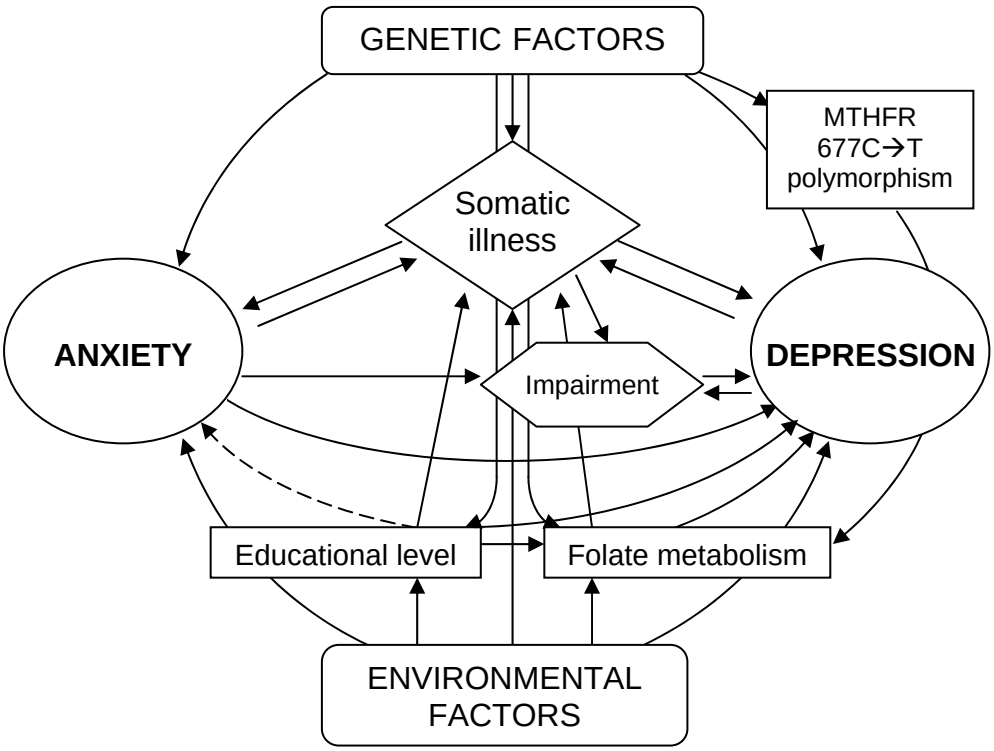
Anxiety and depression in the general population

Issues related to assessment, comorbidity, and risk factors

Ingvar Bjelland, MD



Section for Epidemiology and Medical Statistics
Department for Public Health and Primary Health Care
University of Bergen, Norway

The Norwegian Research Council

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Contents

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2. LIST OF PAPERS

Paper I Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002;52:69-77.

Paper II Bjelland I, Stordal E, Mykletun A, Dahl AA. A dimensional versus a categorical approach to co-occurring anxiety and depression: The HUNT study. Submitted to J Clin Epidemiol

Paper III Stordal E, Bjelland I, Dahl AA, Mykletun A. Anxiety and depression in individuals with somatic health problems. The Nord-Trøndelag Health Study (HUNT). Scand J Prim Health Care 2003;21:136-41.

Paper IV Bjelland I, Tell GS, Vollset SE, Refsum H, Ueland PM. Folate, Vitamin B12, Homocysteine, and the MTHFR 677C→T Polymorphism in Anxiety and Depression: The Hordaland Homocysteine Study. Arch Gen Psychiatry 2003;60:618-26.

