 147). Mental illnesses may be particularly at risk for these processes as exclusion from the labour market is a risk factor for depression (148).

Disability pensioning is more prevalent among lower socio-economic strata than higher (149, 150), but it is not evident from empirical studies whether the effects of social inequalities are mediated by health or other mechanisms. Social inequalities in health are as prominent in Norway as in other European countries, and have been fairly stable over time (151). Relative municipality deprivation seems to be associated with an higher incidence of disability pension award, and this effect contributes to marginalization of people living in less affluent areas out of employment and thus to widening socioeconomic inequalities in the population (152). Medical determinants alone cannot explain either the dramatic variations or the overall increased incidence rates of disability pension in the last two decades in Norway (153). Beyond socio-economic inequalities, disability pension award is also found to be positively associated with age, female gender and being single (100).

Contrary to these involuntary *push factors* for disability pensioning are possible factors *attracting* individuals voluntary *choose* disability pension. Whereas most research under the push model is conducted within sociology and medical sciences, the *pull model* is more common in economy, which is illustrated by the famous quote by Duesenberry (1960):

"Economics is all about how people make choices; sociology is all about how people don't have any choice to make" (109).

It is a conundrum how disability pensioning can increase in most OECD countries parallel to improvement in key health indicators (97, 134). As mentioned above, the pull model hypothesizes that the individual *chooses* disability pension over continued work having rationally considered issues as economic incentives for continued work versus disability pension over increased leisure (123). The theory is based on the presumptions of limited resources in a broad sense (which is uncontroversial). More problematic, though, is the presumption of rational behaviour in employees in competing companies aiming at maximising profit (123, 144). The pull model hypothesizes that individuals become disability pensioners as a result of rational economic assessment of available options (109), and the importance of health is presumed to be marginal. If the model is empirically valid, the obvious intervention would be to lower the potential income from disability pensions and sickness absence, and thus reducing the attractiveness of receiving support from these welfare systems. There is some empirical support for the pull model (109, 154), also from Norwegian studies (144, 155). For example, before 1978, the first day of a continued sickness absence spell was not covered. When this arrangement was changed in 1978, and also the first day off sick was fully covered, the rate of sick leave in men increased (156). In accordance with this finding, the opposite effect was found in Denmark in 1983 when their system was retrenched to the Norwegian system before 1978 (156).

The pull-model has been criticized for not accounting for social inequality in health. Economic incentives can be defined as the ratio between the potential economic situation if on were to become a disability pensioner divided by the current economic situation. According to this definition low income groups will have a higher *incentive* for disability pension (144), but at the same time this is the group where health problems are more

prevalent (149, 151, 153, 157). It is therefore fair to postulate that health can be an obvious confounder in the association between economic incentives and disability pension award. Alas, information on this confounder is usually not available in studies examining these associations.

Despite lack of empirical support, the pull model has had a major impact on policy making. For example, the level of compensation in short term sick leave was slightly reduced in Sweden with the aim of reducing the level of sick leave. A Norwegian Public Report recommended 20% reduction in wage compensation with the purpose of reducing the overall sick leave, and similar interventions were discussed also in relation to disability pension (156). These suggestions for interventions were never translated into policy changes, but they are based on the presumption that pull factors, economic incentives and rational choices have an impact on individual choices over continued work versus sick leave or disability pension.

The recent review of research of causes (and consequences) of sickness absence and disability pensioning hardly covered research of effect of pull factors (98, 99). Addressing future need for research, the authors of the review briefly mentions a need for better scientific knowledge about how the design of the insurance system influences the prevalence of sick leave and disability pension. Further they state that in the public debate, the high level of sickness absence in some nations, such as Sweden and Norway, and particularly the recent strong increase, is explained as a result of changes in attitudes toward sickness absence, and they conclude that few scientific studies have targeted issues related to attitudes and the "absence culture" (101). This is, however, complicated as variables for economic incentives are difficult to operationalize as they rely on multiple factors and as health must be included as a confounding factor. On the contrary, any effect demonstrated of independent assessments of push factors, e.g. health problems are contrary to the pull model.

1.4 Mortality

1.4.1 Registration

Causes of death have in Norway since 1996 been classified according to the 10th revision of ICD-10. All deaths must be documented by a medical death certificate, usually "Death Certificate Issued by a Medical Practitioner / Report of Unnatural Death", alternatively "Report of Death by Local Policemen to Public Health Officer" (158). These certificates are sent to the Probate Court, which issues new death certificates that apply to the administrative and practical aspects of a death. This court will also provide a report of the death to the local population registry, which again forwards it to the Central Population Register. The Cause of Death Register is currently located at the Norwegian Institute of Public Health . All deceased persons who at the time of their death were registered by the Central Population Registry as living in Norway are included in the statistics, regardless of whether the death took place in Norway or abroad (158).

The rate of autopsies has been falling in Norway to 12% in 1999 (159). The main purpose of autopsies is to determine the cause of death and to examine the precision of diagnoses that can be verified by post mortem autopsy. It has been objected that the current autopsy rate is too low and a potential threat to the quality in public health care (159, 160). Deaths that still lack a medical certificate when the statistics are prepared, and for which no other information is available, are registered with unknown cause of death (158). The rate of autopsies varies considerably between geographical regions within Norway (161) and Denmark (162) with higher rates in urban areas then in rural.

The most important source of error or biases as to the cause of death statistic is the clinical examination performed by the physician who is completing the death certificate. Further, the physicians report of the cause (or causes) of death employing a standardized form (158) is a source of error, as is also the process of classification, encoding and electronic

registration at the central administration (163). Classification of cause of death can be a complex matter when several causes of death are reported, multiple sequences are possible, and local cultural variations in encoding are in effect (163, 164). According to routines, the physician is contacted by the Cause of Death Register for additional information if further information is needed to establish the cause of death (158).

Comparisons of mortality statistics between the Nordic countries have been difficult because of differences in empirical material, cultural differences, and differences in encoding, even though the same system of classification is employed (163).

1.4.2 Concepts and classifications: Causes of death

All deaths among inhabitants in Norway have since 1996 been encoded according to ICD-10. According to ICD-10, underlying cause of death is the disease or external cause of injury that, in the opinion of the physician, started the chain of events leading directly to death. In addition, up to six other contributory causes can be are registered. The *underlying* cause of death is defined as the disease or injury that initiated the chain of morbid events leading directly to death or the external circumstances of the accident or violence that was the cause of the fatal injury (158). According to ICD-10, the *immediate* cause of death is the injury or condition directly leading to death and which was caused by the underlying cause of death. Further, the term *complication* is used for any contributing causes of death which are not in a direct causal relation with the disease or condition that has caused the death (158, 165).

The most important difference between the Norwegian cause of death statistics and the original ICD-10 (35) is that a fourth category for R99 (other poorly defined and unspecific causes of death), which in Norwegian mortality statistics is further described as R99.0 causes of death cannot be established, R99.8 cause of death not given (missing information), and R99.9 no information (the death is recorded in the central population register, but not reported

to the cause of death register). There are also some minor differences relating to hip fractions (W19), diseases of the nervous system (category for 'not classified elsewhere' G98), and road traffic accidents (moving versus stationary objects) (158).

Behind the *underlying* cause of death registered in the Cause of Death Register is (for example myocardial infarction) there are obviously also a next level of causes (for example smoking). To be able to study causes of death beyond what is registered in the Cause of Death Registry, record linkages with other sources, e.g. journal registries from hospitals or national health surveys are necessary. This is – in Norway – made possible politically and technically through the national identification number system (163, 164).

1.4.3 Mortality according to the Causes of Death Register

The living age in Norway has been increasing linearly in both genders from the 1950s, and newborns in Norway in 2004 are expected to become 77.5 and 82.3 years (boys and girls, respectively) (166).

On changes in cause-specific mortality, CVD mortality decreased from 49% to 39% of all mortality from 1979 till 2003, whereas cancer increased from 21% to 25% in the same period. Cancer is now the most prevalent cause of death in the population younger than 80. This is not due to an increase in cancer, but due to a reduction in CVD mortality. In the population under 80 years of age, cancer is now the most common cause of death (158, 166).

In year 2002, 5.4% of all deaths were due to external causes and not illnesses. The proportion of non-illness death is strongly associated with age; comprising 61% of deaths in age 15-24 dropping to 3.4% in 75 years and older. The absolute number of suicides is, however, relatively stable across age-groups from 15-24 and older (unsystematically varying between 11.8 and 17.1 of 100 000 inhabitants, the highest rate in the age-group 55-64).

Suicide is also generally more prevalent in men than in women (16.1 versus 5.8 respectively per 100 000 inhabitants in 2002) (166).

There appears to be a decline in the rate of suicides in Norway over the past two decades. In 1991 there was 675 suicides in Norway, which is 1.5% of all deaths that year (95% confidence interval 1.4 – 1.6). This compares to 494 suicides, 1.1% of all deaths, in year 2002 (95% confidence interval 1.0 – 1.2). However, in the same period there have been an increase in number of deaths from mental diagnoses from 2.1% till 2.9% from 1990 till 2000 (166). A death is encoded as suicide if intentionality for death is known, thus there is a burden of proof for the mortality diagnosis suicide, perhaps biasing the results in underestimating the rate of suicide.

In 2003, 469 (2.3%) men and 793 (3.6%) women were registered dead due to a mental disorder (ICD-10 code F00-F99). The majority of the mental disorders registered as causes of death were unspecified dementia (F03) (54% and 87% in men and women respectively) and other organic mental disorders (F00-F09) (6% and 5% in men and women respectively). In men, mental and behavioural disorders due to psychoactive substance use accounts for 36% of mortality for mental disorders, comparing to 5% in women. Affective disorders (F30-F39) were registered as cause of death in 26 deaths, which accounts for 2% of mortality for mental disorders and 0.06% of all mortality in 2003. One man was registered dead due to anxiety disorders (F40-F48, Neurotic, stress-related and somatoform disorders), while five women died from anorexia nervosa (F50) (166). In summary, mental disorders account for very little of the total mortality according to underlying causes of death in the mortality registry. Any effect of anxiety or depression can be suspected to be within suicides, accounting for approximately 1.1% of all deaths, but suicide obviously has causes beyond anxiety and depression and also beyond mental disorders. Mortality due to mental disorders (F00-F99) is mainly registered as dementia, and in men, also behavioural disorders due to psychoactive

substance use. According to the Causes of Death Register, mental disorders in general, and anxiety and depression in particular, have limited impact on mortality.

1.4.4 Anxiety, depression and mortality

Depression is in the literature reported to be a risk factor for mortality beyond what is described as underlying causes of death in the Causes of Death Register (158). The picture is somewhat more unclear as to the effect of anxiety. The following six issues are discussed:

The first question concern whether there is an effect of depression on general mortality. There is broad evidence that depression increases general mortality, both from large scale studies and reviews (167-172), but residual confounding cannot be excluded (169). The effect of psychological distress (as measured with the 30-item General Health Questionnaire (GHQ)) on mortality was explained by adjustment for baseline physical illness in large prospective community study, and the authors suggested that psychological distress is a reflection of baseline physical illness that increases mortality, consequently placing psychological distress on the causal pathway between physical illness and mortality (173). Baseline physical illness is obviously also a relevant confounder in the association between depression and coronary heart disease (174), but there is evidence suggesting an independent effect (23, 174, 175). This is a relevant objection as depression is increased in individuals with physical conditions of many kinds including e.g. cancer (176, 177), CVD (20), diabetes (178) (though questioned as to confounding from comorbid conditions and complaints (74, 75)) and stroke (179).

The second question addresses if severity of depression relate to general mortality. This question is difficult to address by comparing studies that has used different instruments, possibly with non-comparative cut-offs for depression, but there is some evidence for higher mortality in psychotic depression than in severe non-psychotic depression (180). An extensive

review of the literature suggests almost equal effects of major depression and sub-clinical forms of depression (172). It remains unclear if severity of depression relate to mortality.

The third question relates to what mechanisms may be involved in the effect of depression on mortality. A whole range of mechanisms are proposed, but evidence is generally weak (181). The propositions can be presented as two main mechanisms (182): The first relates to lifestyle, namely that depression may be a distal risk factor related to a number of proximal risk factors that increase morbidity and mortality from CVD and other diseases. Candidate agents in this mechanism (182-184) comprise smoking (185, 186), lack of exercise (187), non-adherence to treatment strategies (188), and increased alcohol consumption (189). The second group of proposed mechanisms relates to biological change occurring in depression (182), e.g. increased cortisol (190), increased platelet coagulability (191) and changes in heart rate variability (192, 193). A review of possible mechanisms underlying the effect of depression on CVD mortality (comprising both lifestyle factors and biological change occurring in depression) suggested seven candidate mechanisms including antidepressant cardiotoxicity, associations between depression and cardiac risk factors (such as cigarette smoking, hypertension, diabetes and reduced functional capacity), association between depression and greater coronary disease severity, nonadherence to cardiac prevention and treatment regimens, lower heart rate variability (HRV) reflecting altered cardiac autonomic tone, increased platelet aggregation, and inflammatory processes (191). The authors of this review concluded that they were "struck by the many plausible ways in which depression could have a negative effect on cardiac functioning and coronary disease". They were, however, unable to indicate which, if any, of the suggested mechanisms that is empirically relevant.

The fourth question concerns which mortality diagnoses depression are associated with. Most of the literature on depression in relation to cause specific mortality concerns CVD

mortality (21-23, 179, 182, 194-197). As mentioned above, there are multiple candidate mechanisms proposed for the effect of depression on CVD mortality (191). Suicide is an obvious mortality diagnosis related to depression (184), but as suicide is a rare event in the general population (198), it is unlikely to account for all of the effect of depression on mortality. The risk of suicide has long been overestimated in depression (181). A recent meta-analysis of 47 studies estimated that the lifetime risk of suicide ranges from 2.2% to 8.6% in patients with depression (199), which compares to less than 0.5% in individuals without depression (181). As suicide is a rare event, suicide accounts for very little of the effect of depression on mortality. Follow-up studies of depressed individuals found very few suicides among deaths during follow-up (170, 198). There might, however, be hidden suicides among other mortality diagnoses (181). Also unnatural deaths beyond suicide have been reported to be associated with depression (25, 200). The evidence for effects of depression on mortality is weaker for causes of death beyond CVD mortality and suicide (200). From the existing literature, it is unclear whether the effect of depression varies across mortality diagnoses.

The fifth question concerns hypothesized effect moderation of gender: The effect of depression on mortality is reported to be stronger in men than in women (170, 201, 202), but as these findings are reported with reference to stratified analyses within each gender rather than by demonstration of an interaction between gender and depression in prediction of mortality, the validity of these findings have been questioned (169). It is also unclear if gender moderates the effect of depression on mortality.

The sixth question concerns the role of comorbid anxiety with regard to the association between depression and mortality. This question is relevant for at least two reasons: Anxiety and depression commonly occur comorbid (50), and comorbid anxiety depression is associated with higher levels of impairment (107), more physical diseases (57) and more help-seeking (45) than anxiety or depression alone. However, compared to the

literature on mortality, there are very few publications on the association between anxiety and mortality, and also comorbid anxiety depression. In the few reports available the results are conflicting, with reports of both positive (203) and negative (204) associations. The latter study is probably the best available examining the association between anxiety and mortality; it was satisfactory powered (N=5 057 patients referred for routine exercise testing for chronic coronary artery disease) and employed the HADS (204). However, comorbidity between anxiety and depression was not examined. Anxiety is also reported not to be associated with mortality (205, 206), but these studies are small and possibly under-powered.

There are numerous clinical and epidemiological studies of hypothesized effects of depression on mortality, originating from many different countries. The majority of studies follow up clinical samples, e.g. patients hospitalized for CVD after they have screened them for depression. Residual confounding is likely to be a problem in the literature due to lack of access to information in many of these studies (169). The focus on mechanisms underlying the effect of depression on CVD mortality, and the strong focus on CVD mortality rather than other diagnoses is perhaps unjustified as the evidence for depression being a stronger risk factor for CVD mortality than other mortality is weak.

1.5 Aim of the study

Employing a unique record-linkage between a large health-survey of the general population and the national registries on disability pension and mortality, the aim of the present thesis is to address questions concerning effects of anxiety and depression on work-related disability, general mortality and cause specific mortality.

In the first paper, the specific objectives were to examine if anxiety and depression were independent predictors, adjusted for physical health, both of disability pensions for all causes, and in particular for pensions officially awarded for physical conditions. In order to

examine other factors relevant to the push- and the pull models, we expanded the model beyond physical and mental health to also examine the effects of socio-demographic and behavioural variables on disability pension award.

The second paper concerned general mortality, and the specific objectives were (a) to examine effects of case-level anxiety and depression as well as comorbid anxiety and depression upon mortality, (b) to clarify the shape of the association between mortality and symptom load of anxiety and depression, (c) to investigate possible mediating and confounding factors in these associations, and (d) to test the hypothesis that depression is a stronger risk-factor for mortality in men than in women.

The third paper addressed issues concerning cause-specific mortality in relation to anxiety and depression. Specific objectives were to (a) compare the strengths of the associations between anxiety/depression and mortality across causes of death, (b) to compare confounding and mediating factors in CVD with other causes of death comprised. The analysis also addressed issues on hypothesized hidden suicides in non-illness deaths beyond suicides.

2 Material and methods

2.1 Material

The three present studies all employ historical cohort designs. Baseline information on mental health and confounding factors was obtained from the HUNT-2 study (207). Outcomes of mortality and disability pension award were identified in public registries, and merged with the HUNT-2 study employing 11-digit personal identification numbers.

2.1.1 The Health Study of Nord-Trøndelag County (HUNT)

The first Health Study of Nord-Trøndelag County in 1984-86 (HUNT-1) aimed at screening the entire population of Nord-Trøndelag County age 20 and older for hypertension, diabetes, lung diseases and quality of life. Each participant was asked to complete two questionnaires, and a physical examination with measurements of BMI, chest x-ray screenings, and non-fasting blood glucose. Approximately 40 publications were based on the first HUNT survey by 2003 (207).

The second HUNT study (HUNT-2) was carried out from August 15th 1995 till June 18th 1997, and is the main source of data for the present studies. The number of main objectives in the HUNT 2 study was expanded from the first survey with projects on cardiovascular disease, diabetes, obstructive lung disease, osteoporosis and mental health, in concordance with contemporary priorities of the health authorities (207). The second HUNT study is perhaps the most comprehensive health survey available, with its broad coverage of physical conditions, mental health, and somatic symptoms, and the cohort that participated in both the first and the second data wave are acclaimed as valuable for studies where two-wave

panel data are needed. Inclusion of mental health in the second HUNT study was perhaps the most radical change from the traditional focus on somatic conditions in Norwegian health screenings (208). HADS was found suitable as a screening instrument for mental health as it does not give a floor effect when employed in the general population, it does not included items on suicidal ideation or psychotic thoughts that may be provocative or offensive, and it had previously been applied in several studies within psychiatry and somatic medicine (209). The HUNT-2 data without record linkages have been utilized by research groups in Nord-Trøndelag (208) and Bergen (210).

The population in Nord-Trøndelag County counted 127 000 residents in 1995-97, and is fairly stable with a net migration of 0.3% per year (1996-2000). The population is also homogenous with less than 3% non-Caucasians (207), which obviously represent a limitation with regard to the generalization of findings. The information collection was performed in multiple steps: First, an invitation letter for participation in the study was sent by mail with an attachment of a three-page questionnaire (labelled questionnaire 1) and with an information folder. Questionnaire 2 was distributed at the clinical examination, which included measurements of blood pressure and heart rate, height and weight, waist and hip circumference. In summary, the available data from the HUNT study cover subjective health, diabetes, lung diseases, cardiovascular diseases, thyroid diseases, muscle- and skeletal diseases, mental diseases (especially anxiety and depression), quality of life measures, migraine and other headaches, and physical and mental dysfunction, prostate complaints, urine incontinence, and female reproductive data i.e. on menarche, pregnancies, hormone use, and gynaecological diseases. Information on personal environment includes residence, size of household, education, occupation, in-house environment, neighbourhood characteristics, friendships, and sense of humour. Information on personal habits included food intake, use of drugs, use of alcohol and tobacco, and physical activities. Some items covered family medical

histories and use of health services. Additional questionnaires were used in sub-samples, i.e. questionnaires on lung diseases, diabetes, hypertension, hearing disorders, and vision. Some selected groups were invited to a more detailed (phase 2) examination, i.e. participants in studies on diabetes, prostate, headache, lung function and bone density (207).

Participants in need of further medical attention, e.g. individuals with high blood pressure (diastolic blood pressure above 125 mmHg), elevated non-fasting blood glucose reading (>11.1 mmol/l) (207), or elevated scores on the total HADS sum-score (>25 points on the total HADS scale, and a random sample of individuals with scores slightly below this cut-off) (208) were informed in writing and advised to see their general practitioner for further clinical tests and possible treatment.

A total of 94 194 individuals aged 20 years and older were invited to the HUNT 2 study. As many as 1258 died or moved before attending the study, resulting in a total population of 92 936 eligible for participation. A total number of 66 140 participated in some parts of the study (71.2%). The participation rate was higher among women than men, and lowest among 20-29 year olds (207). The low level of participation among the youngest ones was in large part caused by difficulties in obtaining directories of residency in these age cohorts due to studies, military services, long vacations, and temporary jobs in other counties or abroad. Out of 92 100 individuals aged 20-89 years at the time of the survey, 62 344 filled in valid ratings on HADS (67.7%) (77), and 60 869 (66.1%) individuals also had valid responses on a broad range of somatic and social variables (76).

Shortly after the termination of the data collection in HUNT-2, a 2.5% random sample of non-attendees (n=685) were approached for a study with the purpose of determining reasons for non-participation (211). Approaching non-participants both by mail and telephone resulted in a total sample of 326 individuals (47.6%). In individuals within working age, the main reasons for not attending the study was lack of time, emigration from the county, being

busy at work, that they had forgotten, or no reason at all. Among the age group of 70 and older, many reported regular follow-ups by physicians or at the hospital, and therefore did not see any need to attend. Some individuals (10%) could not attend because they were immobilized due to disease, and some (4%) refused due to long waiting time at the screening site. Rather few (9%) reported that the survey was unnecessary or simply that they were unwilling to participate (207, 211). Previous studies have indicated more mental health problems in non-participants in the context of health surveys (212). This was not examined in the HUNT non-participation study (207, 211), but is most probably relevant for the HUNT study as well.

2.1.2 National registries of work-related disability

Information on award of disability pension was available from registries of the National Insurance Administration. These contain information on date of award, proportion of disability (50-100% disabled), and up to two diagnoses warranting disability pension for each application. Multiple applications are common due to changes in diagnostics and degree, as many initially are awarded a partial disability pension. Accumulated, across the disability pension population, most individuals are recipients of 100% disability pension. Diagnoses in these registries were up until 1998 encoded according to ICD-9, but from then on in ICD-10 categories (30). Data from the HUNT study were linked to the disability registry by employing a personal identification number. Individuals awarded disability pension before participating in the HUNT or in a quarantine period between the HUNT study and start of the follow up period could be identified (with the purpose of exclusion from the study).

2.1.3 The Norwegian Causes of Death Register

The Norwegian Cause of Death Register (158, 164, 166) is presented above (chapter 1.4.1 and 1.4.3). Mortality data were linked to the HUNT database applying the 11-digit national personal identification number (207). The mortality data covered a follow-up period from attendance in the HUNT study (August 1995 till June 1997) till the end of year 2000. Mean follow-up period was 4.4 years (SD 0.68). Mortality statistics were also available for non-attendees to the HUNT study.

2.2 Exposure: Anxiety and depression

Anxiety and depression are the exposure measures in all three papers, and are measured employing the HADS.

Diagnostics within the field of psychiatry is often criticized by other medical specialities for being *vague or woolly*, commonly with reference to lack of biological markers of pathology (213). Consequently, psychiatry was among the first medical disciplines to develop internationally recognized operationalized diagnostic criteria with corresponding standardized approaches to distilling symptoms into diagnoses or scalable traits. These criticisms are therefore today largely misplaced, as the measures applied in the field of psychiatric epidemiology now is perhaps more valid and reliable than even for some biological measures (213).

2.2.1 Scale properties of HADS

HADS is used for measuring anxiety and depression in all papers, and is a self-report questionnaire comprising 14 four-point Likert-scaled items, seven for anxiety (HADS-A) and

seven for depression (HADS-D). To avoid false positive cases in contexts of somatic illness, no somatic items or items regarding sleeping difficulties are included (49).

However, even though information is based on self-report, it is not correct to claim that participants *report having anxiety or depression*, as the report merely are symptoms recognized as core features of these disorders. It is obviously – and possibly also likely – that many individuals report symptom loads above cut-off without agreeing they have anxiety or depression. Items are reported in table 2.

Table 2. HADS items

Scale / item #	Text
A / 1	I feel tense or wound up
A / 3	I get a sort of frightened feeling as if something awful is about to happen
A / 5	Worrying thoughts go through my mind
A / 7	I can sit at ease and feel relaxed
A / 9	I get a sort of frightened feeling like ’butterflies’ in the stomach
A / 11	I feel restless as if I have to be on the move
A / 13	I get sudden feelings of panic
D / 2	I still enjoy the things I used to enjoy
D / 4	I can laugh and see the funny side of things
D / 6	I feel cheerful
D / 8	I feel as if I am slowed down
D / 10	I have lost interest in my appearance
D / 12	I look forward with enjoyment to things
D / 14	I can enjoy a good book or TV programme

Questions are answered on a four-point scale from 0 to 3, labels varying between items. Items 2, 4, 6, 7, 12 and 14 are reversed before summation.

As described above (chapter 1.1.4), HADS-A and D share 30% of the total variance in symptoms of anxiety and depression (50). Despite this strong correlation between the two

sub-scales, Principal Component Analysis extracted two factors according to the originally proposed model (49) in the HADS that accounted for 57% of the variance. The two-factor solution was found in the total HUNT sample, in sub-samples defined by clinical (both mental and physical) characteristics, and in sub-groups defined by age and gender. The internal consistency, as measured with the Cronbach's Coefficient Alpha, was good with values of 0.80 and 0.76 in the anxiety and depression scales respectively. The homogeneity of the scales was also good, as anxiety items loaded more on anxiety factors than on the depression factor, and vice versa for depression. This consistent pattern was found both in the total sample and in the sub-samples. However, items 6 ('I feel cheerful') and 7 ('I can sit at ease and feel relaxed') diverged to some extent from this pattern by loading substantially on both factors (50).

2.2.2 Case-finding abilities of the HADS

The LEAD-principle for diagnosing mental disorders (214) is perhaps still the gold standard within psychiatry (215). LEAD is an abbreviation for longitudinal observations made by clinical experts who have all relevant data for deciding on a diagnosis. The issue of whether the clinical expert is necessary for defining cases with mental disorders is a continuously ongoing debate between epidemiologists and clinicians.

Obviously, self-report instruments like HADS do not subscribe to the LEAD-principle. Employing self-administered screening instruments will limit the assessment of symptoms to what the patient is able to report. A commonly employed screening instrument for depression in primary care is the Montgomery-Åsberg Depression Rating Scale (MADRS) (216), which includes one item on external symptoms of sadness which is not based on self-report. The other nine items are based on self-report, though reported through the physician. Many physicians have, however, known their patients over a long period of time, and rely on their

clinical impression rather than structured interviews. The Clinical Global Impression – Severity (CGI-S) is a standardized dimensional one-item assessment tool that is based on the clinician's judgement of severity of generalized anxiety disorder (GAD) and major depressive disorder (MDD) (217), which corresponds to clinical assessments solely based on the clinician's general judgement. The CGI-S approach is perhaps more in line with the LEAD-principle for diagnosing mental disorders than screening instruments like HADS.

Which of the two approaches is most reliable is also an empirical question that has been examined in a recent Norwegian publication (218), where the more comprehensive instruments Generalized Anxiety Questionnaire (GAS-Q) (219, 220) and the Depression Screening Questionnaire (DSQ) (221, 222) were used as gold standards for DSM-IV diagnoses of GAD and major depressive episode (MDE) respectively. Employing both HADS and CGI-S as continuous measures and GAS-Q and DSQ as dichotomies for DSM-IV diagnoses (and gold standards), the self-rating approach (employing HADS) was a better case-finder for both GAD and MDE than the clinical assessment approach (CGI-S). The area under the curves (AUCs) in receiver operator curves (ROCs) were 0.88 and 0.77 for self-rating and clinical assessment respectively in GAD, and 0.93 and 0.87 respectively in MDE (218). The context of this analysis was a pharmaceutical study for examining hypothesized effects of serotonin noradrenalin reuptake inhibitors on anxiety disorders. General practitioners agreeing to participate in the study could be presumed to be interested in mental disorders, and the study itself might also increase their attention to mental disorders. Consequently, the study is possibly biased in favour of the clinical assessments rather than HADS. In conclusion, even though HADS is far from the LEAD-principle, it is a better case-finder than brief clinical assessments performed by general practitioners.

According to a literature review covering 31 studies, HADS has shown good case-finding properties for anxiety and depression in patient populations in primary care as well as

in hospital settings (56). A cut-off score of 8 on both subscales was found to give an optimal balance between sensitivity and specificity, both at about 0.80, for depression and anxiety according to DSM-III and IV, ICD-8 and 9. This is similar to the sensitivity and specificity of other screening instruments, e.g. the GHQ.

2.2.3 Operationalization of anxiety and depression employing HADS

HADS was operationalized in five ways in the present study:

For most purposes, anxiety and depression were used as categorical variables with case-level for scores of 8 and higher. This is in line with multiple publications using HADS both internationally (56) and in Norway (e.g. 73, 80, 223). Some variance in HADS is lost by this approach, and false negative cases will be prevalent employing cut-off levels at this range. Misclassification at random due to e.g. measurement error is likely to occur, in particular in individuals with scores near the immediate range around the cut-off (41), resulting in underestimation of true effect sizes. However, this operationalization is in accordance with the tradition in the relevant journals, and eases communication of results in milieus familiar to categorical measures rather than continuous ones.

A second categorical approach dealing also with comorbidity was categorization of four groups by the HADS: No case-level anxiety or depression (range 0-7 on both scales), case-level anxiety or depression, or comorbid anxiety depression (range 8-21 on both scales). This approach is also in accordance with multiple publications employing HADS in the HUNT study in Norway (e.g. 71, 224), but is not as widely applied as the categorical approach for analyses involving each scale separately. The advantage of this approach is the possibility of examining issues relating to comorbidity between anxiety and depression, e.g. in associations with work-related disability and mortality. Limitations are as for categorical

measures in general, which will be discussed in more detail in chapter 4.3.2 under residual confounding.

The third approach was to employ anxiety and depression as continuous variables (range 0-21 points on each sub-scale). The main advantage in this approach is less loss of variance, but is disadvantaged as it presumes comparable steps along the entire scale, e.g. that the clinically relevant difference between scores 0 and 2 compare to that between 7 and 9, and 15 and 17. This approach is widely used in publications where HADS is used (e.g. 77). Quadratic terms of these continuous measures were applied to examine U-shaped associations.

A fourth approach was to operationalize anxiety and depression according to quartiles in the distribution, and to include the variables as categorical measures in regression models. This approach combines advantages and disadvantages to continuous and dichotomous approaches, but with the special advantage that the approach is suitable for examining associations also with other shapes than linear and U-shape across the entire distribution. This approach has, to the best of my knowledge, not been applied to HADS previously, but is common in epidemiologic research.

Finally, the last approach is also a categorical one, with groups for severity of anxiety and depression according to the originally proposed model (49): No disorder [range 0-7], mild disorder [8-10], moderate disorder [11-14], and severe disorder [15-21]. This approach is not commonly applied, and the validity of cut-offs and labels are questionable. The approach has, however, advantages for examining dose-response associations between severity and an outcome within the clinical range of the scale.

2.3 Outcome

2.3.1 Disability pension award

Award of disability pension is the outcome variable in the first study. This measure is extracted from administrative registries (30, 225).

As a measure of work-related disability in general, the validity of disability pension award might be questionable. National policies for regulating health related benefits vary, but essentially all adhere to the medical model for awarding disability pension, where physicians are appointed to a gate-keeping function with the purpose of restricting disability pensions to individuals with work-related impairment from a diagnosed medical condition (134).

There is, however, several issues questioning the validity of disability pension award for the construct of work-related disability: The first relates to causes for disability pension award beyond health, including both push- (142, 149-151, 153, 226) and pull-factors (123, 156, 227) as described in chapter 1.3.4. There are reports of fairly good self-rated health among disability pensioners (134, 228), and improvement in public health indicators over the last decades have taken place in parallel to an increasing number of people living on health related benefit schemes (126, 134).

The second relates to the roles of physicians with regard to sick-listing practices (discussed in chapter 1.3.3); issues relating to conflicting roles between gate-keeping in terms of principal agent theory (123) and being the patient's advocate (119, 122). As described above, physicians rarely restrict long-term sick-leave in patients requesting such benefits (113-115). Subjective perceived health is reported to be a strong predictor of disability pension award (229), and the effect of perceived health on disability pension award can hardly be attributed to objective indicators of health (230, 231).

The third issue relates to possible under-utilization of disability pension award in individuals with actual work-related disabilities. Individuals on unemployment benefits are

reported to suffer from more health problems than employed individuals (148). Work-related disability might also in some cases be supported financially within the family, thus not subject themselves to disability pension.

All these factors are reducing the validity of disability pension award as a measure of work-related disability, thus weakening possible effects of mental health on disability pension award.

2.3.2 General mortality and cause specific mortality

General mortality is the outcome variable in the second study, and the information obtained from relevant registries is regarded highly reliable, and the only source of drop-out is emigration from Norway.

More questionable, though, is the reliability in cause specific mortality, which relies on diagnosis for *underlying* cause of death, which is the outcome variable in the third paper. Issues relating to reliability problems in the registration process are described in chapter 1.4.2 and 1.4.3. The problem of deciding on the level in the causal chain leading up to mortality is also an issue (chapter 1.4.4).

2.4 Mediating and confounding variables

A whole range of factors are associated with both mental disorders, disability pension award, and mortality, including physical conditions, somatic symptoms, biological factors (BMI, blood pressure, cholesterol level), socio-demographic factors, and health related behaviour. These will be described in more detail here.

2.4.1 Somatic conditions

Somatic conditions are in HUNT measured by self-report. Questions relating to conditions popularly self-diagnosed are framed in the way *have a physician ever told you that you have [e.g. osteoporosis]*. Copies of questionnaires are available in Norwegian (232). Data on physical conditions were collected by two questionnaires, one to be completed before the physical health examination, the other to be completed after the examination and returned by mail (207).

An index for self-reported somatic diagnoses comprised asthma, angina pectoris, stroke, myocardial infarction, diabetes, goitre, hypo- and hyper-thyroid function, other diseases in thyroid gland, fibromyalgia, osteoporosis, arthritis, rheumatism, ankylosing spondylitis, myocardial infarction, cancer, epilepsy, blood-pressure (being treated or monitored), and one open item for any other illness.

Obviously, the above mentioned conditions are not all equally relevant for the outcomes of interest. Consequently, the single items comprising the index was weighted for medical doctor (MD) certified sick-leave in the paper predicting disability pension award, and for mortality in the mortality papers before summarized as an index. Technical details are described under statistics (chapter 2.6.6).

Self-report of physical diagnoses implies a problem of reliability, which perhaps have received less attention than measures of mental health by self-report (213). In a separate study, we examined the concordance between self-report of cancer (present or former diagnosis) and registrations in the Cancer Registry of Norway (CRN) (233). Excluding basal cell epithelioma, 20% of former (and current) cancer patients did not self-report their diagnosis in correspondence with information from the registry. The deviating cases were more often men, smokers, and had their cancer diagnosis as very young or as elderly. In reverse, among 63347 HUNT-2 participants without any record of cancer according to CRN,

479 individuals (1%) still claimed a cancer diagnosis, resulting in 20% false positive cases of self-reported cancer. As there are no national complete registries of other diagnoses, we have not been able to examine the accuracy of self-report of other somatic conditions. As reported by Prince and colleagues (213), also among the many HUNT-2 study there is less attention to problems of reliability in self-report of somatic conditions then psychiatric conditions, and the publication on self-report of cancer (233) have received surprisingly little attention.

The consequences for reliability in self-report measures of somatic conditions for the present studies relates to residual confounding, which will be further discussed in chapter 2.6.2.

2.4.2 Somatic symptoms

As for somatic conditions, an index for somatic symptoms was included as a confounding factor in all three papers. It is computed from reported somatic symptoms and then counting the number of organ systems these symptoms stem from. These were weighted as described for somatic conditions (chapter 2.4.1, statistical procedure described in chapter 2.6.6). Items in HUNT-2 on somatic symptoms without a hypothesized organic aetiology (e.g. neck pain, but not whiplash injury) were regarded as a somatic symptom.

The organ systems comprised *gastrointestinal symptoms* (four questions on nausea, heartburn, diarrhoea and constipation), *musculoskeletal symptoms* (pain in neck, shoulders, elbow, hands, breast, back (three areas), hips, knees, and ankles), *head* (two questions on headache and migraine), *senses* (two questions on hearing and sight), *heart* (one question on palpitations) and *respiratory function* (one on respiratory problems).

The approach of counting organ systems wherefrom symptoms were reported (rather than counting single symptoms) was inspired by criterion D in the ICD-10 diagnosis for somatization disorder (ICD-10 code F45.0) (35). Again inspired by somatization disorder

(criterion A), empirical examination of confounding effects of somatic symptoms was always performed also adjusting for somatic conditions; this to exclude overestimating the confounding effects of somatic symptoms that could be secondary to any diagnosed physical condition. Criterion B and C could not be included in the operationalization of the index, and even though the index likely will measure the tendency to somatise, it should not be regarded as a proxy for F45 Somatization disorder.

2.4.3 Biological measures

Physical measures of body mass index (BMI), systolic and diastolic blood pressure, and non-fasting total cholesterol were obtained by a specially trained nurse during the screening, and all these variables were encoded in quartiles and regarded as relevant confounders in the mortality papers. Based on available information on risk-factors for disability pension award (98, 101, 105, 110), these variables were not regarded be relevant in the analysis of disability pension award.

2.4.4 Self-rated impairment

Physical impairment was based on four questions on self-evaluated moderate or severe impairments from somatic disease, reduced locomotivity, hearing and sight, added to one index from 0 (no impairment) – 4 (impairments from all four). This index was used in the mortality papers, but to avoid circularity, not in the paper predicting disability. Previous analyses employing this index have shown that it is closely related to mental health and age (76), and inclusion of this factor as a confounder probably leads to statistical over-adjustment.

2.4.5 Socio-demographic factors and health related behaviour

Health related behaviours were included as confounding factors in the mortality paper, and also in a parsimonious model predicting disability pension award. Variables included current smoking habits, physical activity, and alcohol consumption (as measured by CAGE (234)). The two latter variables were obtained from a second questionnaire with about 20% lower response rate; missing responses were encoded as a separate category.

Educational level was encoded according to the highest completed educational level on a three-point ordinal scale from compulsory school only to university level (45). An index for s*ocioeconomic status* according to the Erikson Goldthorpe Portocareros was computed (157).

2.5 Research strategy: Historical cohort designs

Research methods in psychiatric epidemiology have developed in several stages; *Suicide* by Durkheim in 1897 perhaps being a starting point. In the 1930s to the 1960s, non-standardized clinical diagnoses were employed in psychiatry, and the few population-based studies in this period (235) relied on the assumption that common clinical training for psychiatrists would in some way ensure reliability and validity of their diagnostic assessment (96). The second phase of methodological development led up to standardization of assessments e.g. as in the US Stirling County Study (236), which used self-report instruments with psychopathology scaled on a continuum from health to disease. This was certainly no blind alley in the history of psychiatric epidemiology (96). The development diagnostic manuals leading up to today's DSM-IV (34) and ICD-10 (35) marked the third phase of the development of methods in psychiatric epidemiology (96). Whereas observational research relates to describing *what there is*, analytical research concerns issues of *why* (237). The early population based studies

like ECA (2) can, however, be criticised for gathering relatively little information beyond prevalences stratified by socio-demographic factors. Prince et. al. quotes findings of associations between economic deprivation and common mental disorders (238), and also depression and child abuse (239, 240), as examples of more theory driven research of aetiologies based on the NCS (96), but they argue that *the real development* has been in the use and increasing sophistication of analytical designs, including both case-control designs and cohort studies. They emphasize among others Patel et. al.'s findings of effects of mothers' mental health on infectious disease and development in offspring (28, 241) as examples of these more advanced research strategies in psychiatric epidemiology (96).

There are three kinds of cohort studies (242): *Classical* cohort studies select groups on the basis of exposure, and follow them in order to compare incidences of outcomes of interest. *Population based* cohort studies usually select the panel on the basis of convenience, and multiple exposures are ascertained at baseline and related to multiple outcomes of interest over a follow-up period. The *historical cohort* study is a retrospective variant of the population based cohort design in that exposures of interest are measured years before the commencement of the study, typically for other purposes. Outcomes are typically identified in other sources and traced back to baseline. Essential features of cohort studies are that participants are defined by their exposure status rather than by outcome (as in case-control design), and that it is longitudinal with measurements of exposure before outcome. Weich et. al. (242) describe the famous Barker study of effects of being small for gestational age (SGA) on midlife vascular and endocrine disorders (243) as examples employing a historical cohort design, a research design also applied in a record linkage between the Medical Birth Registry and the HUNT study in examination of effects of SGA on mental disorders in early adult life (244).

The present three studies are probably best described as historical cohort designs, as associations between mental health and work-related disability and mortality were hypothesized after the health survey. However, the project of linking HADS and the mortality registry was described prior to HUNT-2 as regards hypothesized effects of the intervention study on suicide prevention (208), and several somatic HUNT-2 projects were aiming at cohort designs with mortality and disability as endpoints (207), thereby providing informed consents and necessary approvals for the present studies.

There are advantages and disadvantages to historical cohort designs (242), and many are relevant for the present studies: Advantages include minimal observer- and subject bias (as registration of outcome is blind to exposure status), as the specific hypotheses of interest were not known for the participants, and even not formulated at the time of the health screening. The longitudinal design with exclusion of individuals where the outcome of interest is manifest prior to the health survey (obviously mortality, but also disability pension award), renders it possible to study the temporal sequence between outcome and exposure.

Prospective cohort designs are indeed very costly and time consuming, but current Norwegian research policy allow us to link data sources like the HUNT study and public registries. This makes historical cohort designs accessible. The large samples at baseline also enable us to study rare outcomes like mortality and disability pension award. Cohort studies are generally prone to selection bias arising from incomplete follow-up. The possibility of record linkages in Norway reduces this problem as outcomes can be identified in complete national registries. This possibility of record linkage is obviously an advantage for cohort studies that exists in very few countries, Norway being among these. For example, in the famous Barker study (243), outcomes had to be traced by names and addresses in the local environment of the hospitals where “small for gestational age”- babies were born. Lack of

record linkage possibilities also limits application of this design in for example the NCS (12, 13).

For the studies on mortality, the only source of dropout was emigration from Norway. In prediction of disability pension award, private early retirement and mortality were sources of dropout which we were unable to address.

Confounding is generally a problem in cohort studies. However, as the HUNT study covers many aspects of health and social demographics, we were able to adjust for a whole range of relevant confounding factors in the prediction of mortality and work-related disability.

Choosing a study population for a cohort study often represents a compromise between validity and generalizability (242). For example, the effect of smoking on mortality (245-247) and dementia (248) was studied in British medical doctors because valid measures of relevant variables could be obtained in this sample. Similarly, effects of psychological distress on coronary heart disease were studied among British white colour employees, the Whitehall II Study (175). With reference to the population-based design, it is commonly argued that the generalizability is good in the HUNT-2 study. However, non-participants differ from participants (211, 212), and Nord-Trøndelag is not fully representative for Norway (or Europe), being less urban and less educated, limiting the generalizability of the study.

Mental illnesses commonly have a long-lasting or chronic course with recoveries and relapses. The HUNT study was performed at a fixed point of time, irrespective of variations in the mental health status of participants. Consequently, the design is biased towards including long-lasting conditions rather than brief episodes. For example will recurrent depressive disorders (F33) and dysthymias (F34.1) within the year of the health screening be captured by HADS in HUNT more often than would depressive episodes (F32) (35), simply because the longer mental disorders are lasting, the more likely they are to be present at the health

screening. In line with the DALY methodology (14, 15), it might be fair to argue that longer lasting conditions are more severe, and the over-sampling of individuals with long-standing conditions might therefore be adequate.

2.6 Statistical analyses

2.6.1 Logistic regression analysis

Logistic regression models (249) were applied in all analyses of effect of anxiety and depression on mortality and disability pension award. The logistic regression model is similar to the linear regression model, the difference is that in the case of logistic regression one is modelling on and predicting the log of the odds of the outcome (mortality or disability pension award) rather than the absolute value of a continuously distributed outcome (250). Multiple logistic regression models have been applied with the purpose of controlling for confounding while testing for hypothesized effects of anxiety and depression on disability pension award and mortality. In predicting disability pension award, logistic regression models were also applied for exploratory purposes to develop a parsimonious model.

When using logistic regression models, relative risks are reported by odds ratios (OR). Strictly speaking, odds ratio values are only approximations to relative risk. For skewed dichotomies (for instance as regards infrequent diagnoses), however, the approximations are rather good. However, a high relative risk for a rare exposure has impact on few individuals. Therefore, associations between the exposure and outcome might also be described in terms of population attributable fractions (PAFs), which signify the proportion of incident cases in the population which would have been prevented if a causal exposure were removed, assuming an unconfounded causal association (242). Both measures are applied when appropriate in the analyses.

Cox proportional hazard regression models were not applied due to three reasons: The proportion of censored individuals at the end of the follow-up period is higher than is recommended for employment of Cox regression models; mortality and disability pension award is after all rare outcomes within the available follow-up time. Second, the semi-parametric modelling of time in Cox regression models is perhaps not entirely applicable when the dates of exposure and outcome are difficult to establish (250). Obviously, we have information as to date of death, date of award of disability pension, and date of the health screening in HUNT. But the exposure variables of interest measure mental disorders chronic of nature (hence discussion in chapter 2.5), so employment of the HUNT data as date for exposure might be arbitrary (compared to for other conditions with more discrete dates of onset, e.g. myocardial infarction). Mortality is obviously relevant to define by date, but disability pension award is a long-lasting process, where the *decision* of disability pension award is perhaps made by the applicant (or the physician) long before award of disability pension, hence the discussion in chapter 1.3.3 and 1.3.4. Third, in post-hoc argumentation, the effect of the exposure measures on outcome was not moderated by follow-up time, perhaps due to the chronicity of anxiety and depression. Consequently, logistic regression models were applied instead of Cox proportion hazard regression models.

Another statistical issue concerns our use of sumscores, which are consistent with formative measurement models for the exposures rather than analyses of latent variables, which are consistent with reflexive measurement models. It is perhaps more accurate to analyse anxiety and depression assuming reflexive measurement models, but as the outcome is dichotomous, available software has until recently been limited. The consequence of employing regression analyses of simple (or weighted) sumscores instead of structural equation modelling with latent variables is that we underestimate the true effects of anxiety

and depression on the outcomes of interest. It is, however, debated whether reflexive measurement models are appropriate for analyzing measures of mental disorders (251).

There are multiple presumptions of relevance as to the logistic regression model concerning specification of the model, measurement errors and error terms (252, 253). The probably most important presumption for the present studies relates to that no relevant confounders should be excluded; this to avoid overestimating the effect of the exposure on outcome. This has probably been a problem in literature on mortality (169), and is perhaps better covered in the present analysis. However, as multiple factors are associated with the outcomes and exposures of interest, this presumption will always be violated. Further, possible mediating factors (being on the causal pathway between mental disorders and mortality and disability pension award) should not be included in the model as confounders (250, 254); this to avoid underestimating the true strengths of the associations between exposure and outcome. This is further discussed in chapter 2.6.3. The problem of colinearity (250, 252), resulting from strongly correlated confounders is avoided by careful examinations of associations between independent variables, and examination of coefficients of tolerance (defined as one minus explained variance by all but one independent variable in prediction of the excluded one) in explorative linear regression analyses with outcomes as dependent variables. No problem of colinearity was identified. The issue of measurement errors and residual confounding for all involved variables will be covered in chapter 2.6.2.

2.6.2 Measurement errors and residual confounding

There are obviously measurement errors regarding exposures (as discussed in chapter 2.2) and confounders. Measurement error in mortality in itself is obviously minimal, but identifying the correct underlying cause of death poses several problems. In addition to random misclassification of mortality diagnoses, there are probably also biases, as presented in

chapter 1.4.1, 1.4.2, and 1.4.3. Regarding disability pension award, measurement errors are likely to be minimal, but the problem of validity is as mentioned in chapter 2.3.1 highly relevant.

Measurement errors relating to misclassification of mental disorders are likely to be random (250), and the consequence of this is limited to weakening of associations with outcome variables.

Measurement errors of confounding and mediating factors are also relevant (as described in chapter 2.4) at the stage of appraisal. Measurement error in a confounding factor obviously reduces the effect of the adjustment of the association of interest, with the consequence that we are probably *underestimating* confounding in all analyses (255).

The issue of residual confounding is an important consideration for interpretation of results. Any measurement error of the confounding variables will reduce the effect of adjustment on the association of interest (255). As discussed above (chapter 2.4.1), this also applies to rather objective entities, like having a cancer diagnosis (233) and medical examinations. For example, to reduce measurement error, all participants in HUNT-2 had their blood-pressure measured twice after an initial measurement not recorded (207). The blood-pressure was in the end defined as the mean of the two last measurements.

2.6.3 Confounders versus mediators

Confounders and mediators are described in chapter 2.4. Statistically, confounders and mediators are treated alike, but interpreted differently. All relevant confounding factors must be associated with both the exposure and outcomes of interest, and not be on the causal pathway between exposure and outcome (250, 255). Alcohol consumption is, for example, from clinical experience known to be increased in anxiety. To the extent increased alcohol consumption is a consequence of anxiety; it is positioned on the causal pathway between

anxiety and e.g. disability pension award, and accordingly a mediator rather than a confounder. This could possibly apply to several other variables of interest, in particular somatic symptoms.

Treating variables that are fully or partly mediators as confounders, causes us to underestimate the true effect of anxiety and depression on the outcomes of interest.

2.6.4 Choice of cut-off for case-level anxiety and depression

The applied cut-off for case-level anxiety or depression of 8 or higher in both scales has been described in chapter 2.2.3. Dose-response associations (242) are often reported between mental disorders and outcomes. Consequently, higher cut-off for case-level will strengthen the association of interest. This precludes direct comparisons of effect sizes among studies applying different case-levels for mental disorders.

2.6.5 Moderators

Hypotheses on effect-moderation by age and gender in all associations between exposures and outcomes were tested. Also, hypothesis on a buffer-effect in anxiety comorbid to depression was examined in the general mortality paper. All tests of interactions were performed with both the exposure variable (e.g. depression) and the hypothesized effect moderator (age) operationalized as dichotomies, and included as a product in addition to both variables alone (main effects). The applied test of significance was the increase in F-value in the regression model when adding the interaction term to all other relevant variables. This is a more conservative test of statistical significance of effect moderation than the t-test of effects from the interaction term.

2.6.6 Weighting procedure for somatic symptoms and somatic diagnoses

Items comprising indexes for somatic symptoms and diagnoses were weighted for their relevance to outcomes, as described in chapter 2.4.1 and 2.4.2. Weights were established employing linear regression models. Regression coefficients were used as weights, and the indexes were computed as a sum of products between the standardized symptoms and diagnoses and their weights. All analyses were also performed applying un-weighted sum-scores, and these generally explained less of the effects of exposures on outcomes. The indexes were generally used as continuous and ordinal measures.

2.7 Ethics

The HUNT study (including all sub-studies) was approved by the Data Inspectorate of Norway and recommended by the Regional Committee for Medical Research Ethics (region four, *REK-4*). Each participant signed a written consent regarding the screening, subsequent control and follow-up, and with regards to the use of all data for research purposes. They also consented to linking their data to other registers. This issue is, however, also subject to approval of the Data Inspectorate for each record linkages of data sources. All involved researchers work with files where names and personal identification numbers have been removed (207).

3 Results

3.1 Anxiety and depression predicting disability pension award

Of the 45 782 participants in HUNT aged 20-66, 1065 were awarded disability pension during the two year follow-up starting 6 months after the health survey.

In summary, we found that anxiety and depression at baseline were strongly associated with subsequent award of disability pensions, an effect only partly explained by adjusting for comorbid somatic symptoms and diagnoses. The effect of comorbid anxiety depression was stronger than that of either anxiety or depression alone, probably from being an additive effect from the higher mean total symptom in comorbid cases. The effect of psychological morbidity appeared to be stronger for younger persons (20-44) than older (45-66). We found no effect-moderation for gender.

Anxiety and depression were also strongly and independently associated with disability pensions granted for physical conditions and diagnoses, indicating that administrative data may have underestimated the contribution of mental disorders to the award of disability pension.

In the parsimonious model included, we found that the strongest independent predictor of disability pension award for any reason was age (PAF of 0.60), followed by somatic symptoms (0.37), not being active in any voluntary organizations (0.18), somatic diagnoses (0.16), educational level (0.14), work-status (0.08), anxiety and depression (0.07), and physical inactivity (0.05). Alcohol consumption, not having enough good friends, and living with a partner did not explain disability pension award in the fully adjusted model, and were therefore not included in the model presented.

3.2 Anxiety and depression predicting general mortality

Of the 61 349 participants of 93 138 eligible for the study, 2 309 died during the follow-up period (mean 4.4 year follow-up time). Non-participants were older, more likely to be institutionalized or in hospitals and the mortality rate during follow-up in non-participants was higher than in participants (15% versus 4%).

Case-level depression was found to be a risk factor for general mortality, robust for all available adjustments. Factors confounding the association, listed in descending order from the strongest confounder, included somatic symptoms and diagnoses, physical impairment, physical activity, smoking and alcohol problems, educational level and socioeconomic status, and physical measures (blood-pressure, cholesterol level, and BMI). There was a dose-response association between depression symptom load and mortality, with increasing mortality with increasing severity of depression, particularly within the clinical range of the scale (range 8-21 on HADS-D).

The association with anxiety scale scores, however, was U-shaped, with higher mortality in individuals with both low and high levels. Adjusted for physical health, we found no association between case-level anxiety and mortality.

Depression alone was a stronger risk-factor for mortality than was comorbid anxiety depression, and this interaction effect remained statistically significant after adjusting for relevant confounders.

The association between depression and mortality was equal in men and women, but stronger in participants aged 65 and younger than among those older.

3.3 Anxiety and depression as risk-factors for cause specific mortality

Employing the same empirical material as in the general mortality paper, the last paper expanded the analysis to also examining causes of death. In the first analysis, we compared CVD mortality versus all other causes combined. We found no difference between the effect of depression on CVD and the effect of depression on other causes of mortality (OR=1.67 and 1.66, respectively), and confounding factors were markedly similar. Unlike depression, associations for anxiety and comorbid anxiety depression showed some differences between CVD and other cause mortality: Adjusted for age and gender only, anxiety and comorbid anxiety/ depression were not associated with CVD mortality, but weakly associated with other cause mortality (OR=1.25 and 1.64 for anxiety alone and comorbid anxiety depression, respectively).

We further subdivided cause of death into 11 groups in addition to CVD mortality, performing nested logistic regression analyses for all these separate groups. Case-level depression predicted mortality for all diseases except smaller groups for *other diseases* (N=71) and *gastro-intestinal diseases* (N=47).

Whereas most disease-related mortality was only associated with depression (and not with anxiety or comorbid anxiety depression), the picture was different for external causes of death: Comorbid anxiety depression predicted suicide, accidents, and mortality without any certificate.

Suicide accounted for very little of the effect of depression on mortality, being a rare cause of death (29 out of 2309 deaths), and being preceded by case-level anxiety and/or depression in only 12 of these.

4 Discussion

4.1 Main results

The three papers all concern long-term consequences of anxiety and depression with the following main results:

1. *All three papers indicate that long-term consequences of depression are underestimated:* (i) In the disability paper, this is indicated by the independent association between depression and subsequent disability pension allegedly awarded for somatic diagnoses only. (ii) The effect of depression on general mortality has been questioned in literature reviews (e.g. 169), due to poor adjustment for confounding factors in most studies available. The general mortality paper shows a positive effect of depression on mortality after adjustment for a comprehensive list of possible confounding factors. (iii) As for cause specific mortality, present evidence of effects from depression is largely limited to CVD mortality and suicide. The cause specific paper indicates that depression is a risk factor for mortality in general not specifically related to suicide and CVD mortality.
2. *Whereas depression seems to be a general risk factor in relation to disability pension award as well as general and cause-specific mortality, the effect of anxiety varies across these outcomes:* The general expectation from the literature would be that anxiety alone has an independent effect on adverse outcomes comparable to that of depression alone (as described in chapter 1.1.2), and that comorbid anxiety depression would be more strongly associated with the outcomes of interest than either alone (hence chapter 1.1.4). This pattern is found in cross-sectional analyses of HUNT-2 data employing HADS with self-reported somatic conditions as outcomes (57). The findings for disability pension award were in accordance with this hypothesis; both anxiety and depression independently

increased disability pension award, and highest risk was found in comorbid anxiety depression. For mortality, however, the results were markedly different from the expectations: The weak effect of case-level anxiety was entirely explained by adjustment for depression. Anxiety symptoms measured by a continuous variable was negatively associated with mortality, but a better fit with data was observed using a U-shaped model. Finally, comorbid anxiety depression *decreased* mortality compared to depression alone.

3. Also the effect of somatic *symptoms* and somatic *diagnoses* differed strongly between the outcomes: While somatic *symptoms* were a far stronger predictor for disability pension award than somatic *diagnoses*, the opposite was found for mortality. The same was observed for confounding: Somatic *symptoms* confounded the effect of anxiety and depression on disability pension award more than somatic *diagnoses*, while the opposite was found for mortality.
4. The effects of mental symptoms on both mortality and disability pension award were stronger in the younger than the older part of the HUNT-2 population. No effect-moderation was found for gender in either of the outcomes.

4.2 Strengths

As the three papers share exposure and most confounding variables and historical cohort designs are used in all papers, strengths are principally the same across the papers, and most of them are presented in the manuscripts. Mainly, the strengths of the three studies arise from the cohort designs. The study-sample is large and the participation-rate at baseline was high. Both measures of exposure and outcomes are relatively unbiased. The process of screening for anxiety and depression was *double-blind* (in terms of randomized controlled trails), that is, neither participants nor administrators were aware of the specific research hypotheses in these studies at baseline health screening. Ascertainment of outcomes at follow-up was obtained

from national registries, which are complete registries with the exception of emigration from Norway, and also independent of exposure status. As several somatic and socio-demographic variables were included in the health surveys, we were able to adjust for many factors expected to confound the associations.

4.3 Limitations

Parallel to the strengths of the studies, most of the limitations are also common across the three papers. Detailed aspects on operationalizations of anxiety and depression from HADS, and the corresponding gains and losses, are due to format and journal guidelines, not thoroughly covered in the papers. This will be described in more detail in the following, and the most important limitations in the papers will be presented.

4.3.1 Operationalization of anxiety and depression from HADS

Operationalizations of anxiety and depression from a screening instrument based on symptom count and symptom severity, like the HADS, give rise to a number of limitations. The operationalizations employed, included conventional cut-offs for each scale separately (two dichotomous variables), a nominal variable with four categories for case-level anxiety and/or depression, continuous measures, quadratic terms of continuous measures (for examination of U-shaped associations), cut-offs for quartiles, and by cut-offs for severity within the clinical range of each scale (details described in chapter 2.2.3). Restrictions on word counts of manuscripts in international journals do usually not allow for examinations of associations across various operationalizations. The model's ability to describe the association between exposure and outcome is obviously restricted to the model specified, including the limitations from operationalization of exposure. For disability pension award for example, we reported only results based on the four category nominal variable defining anxiety, depression,

comorbidity and a reference group. In this model, we were not able to demonstrate the factual dose-response association between exposure and outcome. In a dose-response association, recoding the exposure into a dichotomy restricts the variance, which in turn reduces the strength of the observed association.

By definition, the number and severity of symptoms are higher in comorbid anxiety depression than any of the two alone. We found that comorbid anxiety and depression carried a higher risk for disability pension award than any of the two alone, but the specified model did not allow for any examinations on whether this is a result of higher symptom load in comorbid cases than those with anxiety or depression alone.

An inherent limitation to any quantitative approach is the problem of measurement error, which in these data is likely to be random (213, 250), but also contributes to an underestimation of the true associations. However, bias cannot be excluded, and might occur from the missing substitution procedure (where a maximum of two missing values on each sub-scale are replaced with that individual's mean on the valid items) (77). Further, bias might stem from under-report of symptoms as a consequence of denial. Both these possible biases are in the direction of underestimating the true symptom load. Employing categorical measures, measurement error might imply misclassification in symptom-loads around case-level, resulting in arbitrary classifications (41).

As is inherent from the observed distribution of reported symptoms in HADS, co-occurrence of symptoms of anxiety and depression is not only relevant above case-levels, but occurs also at sub-threshold levels. The HADS total sum-score of 14 can be split into two sub-scores of 7, alternatively as 9 and 5, translating into reference group or case on one sub-scale respectively. For most adverse clinical outcomes, anxiety and depression have the same correlates (e.g. 57), and comorbid anxiety depression is more strongly associated with such outcomes than any of the two alone (probably due to higher total symptom load). There is

little evidence that an even distribution of symptoms on anxiety and depression (hence the example of 7 on each sub-scale) involve less psychopathology than an uneven distribution (e.g. the second example with 9 and 5 on subscales). Consequently, it might be argued that employment of case-levels for anxiety and depression separately will consistency under-recognize comorbid sub-threshold psychopathology (41). This objection applies not only to HADS, but also to diagnostic classifications like ICD-10 and DSM-IV. A one-dimensional symptom load for anxiety and depression comprised is an obvious alternative. The results from the general mortality paper, however, provide a rare example of a correlate being markedly stronger on one dimension (depression) than the other (anxiety).

Beyond general problems with dichotomization of symptom-scores for anxiety and depression, there are specific problems with any choice of cut-offs. As described in chapter 2.2.2, case-level with cut-off at 8 is across studies found to give a sensitivity and specificity of 0.80 on both sub-scales (56). Despite accordance in the literature, at least two problems apply to this convention: As demonstrated in the general mortality paper, the strength of the association increases with higher cut-off levels, which is a logical consequence given a dose-response association. This problem precludes comparisons of effect-sizes across studies employing different means of case identification or cut-offs, e.g. the many studies of depression on mortality where the mental health is based on clinical interviews. Further, it is not self-evident that the cut-off for a condition should be defined aiming at equal sensitivity and specificity. As the prevalence of non-depressed individuals is higher than the prevalence of depressed, a cut-off for equal sensitivity and specificity will identify more false negative cases than false positive ones, and often more false negative than true positive. Lowering the case-level would simply include more false positive cases, and vice versa.

Screening instruments for anxiety and depression are often criticised for lacking the added reliability from clinician's evaluations, hence the discussion in chapter 2.2.2. As

mentioned there, HADS is better than an unstructured clinical evaluation of anxiety and depression dimensionally across two dimensions (218). However, fully structured clinical interviews, like employed in the NCSs (11-13) and the Norwegian replication (7), not only increase reliability, but also provide more detailed diagnoses. For example, one item in the HADS anxiety subscale measures panic attacks, and the other six items cover symptoms of GAD. The anxiety subscale has also been found sensitive to other anxiety disorders (57), but cannot differentiate between these. Screening tools are designed either to screen for probable cases or to be used as scalable measures in their own right (213). HADS is in this study and elsewhere used as both.

Most of the above mentioned limitations relate to HADS employed as a categorical measure. Employment of HADS as a continuous measure is often the suggested antidote, but again, there are problems with this approach as well: It is commonly argued that symptom rating scales for psychopathology are ordinal rather than arithmetic, i.e. that the difference between a HADS depression score of 7 versus 10 does not translate into the difference between 3 versus 6 (213). Further, associations between exposure and outcome might not be linear, as demonstrated with depression on general mortality. Finally, with few exceptions (e.g. Psychosomatic Medicine), journals within psychiatry and medicine seem to favour categorical operationalizations above continuous. This as discussed in the chapter on continuous versus discrete measures in psychiatry (chapter 1.1.3).

In conclusion, there are limitations to all opearationalizations of mental disorders. The common use of separate dichotomies for anxiety and depression are perhaps more a convention than optimal operationalizations in a psychometric sense. The perhaps best approach is to examine associations between exposure and outcome applying multiple operationalizations of anxiety and depression, with particular attention to strength and shape of associations and issues of comorbidity between anxiety and depression. This multi-analysis

approach must, however, be weighted against the increasing risk of type I errors when multiple tests are performed.

4.3.2 Residual confounding

The issue of residual confounding applies to all three papers. Information on somatic diagnoses and symptoms in the base-line screening is self-reported, and the categories used are not exhaustive. Consequently, the effect of somatic diagnoses and symptoms may be somewhat underestimated, and the effects of anxiety and depression, when adjusted for somatic symptoms and diagnoses, overestimated. This issue of residual confounding resulting from problems of reliability and variables not covered also applies to other confounding variables included, e.g. health related behaviour, biological health-related measures, and variables on socio-demographics.

4.3.3 Over-adjustment

As described in chapter 1.2, there exists the complex relationship between psychiatric and physical disorders. HADS includes no somatic symptoms of anxiety or depression and identify symptom load on the mental or cognitive aspects of anxiety and depression only. By later adjusting for somatic symptoms, we attempt to disentangle mental from somatic symptoms. HADS was developed for screening for mental symptoms in contexts of somatic disease (49), and somatic symptoms of mental disorders were excluded to avoid false positive cases in these settings as inclusion of somatic symptoms could give a ceiling effect. This feature makes HADS particularly suitable for disentangling the effect of *pure mental* symptoms from somatic symptoms and somatic conditions, if the major concern is confounding by these somatic factors. However, using this approach, we probably over-

adjusted our model, and thus under-estimated the effects of anxiety and depression upon disability pension award for physical conditions. This is so because several of the somatic symptoms might be manifestations of the psychiatric disorder (84). Somatic symptoms are common in mental disorders, and also part of diagnostic criteria according to ICD-10 and DSM-IV. The over-adjustment from employing this approach is therefore likely to be notable. For three reasons, this problem is perhaps more evident when predicting disability pension award than mortality: Somatic symptoms are by definition more than somatic conditions closely related to mental disorders; somatic symptoms have independently a strong effect on disability pension award; and adjustment for somatic symptoms attenuate the effect of mental disorders on disability pension award more than on mortality.

Why, then, do we specify a model so that over-adjustment is likely to occur? There are at least two reasons for this: As researchers, we are obliged to attempt to falsify our hypotheses, which include searching for alternative explanation for the hypothesized associations. The more thorough attempts to adjust for somatic confounding factors, the more likely over-adjustment will be. Partially, this is caused by the power balance between medical disciplines, where the burden of proof can be claimed to rest heavily on mental health disciplines. As a practical example, in the review process re-submitting the disability paper to the American Journal of Psychiatry, most of the discussion concerned residual confounding stemming from symptoms and conditions not available for inclusion in the model. The weighting procedure (described in chapter 2.6.6), where somatic conditions and symptoms were weighted for their relevance for sick-leave last year (and correspondingly for mortality in the mortality papers) was a result of this discussion with the reviewers. The weighted sum-scores of somatic symptoms and somatic conditions explained slightly more of the effect of exposures on outcomes in all three papers. Yet another source of over-adjustment resides in

that we adjusted for health-related behaviour (e.g. smoking, alcohol consumption, and lack of exercise) that may be causally related to anxiety and depression.

This tradition of over-adjustment when examining correlates to mental disorders is commonly requested by reviewers in psychiatric journals, and might reflect the power-balance between psychiatry and other specialities in medicine, perhaps illustrated by Eaton's formulation that psychiatric diseases tend to be defined by failure to locate a physical cause (95, referred in 96).

4.3.4 Protopathic bias

Early symptoms in development of somatic illness not yet diagnosed can be confused with symptoms in mental illness. The tendency to incorrectly diagnose mental disorder in this situation is called protopathic bias. This bias might apply to all three papers, as we have no measures of onset of somatic diagnoses after the HUNT-2 screening. Thus can the effect of anxiety and depression on mortality and disability pension award for somatic diagnoses be overestimated. But for all outcomes, we examined if the effect of the exposure was different in the first versus the second half of the follow-up, and while none of these were significant there were weak and un-significant trends of the effect declining over time. We are able to discount protopathic bias emerging from physical conditions that give rise to psychiatric symptoms from these findings.

4.3.5 Biased non-participation in HUNT

Several reasons were reported for non-participation in the HUNT study, including both good health and lack of time in young individuals, and also poor health in elderly (211). Our finding of strongly increased mortality in non-participants is obviously indicating a strong participation bias in the direction of good health. Regarding mental health, there are reports of

more psychopathology among non-responders to general health surveys (212). We have no information on the rate of disability pension among non-participants. This healthy-participant bias restricts the variance in both exposure and outcome, and consequently increases the likelihood of underestimating true associations between exposures and outcomes.

4.3.6 Stronger symptom stability in GAD than in depression

As GAD typically follows a more chronic course than depression; the risk of misclassifying individuals with depression (e.g. those being in remission between depressive episodes at the screening) surpasses the corresponding for anxiety. This limitation, being relevant across all three papers, precludes direct comparison of effects of anxiety with effects of depression upon disability pension award. However, the problem is limited by the cross-sectional design in the general population being more prone to identify chronic cases than shorter episodes. This issue is described more in detail in chapter 2.5.

4.3.7 Limitations specific to the disability paper

There are a number of particular limitations in the disability paper, many of whom relate to issues of validity of the disability pension award as a measure of work-related disability.

As discussed in the paper, the number of diagnoses reported by general practitioners (GPs) in an application for disability pension is limited to two. Our analysis of anxiety and depression as predictors of disability pension awarded for alleged non-psychiatric diagnoses only is limited to the physicians' skills in correctly identifying primary and secondary contributing diagnoses. In cases where GPs intended to report mental diagnoses, but were hindered by the restriction of a maximum two applicable diagnoses, this might contribute to over-estimation of the effects in this analysis. However, this problem is limited as F-

diagnoses, when used, usually (in 73%) is reported as primary diagnosis. Further, 46% of applications reported one diagnosis only.

A perhaps more important concern is the validity of the outcome measure as a measure of health-related disability. This argument applies for causes for disability pension beyond health and impairment, but also for impairment in the economically inactive part of the population: Despite the restriction that disability pension should be awarded only for work-related impairment attributable to a diagnosable condition, there are several identified risk factors for disability pension award beyond health. As described in chapter 1.3.4, these include push-factors, for example factory closings (142) and downsizing (111). There is support for the hypothesis that disability pension is used for early retirement (143), which also could be supported from the strong independent effect of age on disability pension award in our study. Such use of health related benefits is an example of medicalization where problems on a structural level find its solution by implicating the individual and benchmarks the individuals health as the factor leading the individual out of the work force (144).

In addition to push-factors, the conundrum of an increase in disability pensioning that is observed alongside improvement in key health indicators (134), has stimulated arguments using a pull model (123), hypothesizing that disability pension is a result of rational choice, as described in chapter 1.3.4. Despite limited empirical evidence, the existence of applicants with primarily economic motives cannot be excluded. All these factors limit the validity of disability pension award as a measure of work-related disability from decremented health in terms of specificity, and contribute to under-estimation of the true effect of anxiety and depression on work-related disability.

In addition to factors beyond health-related impairment being causes for disability pensioning, the opposite cannot be excluded, namely that medically impaired economically inactive individuals are provided for by family members and do not apply for disability

pension. Erroneously rejected applications could also add to this, as well as sickness presence (133). All these factors limit the sensitivity of disability pension award in measuring work-related disability, and further contribute to under-estimation of the true effect of anxiety and depression on work-related disability.

Finally, to what extent the results of the disability study are applicable for generalization, can be questioned. The disability pension schemes in Norway are similar to other OECD countries, and secular increases in psychiatric diagnoses in new cases have been reported throughout these countries (134). However, Norway is among the countries in the OECD region with the highest proportion of individuals within working age on disability pension. The fact that public expenditure on disability benefits is relatively higher than expenditure on unemployment benefits in Norway than in any other OECD country (134) is also an indication that the bias in direction of medicalization is strong in Norway.

These issues obviously limits generalization, but on the other hand, if the higher proportion of disability pensioners truly reflects causes beyond health, we probably have underestimated the relative effect of anxiety and depression on disability pension award compared to other OECD countries.

4.3.8 Limitations specific to the mortality papers

As described in chapter 2.1.3 and 2.3.2, information on mortality is reliable and complete, and consequently does not introduce any major additional limitations. The reliability in determining the *underlying cause of death* is, however, questionable, and consequently a limitation of the study. There are reports of trends in causes of mortality, like an alleged decline in suicide in Norway from 1990 till 2000 (166). However, this should be discussed with reference to a parallel increase in mortality from causes where occasional misclassifications of suicides could occur (as discussed in chapter 1.4.3). If this bias is

present, we have underestimated the effect of suicide from anxiety and depression. This will be discussed in more detail in chapter 4.6.2.

4.4 Relations between the two outcomes disability pension award and mortality

4.4.1 Disability pension award and mortality both relate to health

Both disability pension award and mortality can largely be regarded as adverse outcomes of exposures relating to health. Although, according to public registries, 5.4% of all deaths were from external causes and not illnesses (see discussion in chapter 1.4.3). This proportion is strongly associated with age, with a higher proportion of non-illness mortality in younger individuals. Disability pension award is also caused by factors beyond impairment from health problems as described above in chapters 2.3.1 and 4.3.7.

The findings across the three papers indicate how aspects of health relate to mortality and disability pension award. As described above (chapter 4.1), depression increases both outcomes, while the role of anxiety, somatic symptoms, and somatic diagnoses differ throughout the three papers. In summary, both outcomes are related to health, but evidently to different aspects of and factors beyond health.

4.4.2 Are there any associations between disability pension award and mortality?

Given that disability pension award and mortality both are outcomes related to health, a positive association between these two might be expected. However, as described above in chapter 4.1, they relate partly to different health characteristics which suggest a not very

strong association. In particular this is the case for somatic symptoms that were strong predictors of disability pension award, but only weakly related to mortality.

To the best of my knowledge, there are no studies of whether disability pension award increases mortality. However, from the Whitehall II prospective cohort study, having more than five certified sickness spells per 10 years increased mortality beyond the effect of self rated health, presence of longstanding illness, and a measure of common clinical conditions (256). The association between sick-leave and mortality was not linear, and a protective effect of a small number of self-certified absences was reported. The study justifies the hypothesis that disability pension award might increase mortality, but this is yet to be empirically examined. Beyond this study, we know very little about health-related consequences of being on disability pension (as discussed in chapter 1.3.2).

According to the pull-perspective (123), being provided for by the public and having the days off work is an attractive position. We cannot exclude disability pension being a relief from harsh working conditions deteriorating health, which suggests a negative association between these two outcomes. It is, however, likely that disability pension for some leads to increased passivity and reduced social network, which could deteriorate health. As mentioned above (again in chapter 1.3.2), health consequences of sickness absence was the theme of the 3rd pre-conference meeting at the EUPHA conference in Graz (November 9th 2005), and despite a consensus that there is little evidence of consequences of long term sick leave on health, most researches suggested hypotheses indicating a deteriorating effect of long-term sick-leave on health. These postulations might, however, be biased by that researchers perhaps personally are more invested in their work than is the common employee.

4.5 Interpretation of findings: Disability pension paper

4.5.1 Is the impact of anxiety and depression on disability pension award underestimated?

The main conclusion in the first paper is that the impact of anxiety and depression on disability pension award is underestimated compared to public statistics for diagnoses for award of disability pension. Across most OECD countries, approximately one third of disability pensions are awarded for mental disorders (any F-diagnosis according to ICD-10) (134), and in 2004, 28% of disability pensioners in Norway had a mental diagnosis in their application for disability pension. Limitations of this conclusion are covered above (chapter 4.3), and include mainly issues relating to residual confounding.

Many physicians report that issues related to sick-leave can be problematic (113). Patients applying for disability pension award commonly present mixed and undefined symptoms. In Norway, muscle-skeletal disorders was the largest diagnostic group (39.1%), followed by mental disorders (28%) in 2004 (30), but the proportion of disability pensions awarded for mental disorders has increased over the last decades (102, 134). As there is little evidence for an increase in mental disorders in the population (11), this increase is perhaps indicating increased recognition rather than trends in the prevalence of mental disorder. Alternatively, an increased effect of mental disorders on work-related disability resulting from brutalization of working life (111, 142) cannot be excluded.

Based on the finding that anxiety and depression were independent predictors of disability pension awarded for non-psychiatric diagnoses, we reached the conclusion that the impact of mental symptoms on disability pension award is underestimated as it appears in the medical certificates. The finding is obviously subject to the limitations discussed above (chapter 4.3), but the conclusion is supported by a number of other observations:

In the parsimonious model in the same manuscript, the effect of somatic symptoms on disability pension award was very strong, and far stronger than somatic diagnoses, anxiety and depression. Some of this effect should be related to mental disorders, through somatic symptoms being part of the spectre of symptoms of mental disorders, but also through somatization disorders. How to label the effect of somatic symptoms that cannot by indications alone be attributed to somatic conditions and organic aetiology is also shown to be a question of which medical speciality is consulted, including mental health professionals (78, 91, 92). It should, however, be quite uncontroversial to argue that at least some of the effect of somatic symptoms on disability pension award in general represents mental disorders. This relates to the discussion of how to define, understand, and label somatic symptoms (chapter 1.2), and also to the issue of over-adjustment, perhaps reflecting the power-balance between medical specialities (discussed under limitations, chapter 4.3.3).

A secondary analysis based on the same data as the first paper examined if insomnia is an independent risk factor for disability pension award (257). Applying principally the same model as in the parsimonious model in the first paper, but also including anxiety and depression as possible confounding factors, we found an independent effect of insomnia on disability pension award to be not much weaker than the effect of anxiety and depression combined. Insomnia is not reported in any application for disability pension award registered among participants in the HUNT study, and we have not been able to identify this diagnosis in any public statistic over diagnoses for disability pension award (30). Consequently, also the effect of insomnia on disability pension award seems to be underestimated (257).

Another common mental disorder is substance dependence, in the general population dominated by alcohol dependence. This is not accepted as a diagnosis awarding disability pension (though medical consequences following alcoholism are). It would consequently be fair to hypothesize an independent effect of alcohol problems on disability pension award

along the same line of arguments as for the insomnia study (257). We did, however, exclude this variable from the parsimonious model in the first paper as it did not predict disability pension adjusted for the variables included. Alcohol problems are in the HUNT study measured with CAGE (234) and questions are framed in a lifetime perspective. The information about the study stated that identified high-risk groups would be targeted for clinical interventions (207). This may have compromised the sense of anonymity, which accordingly may have biased the responses to CAGE. Acknowledging these limitations, there is no evidence from this study that alcohol problems contribute to mental disorders and is underestimated as a cause for disability pension award.

British studies have showed that GPs' skills in recognising mental disorders are limited, and interventions aiming at improving this capacity through educational efforts have a detectable effect if measured dimensionally (258, 259). Similar positive effects of training on detection of depression have been found in care staff in nursing homes for elderly (260). This limited ability to recognize mental disorders is perhaps one reason that most individuals with case-level mental disorders report never having sought help (11, 45). A submitted Norwegian study based on secondary analyses of data gathered for a pharmaceutical study (218) indicates that general practitioners overestimate their ability to recognize mental disorders, and that there is no association between self-reported diagnostic skills (regarding mental disorders) and true skills (defined as concordance between GPs identification of major depression and GAD compared to external gold standards) (261). As presented in chapter 2.2.2, HADS is a better case-finder for both anxiety and depression than GPs are among their own patients (218). Knowing that physicians tend to be biased by their speciality when facing patients with unclear somatic symptoms or absent organic aetiology (78, 91, 92), it is plausible to hypothesize that GPs are biased towards choosing somatic (e.g. muscle-skeletal diagnoses) before mental diagnoses (e.g. somatization) in patients fulfilling criteria for both.

Furthermore, we cannot exclude preferences among patients and authorities in the same direction.

According to public regulations in most OECD countries, medical rehabilitation (usually treatment as usual) must be attempted prior to disability pension award. Based on the studies examining GPs problems in detecting and treating mental disorders, we hypothesized that this problem also would be reflected in patients awarded disability pension for mental disorders. This hypothesis was examined in an ongoing study based on secondary analyses of the HUNT data on help-seeking for mental disorders (45), and results were recently presented at a conference (262): Thirty four per cent (95% confidence interval 30-39%) of the population awarded disability pension for a mental disorder five years prior to participation in HUNT reported never having received any professional help for mental disorders. An objection to the result is that patients might fail to self-report this kind of information or to have insight in what a treatment scheme is targeting. On the other hand, it is fair to expect that treatment in the face of a possible disability pension award to be comprehensive and explicit enough for the patient to be aware of what the interventions are aimed at. These findings might be regarded as a consequence of inadequate case-finding and treatment for mental disorders in primary care, and an indication of mental disorders being under-recognized for disability pension award.

As presented in the introduction (chapter 1.1.3), sub-threshold depression is found not only to increase sick-leave, but to account for more days of work than major depression (37). Obviously, the risk for sick-leave in major depression is greater than in sub-threshold conditions, but as the prevalence of sub-threshold conditions is higher than the prevalence of major depression, sub-threshold conditions account for more days of work than major depression. This can be demonstrated mathematically by employing population attributable fractions (242). There exist no such study for disability pension awards, but given that the

findings are of relevance to disability pension award, it is relevant for the line of arguments on the underestimated impact of anxiety and depression on disability pension. It is more likely, and perhaps also reasonable, that physicians (mostly GPs) fail to recognize sub-threshold depressive conditions than case-level depression, as sub-threshold conditions per definition do not fulfil diagnostic criteria. This failure in recognition is likely also reflected in applications for disability pensions, and consequently contributing to the underestimation of the impact of mental disorders on disability pension award on an aggregated level.

In summary, the finding that anxiety and depression are risk factors for disability pension award for non-psychiatric diagnoses is novel, while the conclusion that this represents an underestimation of the impact of anxiety and depression on disability pension award is supported by other studies.

4.5.2 How do the finding of independent effects of mental disorders on disability pension award relate to the push- and the pull models?

The position of health as a causal factor in disability pension award has been challenged on the background of observed increase in disability pensioning in most OECD countries parallel to the improvement in key health indicators (134). As mentioned in chapter 1.3.4, the pull model suggests that if sick-leave benefits are attractive, it will increase economically motivated applications. This perspective has had major influence on public policy in Norway (156). Employing the pull perspective, the health information obtained in the context of applications for disability pension award will be influenced by the applicant physicians' choices of acting as the patients advocate or as a gate-keeper on behalf of society: In the role of patient's advocate, the physician can emphasise diagnoses that knowingly increases the chance of approval. Also, the validity of the diagnoses from physicians emphasizing the role as gate-keepers can be questioned, as most diagnoses for award of disability pension are based

on information presented by the patient. This problem also applies to the very relevance of health problems as primary motivation for applying for disability pension: From the perspective of rational choice theory (123), it is objected that report of health problems in the context of applying for disability pension award can be biased by economic incentives.

The disability paper provides relevant data for the debate between the push and the pull perspective: First, the health information reported in the HUNT study is not biased by possible economic incentives for disability pension award. Consequently, any prospective effect of health in the HUNT study on disability pension award is supporting the push model. In the discussion on push- versus pull model, this is particularly relevant for the effects of somatic symptoms, and perhaps also anxiety and depression, as these are all based on self-reported symptoms. In conclusion, somatic symptoms and mental disorders combined, despite being *vague and woolly* (borrowing a term from Prince (213)), are more than three times stronger than somatic conditions in prediction of disability pension award, *also when reported in a context without incentives for disability pension award.* This is by far the largest study of its kind and also the most complete one with regard to measures of health and adjustment for confounding factors, and conclusions are generally in accordance with findings from previous studies (104, 229).

As the push and the pull models must be regarded as conflicting, support for one may contribute to weakening the other. However, as the two models can be empirically valid simultaneously, evidence in support of the push model can by no means falsify the pull model.

4.5.3 *How* do anxiety and depression cause work-related impairment?

The independent effects of anxiety and depression do probably increase work-related impairment in different ways relating to diagnostic criteria. Both anxiety and depression have

a whole range of aspects, and it is an empirical question if all of these or some in particular, are relevant for explaining the association with work-related disability. As discussed above (4.5.1), the brutalization of working life might increase the burden of continued work for individuals with mental disorder experiencing e.g. organizational changes or downsizing.

By face validity, many symptoms of anxiety and depression might seem rather incompatible with work. Borrowing random items from the HADS scale (50): *Being tense or wound up*, *having a frightened feeling as if something awful is about to happen*, *having worrying thoughts going through the mind, getting sudden feelings of panic, feeling slowed down, having no interest in ones appearance, finding no joy in things previously enjoyable, and not being able to look forward with enjoyment to things.* These may all comprise work disability in a global fashion and not specifically.

Beyond speculations on how anxiety and depression are characterized by thoughts and feelings incompatible with work, associated somatic symptoms encompass mental disorders and may contribute to limitations in work ability. Finally, the long-lasting or chronic course with recoveries and relapses in mental disorders increase the problem of impairment in work.

4.6 Interpretation of findings: Mortality papers

4.6.1 Contributions to the literature

As described in the introduction (chapter 1.4.4), six questions were examined for the hypothesized effects of anxiety and depression on mortality:

The very existence of an effect of depression on mortality has been questioned, based on possible residual confounding in a review of population-based studies (169), and that most reviews and meta analyses do in general base their estimates on poorly adjusted or crude estimates of effects of depression on mortality (21, 172, 200). We were able to address this

issue of confounding as the HUNT-2 study covered broader range of potential confounding factors. Weighting procedures of somatic diagnoses and symptoms by their association with mortality further increased our ability to adjust for confounding in this association. The effect of depression was highly significant in prediction of mortality even in the fully adjusted models, and despite possible over-adjustment, particularly regarding adjustment for somatic symptoms as discussed in chapters 1.2 and 4.3.3.

The second question relates to whether severity of depression relates to mortality. A literature review suggested equal effect of major depression and sub-clinical forms of depression (172) on mortality. We found little variation in mortality within the first three quartiles of the depression scale. However, within the fourth quartile, there was a dose-response association between symptom load and mortality. This finding is contrary to the conclusion in the referenced literature review.

The third question relates to mechanisms hypothesized for the association between depression and mortality. Two main mechanisms are proposed (182), the first relating to lifestyle, namely that depression may be a distal risk factor related to a number of proximal risk factors that increase morbidity and mortality from CVD and other diseases. We were unable to identify any relevance of smoking, lack of exercise and alcohol consumption in relation to mortality, and our findings thus suggest marginal relevance of these factors as mechanisms underlying the association. Unfortunately, we had no information on non-adherence to treatment strategies, also hypothesized as a mechanism underlying the effect of depression on mortality.

The second main mechanism proposed (182) includes biological changes occurring in depression, e.g. increased cortisol, increased platelet coagulability and changes in heart rate variability (182). We were unable to adjust for these factors as they were not included in the

initial screening. They are, however, all strongly related to CVD mortality, and consequently less relevant for the effect of depression on mortality beyond CVD.

Fourth, the studies add to the existing knowledge as to whether the effect of depression on disease mortality is specific for CVD: Most of the evidence on depression in relation to disease mortality has focused on CVD mortality; there exist meta analyses (21, 196) of these associations, and even an review of potential mechanisms (191). This strong tradition might leave the impression that the effect of depression is specific for CVD mortality. Our finding that depression is no stronger a risk-factor for CVD mortality than other-cause mortality comprised, adds to the existing knowledge by indicating that hypotheses on underlying mechanisms for the association should not be limited to CVD mortality.

Fifth, the general mortality study adds to the existing knowledge on whether the effect of depression on mortality is stronger in men than in women, which has been repeatedly reported (170, 201, 202), although generally not based on tests of interaction effects between gender and mortality in prediction of mortality (169). Despite stronger statistical power than any previous study examining the effect of depression on mortality, we were unable to confirm the hypothesized effect-moderation by gender. We did, however, find an effect-moderation by age, with stronger effect of depression in young age. This issue has not been a major focus of attention in the literature.

Finally, the study also adds to the present knowledge of the effect of anxiety on mortality. The literature on anxiety in relation to mortality is scarce but includes reports of both positive (203) and negative (204) associations. In addition, previous studies of depression in relation to mortality have generally not examined comorbid anxiety. Applying a linear model, anxiety is negatively associated with mortality, which is in line with a previous finding of a study also applying HADS (204). The remaining findings regarding associations between anxiety and mortality are generally new contributions to the literature. This includes

the findings that the effect of case-level anxiety on mortality was entirely explained by adjustment for depression (however not vice versa); the U-shaped association between symptoms of anxiety and mortality; and the lower mortality in comorbid anxiety depression than in depression alone. The lower risk in comorbid anxiety depression than in depression alone was contrary to our expectation as comorbid conditions generally are more strongly associated with adverse outcomes.

4.6.2 How much of the effect of depression on mortality is accounted for by suicide?

The cause specific mortality paper provided potentially important knowledge as to whether there are hidden suicides among other causes of death. The results supported suicide as a relevant mechanism underlying the effect of depression on mortality (200), but only in comorbid anxiety depression, thus indicating a different pattern than in disease mortality from depression. A similar pattern of comorbid anxiety depression predicted mortality without certificate (N=40) and accidents (N=80). This might indicate that the proportion of suicide among deaths is slightly underestimated.

However, suicide accounts for very little of the effect of depression on mortality. Of the 2309 deceased individuals, 29 (1.3%) had suicide registered as their cause of death. Even if this is an underestimate, the effect of depression on disease mortality accounts for a much higher number of deaths from depression than does suicide. In summary, our results support suicide as a mechanism underlying the effect of depression on mortality, but indicates that this mechanism accounts for very little of the total effect of depression on mortality.

As mentioned above (chapter 2.1.1), individuals with HADS sum-scores above 25 points and a random sample of individuals with scores slightly below this cut-off were informed in writing and advised to see their general practitioner for further clinical tests and

eventually treatment (208). Also, general practitioners in the county were offered a simplified diagnostic instrument including a brief course. One of the main objectives of this intervention was to reduce suicide in the county through improved detection by screening employing HADS, and also improved treatment through educational programmes for GPs. The regional ethical committee did not allow a randomized controlled trail; consequently we do not know whether the intervention actually reduced suicide among those contacted. From the cause specific mortality paper we do, however, know that the majority (n=17, 59%) of those committing suicide during follow-up were neither cases of anxiety nor depression at the time of the screening. Twelve suicides were among a group of 3 640 individuals with comorbid anxiety depression at time of the screening, thus 0.3% of the total group, indicating a rather poor specificity of the HADS detecting potential suicides. Consequently, employing HADS with comorbid anxiety depression as positive screening criteria, a major screening task remains for physicians in primary care. As mentioned above, GPs' abilities to recognise mental disorders is limited (258), and a review of the literature on mental health education for primary care physicians concluded that long term outcomes were less positive (263), although secondary analysis of data from the Hampshire Depression Project (258) employing dimensional approaches indicated some effect (259). Training of care staff in residential homes for elderly has also been reported to increase detection of depression (260). In summary, we can conclude that (a) there were relatively few suicides (n=12) among those with comorbid case-level anxiety depression (n=3 640); (b) the majority of suicides (59%, n=17) were in individuals without case-level anxiety or depression at baseline; (c) detecting 12 suicides among 3 640 screening positive from HADS implies a case-finding task for general practitioners, who are not the best case-finders in mental disorders; and (d) the case-finding ability in GPs is not easily improved. Despite suggestions that increased utilization of antidepressants might reduce suicide rates (264), it might be fair to conclude that there is little

empirical ground for reducing suicides by interventions (like the one in HUNT-2 (208)) that involve screening for anxiety and depression in the general population with subsequent treatment in primary care.

However, intervention (treatment or prevention) aiming at reducing depression in the general population might have impact on mortality, but more likely through reduced disease mortality than from preventing suicide.

4.7 How can anxiety and depression as exposures be reduced?

Studies from the US general population offer limited evidence for an increase in the prevalence of mental disorders (11). From British studies among adolescents there is evidence for an increase over the last 25 years in conduct problems, and perhaps also for a recent rise in emotional problems, but not for hyperactive behaviour (265). There is also little evidence for an increase in the impact of mental illness on adverse outcomes as disability or mortality, but there are some speculations over whether brutalization of working life increasingly expel individuals from the work-force. The mortality and disability pension studies for this thesis strongly indicate adverse outcomes of anxiety and depression. A plausible question is then how these exposures can be reduced?

4.7.1 Treatment

Mental disorders can be treated both with psychotropic medication and psychotherapy. Antidepressants in general have effect in about two thirds of patients in clinical trails (266). Selective Serotonin Reuptake Inhibitors (SSRI) have been demonstrated effective in depression, but it is not known if this effect is specific for SSRIs or if similar effect is attainable through other classes of antidepressive medication (267). Medication originally

designed for treating depression is also shown effective in treating anxiety disorders, however not as effective as in treating depression (268, 269).

Also psychotherapy is an effective treatment in mental disorders (270), in particular cognitive behavioural therapy (CBT) is well documented as an effective treatment for depression and anxiety disorders (271, 272). Some studies indicate that CBT is more effective than expected effect from treatment with psychotropic medication alone (273, 274). In mild and moderate depression, psychotherapy has been shown equally effective as medication (275), and more effective than medication in treatment of anxiety disorders (276).

It is estimated that maximally half of the burden of common mental disorders in young people can be averted with existing psychological and pharmacological treatment methods given maximum coverage (the number of people seeking treatment), clinical competence, and patient compliance to treatment (277). However, these presumptions are at present not by far met. Theoretically, inspired by the *filters to treatment* by David Goldberg (278, 279), the total effect on the mental health of the population, by means of all mental health care comprised, can be estimated as the product of five proportions: (i) The proportion of the population that seek professional help (for anything, usually seeing GPs for physical complaints); (ii) The proportion of cases of mental conditions detected in primary care; (iii) The proportion of detected cases offered treatment (either in primary care or by referral); (iv) The proportion of patients offered treatment that comply and complete the treatment; and (v) the effect of the treatment offered. Being realistic, or perhaps even optimistic, presuming all these proportions to be 50%, the total effect of treatment on the mental health of the population is 3%. A limitation to this theoretical model is the presumption that all five proportions are dichotomies.

Almost the entire attention in education of psychiatrists and psychologist is at the fifth level (effect of treatment). The cost effectiveness of further development of interventions

delivered in mental health care of the general population is perhaps better in any of the four first levels rather than the fifth. However, money (both in pharmaceutical industry and public funds for research) are generally more easily raised for research on effects of treatment rather than the first four filters to treatment for mental disorders.

4.7.2 Prevention

The development of prevention programmes for mental disorders must be based on knowledge about the causes of mental disorders, and also factors that can promote and accelerate restitution and hinder relapse. Obviously, a whole range of factors do contribute to the development of mental disorders. There is also focus on *resilience* factors; factors protecting onset of mental disorders. A thorough model on these complex relationships providing good face value is offered by Goldberg and Goodyear and focuses on *vulnerability*, *destabilisation* and *restitution* as phases in the course of mental illness (280):

Vulnerability is defined as a process that increases the probability for mental disorder but is in itself insufficient to cause a disorder (280). Vulnerability is found vertically, that means that it involves social, psychological, and neurochemical processes. Commonly, each factor that increases the vulnerability carries little risk, but risk factors are often clustered in groups. For example, in families where childhood sexual abuse occur, other family background risk factors are also increased, both independently increasing psychopathology in the victims in adult life (281, 282).

Genes account for about 40% of the determinants and symptoms of both anxiety and depression, most likely resulting from multiple recessive genes. The location of these genes is *still a matter of conjecture* (280). It is unlikely that specific genes are controlling specific disorders. Genes associated with anxiety and depression is hypothesized to be shared (283), but there is evidence for specific genes responsible for vulnerability to disorders related to

fear like in panic and phobias (280). Goldberg and Goodyear suggest that genes associated with anxiety and depression mainly control emotional traits emerging through childhood, as fearfulness and shyness, rather than being specific for more complex states like anxiety and depression (280).

A gene responsible for transporting serotonin labelled 5HTT gene found on paired chromosome 17 (17q11.2) can be either be of both long alleles, both short, and heterozygous. In a prospective longitudinal study, the individuals with homozygous short allele of the 5-HTT promoter polymorphism (17% of the population) exhibited more depressive symptoms, diagnosable depression, and suicidality when exposed to stressful life events than individuals homozygous for the long allele as compared to the group with homozygous long alleles (31%). Heterozygous people responded to stressors in an intermediate fashion compared to the two homozygous groups' responses (284). The authors demonstrated a gene-by-environment interaction, thus not merely an additive effect of genes and adverse environment, which is a far more common model in this literature. With reference to this gene, it has been suggested that gene environment interactions are particularly important in depression (280).

The most important early environmental contribution to later anxiety an depression is the quality of maternal attachment (280). John Bowlby's seminal writings on the primary importance of the affectional bond between mother and infant (285) have generally been supported in e.g. follow-up studies of adopted children deprived in first living years (286). According to Bowlby, particular adults (most often the mother) function as a secure base for the infant. The emotional responsivity of the mother to the infant is hypothesized to result from evolutionary adaptation. Failure to develop optimal pair bonding may develop from either the caregiver or the infant, and might have adverse consequences in adult life (287). According to the Strange Situation experiment (where the child's responses to the mother after a brief separation is evaluated as secure or insecure), most children (65%) are securely

attached, and 35% show one of the subcategories of being insecurely attached (288). Numerous studies have shown that securely attached children develop better; they socialize more competently and are more popular with their peers (289). Secure attachment have also been reported to increase adaptation in more demanding social and educational worlds, including positive self-concept, high levels of attention and concentration, and good semantic memory.

Maternal depression represents a risk to the child in many ways, including e.g. poor nutrition and general instrumental care, but might also influence mother-child attachment. Effects of mothers' depression on cognitive abilities in offspring are broadly reported in 9 to 18 month olds, but seem to normalize at about 5 year of age (290). Children of depressed mothers have higher rates of aggression, hyperactivity, worry about self-efficacy and depressogenic cognitions at around age of 5 (287). Murray and colleagues observed that 5-year-old offsprings of mothers with postnatal depression responded with negative statements about themselves when placed in circumstances involving an interpersonal challenge from another child that may involve potential failure (287). There is strong evidence both from studies on humans and animals that early deprivation causes changes in the sensitivity of the Hypothalamic-pituitary-adrenal (HPA) axis (280).

Vulnerability for mental disorders is also shaped during childhood and adolescence. Effects of poor parenting practices are, however, less dramatic than poor attachment. The list of risk factors for later incidence of mental disorders is long, including marital discord, failure to develop friendships and sexual abuse. In adolescence, being unpopular with peers seems to be a risk factor for later development of psychopathology, particularly among girls (280).

Destabilisation is the label used by Goldberg and Goodyear to describe the effect stressful life events or major social difficulties, commonly preceding onset of depressive or anxious symptoms (280). Their vulnerability-destabilisation-restitution model suggests that

the threshold for developing symptoms of anxiety and depression is roughly inversely proportional to the level of vulnerability (that is, the severity of the childhood adversity). However, with sufficiently severe stress, symptoms can develop in the absence of earlier adversity.

Restitution, again according to Goldberg and Goodyear's model (280), refers to recovery from case-level anxiety or depression. Spontaneous recovery without treatment is common, but will often be followed by relapses.

Prevention programmes for anxiety and depression can be developed and directed at all the suggested elements in the vulnerability-destabilisation-restitution model. It follows from this model that a child with low vulnerability (e.g. good maternal attachment, no abuse or maltreatment, friends during childhood and adolescence, etc.) will be resilient to later life stress. High self-confidence and self-esteem, a repertoire of social problem-solving approaches, a secure stable affectionate relationship with another person, and experiences of success and achievement are all key features of resilience (291).

The aims of preventive programmes are to reduce incidence of mental disorders through reducing vulnerability factors, reduce factors that causes destabilization of vulnerable individuals, and to facilitate restitution. Genes and early dysfunctional maternal attachment are among vulnerability factors not easily reached.

Prevention of mental disorder can be *primary* as in aimed at the general population (again divided into those with universal versus selective measures), *secondary* as in aimed at groups presumed to be at risk for development of mental disorders, or *tertiary* as in aimed at prevention of further consequences of manifest disorders (292).

Primary prevention aims at hindering the disorder to occur at all. *Universal measures* in primary prevention aim at lowering the general level of symptoms in the entire population, and interventions are generally on a political level (291). An example of a successful primary

intervention more or less specific for Norway is the high prices on alcohol, which is a likely explanation as to the lower prevalence of alcohol dependence in Norway (7) compared to the US population (8), a difference not found for other mental illnesses. The preventive effect of taxation on alcohol is, however, restricted by the growing economic wealth. An example from the UK, is the recent public debate on whether physical punishment of children should become banned. Goldberg and Goodyear summarizes a series of successful primary preventions through universal measures (291): Suicide rates have been found to be reduced by limiting the way suicide is reported in the media; prevention programmes in schools aimed at reducing drug use have been demonstrated as effective; victimisation and bullying is reduced by whole-school interventions employing the Olweus programme; brief educational programmes aiming at improving parenting are shown effective; and school-teacher delivered fully manualized CBT programmes have been demonstrated impressive results in the short term, but not at one year follow-up.

Some risk factors are only marginally attainable within political measures, but are merely a result of political climate in the population: Association between conservative governments and suicide have been reported (293, 294). Many indicators of health have been shown to be associated with socioeconomic class (149, 150, 157).

Many primary prevention programmes employing *selective measures* have been found relatively successful, and Goldberg and Goodyear lists some that have produced evidence for their efficacy (291): Home visits by health visitors have been shown to prevent postnatal depression. Pregnant women at risk visited by trained nurses on nine occasions during pregnancy reduced verified cases of child abuse in addition to numerous other benefits (reduced smoking during pregnancies, fewer pre-term deliveries and a reduction of reported sexual abuse).

An example of a *secondary prevention programme* is routine early psychological debriefing after exposure to trauma. There exist few randomized controlled trails in this area, and some studies have indicated an adverse effect of these interventions (295-297). However, this example is an exception, as a meta-analytic review of prevention of incidence of new cases of mental disorders (mainly secondary and tertiary interventions) concluded with a general preventive effect of interventions aimed at mental disorders (298). A problem in studies of prevention of incidence is the lack of statistical power (299), and as a consequence, the number of good studies is limited.

As to *tertiary prevention*, most efforts have been invested on faster recovery and preventing relapses. Most depressions respond to simple measures like single antidepressants or problem-solving therapy, but a little more than one in four will need CBT by specifically trained clinicians, often in combination with various antidepressant drugs (291). However, resources available for delivering CBT are scarce, and the few are generally not provided to those needing them the most.

In summary, there exist available preventive means for mental disorders on primary, secondary and tertiary levels. However, far more resources and expertise is invested in treatment of mental disorders than prevention. (This problem corresponds to that of the many filters to treatment discussed in the preceding chapter 4.7.1, where almost all effort is invested in further development of fairly effective means, but not on the under-recognized problems of bringing individuals in need into treatment in the first place). Most well educated psychiatrists and psychologists would agree that preventive measures give far more value for money in terms of public health spending; yet most invest their careers in treatment of single individuals. This might be explained by the way humans are motivated. As formulated by Jennifer Newton (300): "… there is the issue of motivation. Clinicians are trained to respond to clinical problems and invariably gain satisfaction from doing their best to make ill people

well. Where a problem is not already manifest, there is not much satisfaction to be derived from developing anticipatory actions to prevent something that in any case might not. And there is no feedback to reward the practitioner for his efforts as there is when an ill person recovers […] While the value of cures for distressing and life-threatening illnesses is apparent to everyone, what person stops to think about the illnesses they have avoided?"

4.8 Future research

4.8.1 Disability pension award

The general question of why some individuals become disability pensioners while others do not is not well answered in the existing literature (98, 110). The significance of health is questioned with reference to the inverse association between changes in key public health indicators and incidence of disability pension. There is strong evidence for an impact of health on disability pension award from the disability pension paper, though more so from somatic symptoms (rather than diagnoses) and mental health. In the same paper, there is strong evidence for risk-factors of relevance beyond health, including age and educational level. At present, 12% of the Norwegian population within working age is recipients of disability pension, representing a large financial burden to society and a potential threat to welfare systems as we know them today. The very most is yet to be understood in relation to disability pension, and the disability paper inspires three major questions:

The first main question concerns how poor health increases disability pension award: (i) From the parsimonious model in the disability pension paper, somatic *diagnoses* seems to be more loosely related to disability pension award than somatic *symptoms* (both being adjusted for the other). However, according to regulations, all applications for disability pension must be accompanied by a medical certificate confirming presence of a *diagnosis*

causing work-related impairment. Consequently, statistics based on medical certificates will be biased in the direction of diagnoses at the cost of more vague symptoms. This discrepancy between the impact of somatic diagnoses and somatic symptoms needs further attention. (ii) Further, sickness presence (defined as continuing work despite health problems) is highly prevalent, which is also sickness absence without any illness or disease (301). We know little about reasons for, and consequences of, sickness presence and this needs further attention. (iii) Subjective components such as health beliefs, sick roles and attributions about own health need more attention, as they might contribute substantially to the risk of disability pension and sickness presence, and they might also influence prospects of return to work in shorter absences. (iv) Preliminary findings from an ongoing study suggest under-treatment for mental disorders prior to disability pension award for a F-diagnosis (262). A clinical interview-based study of individuals recently awarded disability pension should be performed with the purpose of determining the quality of treatment offered. From these preliminary findings based on epidemiological data and self-report, as well as knowledge on the quality of case-finding and treatment offered in primary care, it might be fair to hypothesize a substantial potential in preventing disability pension awards.

The second main question that needs further attention is risk factors for disability pension award beyond health. According to public statistics, all disability pensions are caused by a diagnosable medical condition (30). As discussed in chapter 1.3.4, macro-economic factors influence disability pension award (111, 142), and the parsimonious model indicated strong and independent effects of age and educational level. Specific objectives to be further examined in this are many, but the following four seem imperative: (i) How large proportion of disability pension awards represents processes of medicalization? In other words, how strong is the independent effect of push-factors on a societal level compared to the independent effect of health in prediction of disability pension award, and what proportion of

such effects are overlapping? (ii) There are multiple reports of effects of social class, both defined by educational level and type of job (149, 152, 153). As corresponding social inequalities in health are reported (157), it is plausible that health is a mediator of the association between socioeconomic status and disability pension award. Competing hypotheses beyond health on the mechanisms underlying associations between socioeconomic status and disability pension award include both push-factors (being excluded from the labour marked) and pull-factors (finding disability pension a viable and attractive alternative to work as a source of income). The mechanisms underlying the effect of socioeconomic status and disability pension award thus need further attention. (iii) The pull-model hypothesizes a positive association between disability pension award and economic incentives for this. Economic incentives for disability pension can be operationalized as the ratio between the potential income from disability benefits and current level of income. There is some support for this hypothesis (143, 144, 156), but none of the relevant studies have accounted for the possible confounding by health which is a major shortcoming due to the following: Low socioeconomic status is associated with both high relative compensation from a potential disability pension, and at the same time poor health. The question of whether public welfare schemes are *attracting* individuals from work is on the political agenda both in Norway (156) and in other OECD countries (134, 143). These issues can be addressed empirically by employing data from HUNT-2 in record linkage with public registries of work, tax, income and pension (155).

The third main question concerns whether being awarded disability pension improves or deteriorates health (hence discussion in chapter 1.3.2). We know very little about consequences of being a recipient of any long-term disability benefit (110). Two divergent positions both seem plausible: Disability pension might deteriorate health through reduced physical activity, isolation, stigma and loss of work-role; or improve health through relief

from work-related strains and burdens, and relief from financial worries in cases where marginalization from the labour marked is present. Randomized controlled trails is obviously impossible due to ethical concerns, but a longitudinal approach might be an option with baseline health data from HUNT-2, sub-sequent exposure in the disability pension registry, and outcome in the mortality registry, or by self-report of health status in HUNT-3 (in 2007).

4.8.2 Mortality

As introduced in chapter 1.4.4 and discussed in chapter 4.6.1, the two mortality papers addressed six questions. The analyses have added evidence to some questions, and raised others:

(i) The first issue concerned residual confounding in the association between depression and mortality (169). As discussed above in chapter 4.3.2, residual confounding will always be an issue. However, our analysis is adjusted for a number of somatic symptoms and conditions, so it is unlikely that the effect of depression on mortality is confounded by somatic conditions not accounted for in the model. Consequently, the issue of residual confounding is perhaps not the first in need of attention in this field.

(ii) We have provided new evidence for a dose-response association between severity of depression and mortality, which might be an issue for future replications.

(iii) Our analyses might inspire new approaches for identifying mechanisms underlying the association between depression and mortality. The finding that depression predicts CVD mortality equally strong as mortality from other causes comprised, does not exclude the existence of specific biological mechanisms for CVD and other causes of death; we cannot exclude the possibility of separate biological mechanisms with equal effect size underlying each mortality diagnosis. However, the finding does increase the relevance of searching for common mechanisms across mortality diagnoses. For CVD mortality, candidate

mechanisms proposed include antidepressant cardiotoxicity, lower heart rate variability reflecting altered cardiac autonomic tone, and increased platelet aggregation (191). Our analyses explored possible biological mechanisms through including BMI, cholesterol level, and blood pressure, and none of these accounted for the association.

Socioeconomic differences in health (150) did account for some of the association. Further, we found support for the hypothesis that health related behaviours found in depression also could account for some of the association. We were, however, only able to adjust for available data on health related behaviour, which comprised physical activity, smoking and alcohol problems (CAGE). These three factors are not covering all aspects of health-related behaviour related to depression, as factors like nutrition, sleeping patterns, physical activity beyond exercise and help-seeking behaviour were not covered, and might all be candidate mechanisms for explaining the association. Furthermore, residual confounding from health related behaviour is likely, as the three included aspects of health-related behaviour are measured with single or few items only (details in chapter 2.4.5). As discussed in chapter 4.5.1, there might be particular problems of validity relevant when measuring alcohol problems through CAGE, which further increase the likelihood of residual confounding.

(iv) We provide new findings relevant for the question of which mortality diagnoses are associated with depression. These findings inspire new questions: We found an effect of depression on all causes of mortality except mortality from gastrointestinal causes (N=47, 2% of deaths during follow-up) and for a residual category (N=71, 3%) comprising certain infectious and parasitic diseases, diseases of the musculoskeletal system and connective tissue, diseases of the genitourinary system, congenital malformations, deformations, and chromosomal abnormalities. As the power in prediction of mortality in these small groups is low, we cannot exclude type 1 error, but non-significant effects in these groups did not

indicate any effect of depression. Whether depression predicts disease mortality in general, or if there are exceptions, is yet to be answered.

Our finding that the effect of depression is equally strong in CVD mortality as mortality from other causes comprised is new, and replications applying other data sources are needed. Most available health surveys will, however, lack the sufficient statistical power to provide a necessary baseline for this purpose, and few countries provide personal identification numbers that can be applied for identification of mortality in public registries.

Cancer is the second largest cause of death, and it is not clear from the literature whether depression increases cancer mortality. An extensive review examined if psychological factors cause cancer (302). Despite certain intriguing findings warranting further studied, the authors concluded that the evidence failed to support the hypothesis that depression was a risk factor for cancer. The same group of researchers reached the same conclusion in a large registry-based study of patients hospitalized for affective disorders (303), and psychosocial interventions have not been found to increase survival in cancer patients (304). There are, however, some reports of effects of depression on mortality in selected groups of cancer patients (305, 306). Our finding of increased cancer mortality in depression is therefore in need of replications. However, our finding of equal effect of depression in CVD mortality and other causes combined suggests that future attempts of examining mechanisms driving the association should not be restricted to hypotheses relevant for cancer mortality only.

As presented above, we employed the *underlying cause of death* (as described in chapter 1.4.2) for the purpose of categorization in predicting cause specific mortality. Other mortality diagnoses might be relevant in further explorations of mortality from depression. Mortality diagnoses beyond underlying cause of death might also represent an issue of

confounding or misclassification, for example represented by comorbid CVD in cases where cancer or respiratory diseases are encoded as underlying cause of death.

We found an effect of comorbid anxiety and depression in both mortality from accidents (N=80) and mortality without medical certificate for cause of death (N=40), a pattern similar to that of suicide (N=29). The effects were, however, weaker and non-significant after adjustment for possible confounding or mediating factors. It is unclear what these effects represent: Possible hypotheses include hidden suicides among non-illness deaths (caused by bias in direction of under-report of suicide in unclear cases), increased hazardous behaviour, or perhaps also other causes.

(v) The issue of effect-moderation by gender might be settled from our analyses, but replication employing other measures of depression than HADS might be useful, as when employing HADS, prevalence estimates of depression diverge from other measures by being equal in men and women (77). Evidence of effect-moderation of gender with proper testing for interactions (rather than reports based on stratified analyses) are lacking (169). We have no explanation of the stronger effect of depression on mortality in the younger part of the population, which adds to the issues in need of further attention.

(vi) Our finding of a U-shaped effect of anxiety on mortality is novel. The effect of low anxiety (first quartile, compared to third) accounts for far more mortality than does case-level depression. (Whether adverse consequences of *low* levels of symptoms of psychopathology belong to the field of mental health is uncertain; symptom rating scales like HADS are usually scaled from good health to psychopathology, and in this case, the adverse outcome is most strongly associated with what we usually regard as good health.) Obviously, it would be interesting to examine the effect of low anxiety in relation to cause specific mortality, and also to examine confounding and mediating factors in more detail. A plausible hypothesis is that low anxiety predicts accidents, as it can be argued that at least some

minimum level of anxiety aids survival. However, as non-illness mortality is relatively rare, this can probably not account for the entire effect.

In combination, the findings of lower mortality in comorbid anxiety and depression than in depression alone, higher mortality in low anxiety than medium levels, and high mortality in depression actualize a hypothesis of anxiety and depression being proxies of *activation level*, which again is positively associated with mortality. Continuing this line of argumentation, low level of activation would be indicated by high depression and low anxiety (and indeed both), whereas high level of activation would be found in high anxiety without depression.

4.9 Conclusion

Employing a historical cohort design, we utilized unique links between a large epidemiological cohort study (the HUNT-2 study) and comprehensive national databases of disability pension award and mortality.

Anxiety and depression were robust predictors of award of disability pensions in general, and also for awards for alleged non-psychiatric conditions according to the applications for disability pension. Depression predicted general mortality, also after adjustment for multiple confounding factors. Associations between anxiety symptoms and mortality were U-shaped. The effect of depression on mortality was not limited to CVD mortality and suicide, but included most disease-mortality, and also non-illness deaths beyond suicide. Lower mortality was found in comorbid anxiety and depression than in depression alone in disease mortality. On the contrary, suicide was associated with comorbid anxiety depression rather than depression alone. The marginal effect of case-level anxiety on mortality was entirely explained by adjustment for depression.

Somatic symptoms were also strong predictors of disability pension award, and did also account for much of the effect of anxiety and depression. In contrast, somatic diagnoses were strong predictors of mortality, and accounted for much of the effect of depression on this outcome.

The finding that anxiety and depression predict disability pension awarded for non-psychiatric diagnoses indicates that the cost of common mental disorders in terms of disability pension and lost productivity may have been considerably underestimated by official statistics. The finding that depression increases mortality beyond CVD mortality and suicide might be yet another indication of underestimation of the consequences of depression.

On the individual level, anxiety and depression can be reduced by psychotropic medication and psychotherapy. Despite the existence of quality treatment for anxiety and depression, only a minor proportion of the population with common mental disorders will ever find their way to treatment. Combined with variable quality of treatment as usual, the impact of treatment on common mental disorders of the population is marginal. Several preventive treatment strategies are found to have good effect, but resources are generally spent on treatment rather than prevention. There exists a potential for reduction of anxiety and depression in the population by improved treatment strategies and prevention.

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