Paper V Bjelland I, Krokstad S, Mykletun A, Dahl AA, Tell GS. Education as predictor for anxiety and depression - A population based cohort study. Submitted to Am J Epidemiol

3. ABBREVIATIONS AND DEFINITIONS

ABBREVIATIONS

- ADI-12 Anxiety-Depression Index-12 (continuous measure of mental distress)
- AUC Area Under Curve
- BMI Body Mass Index (kg/m^2)
- CI Confidence interval
- CIDI Composite International Diagnostic Interview
- DIS 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 revised edition
- DSM-IV Diagnostic and Statistical Manual of Mental Disorders, fourth edition
- ECA Epidemiologic Catchment Area
- GAM Generalized Additive Model
- HADS Hospital Anxiety and Depression Scale
- HADS-A Anxiety subscale of HADS
- HADS-D Depression subscale of HADS
- HUNT 1 The Nord-Trøndelag Health Study 1984-86
- HUNT 2 The Nord-Trøndelag Health Study 1995-97
- HUSK The Hordaland Health Study 1997-99
- ICD-10 International Classification of Diseases, tenth edition
- MDD Major Depressive Disorder
- MTHFR Methylenetetrahydrofolate reductase
- NCS National Comorbidity Survey
- OR Odds ratio
- ROC Receiver Operating Characteristics
- SES Socioeconomic status
- tHcy Total homocysteine
- PPV Positive Predictive Value: proportion of true cases among the test-positive subjects
- NPV Negative Predictive Value: proportion of true non-cases among the test-negative subjects

DEFINITIONS

- Anxiety disorder (= ”pure anxiety disorder”) — HADS-A $\geq$ 8 and HADS-D < 8
- Comorbid disorder — Comorbid anxiety disorder and depression: HADS-A $\geq$ 8 and HADS-D $\geq$ 8.
- Concurrent validity — 1) The correlation between two instruments that were meant to measure the same construct. 2) A comparison of the case-finding properties of a test compared to another against a common external “gold standard” criterion.
- Confounder — A variable that is imbalanced between the exposure groups to be compared (i.e. associated with the exposure), and associated with the outcome, leading to a biased effect of the exposure. It should not be a cause of the exposure or the outcome.
- Depression (= ”pure depression”) — HADS-D $\geq$ 8 and HADS-A < 8
- Determinant — A (risk) factor that brings about change in a health condition.
- Discriminant validity — The correlation between two measures that are assumed to assess different constructs. A low correlation indicates good discriminate validity.
- Endophenotype — Neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological (including configured self-report data) measurements, reflecting some aspects of a disorder.
- Factor analysis — Statistical technique examining the underlying dimensions reflected by a set of item scores.
- Mediator — An intermediate variable, mediating the effect of the exposure on the outcome
- Incident cohort — Individuals from the study population in Paper V with ADI-12 scores $\leq 80^{th}$ percentile.
- Internal consistency — The average inter-item correlation.
- Persistent cohort — Individuals from the study population in Paper V with ADI-12 scores > 80^{th} percentile.
- Sensitivity — The proportion of true cases that are identified by a test.
- Specificity — The proportion of true non-cases that are identified by a test.
- Test-retest reliability — The coefficient quantifying the agreement between two test scores separated by a specified period of time.

4. BACKGROUND

This dissertation addresses two of the most common mental ailments, namely anxiety and depression. For an understanding of these vaguely defined and multi-factorial symptoms and disorders, a wide spectrum of research approaches is required. Various concepts of psychopathology and assessment methods illuminate different aspects of anxiety and depression, and the reciprocal relation between these constructs. Examination of the co-occurrence of anxiety and depression, as well as their co-morbidity with somatic illnesses elucidates the broad role of anxiety and depression within the field of health care. Likewise, studying associations with neurobiological and psychosocial factors will give a more comprehensive understanding of the mechanisms involved in the development of anxiety and depression.

Hence, the studies of this dissertation address how anxiety and depression can be assessed by a simple questionnaire, how the relation between anxiety and depression can be viewed by two different approaches to psychopathology, how anxiety and depression are co-occurring with some somatic illnesses and symptoms, and finally how anxiety and depression are related to some neurobiological and psychosocial factors. These studies are based on the use of data from three Norwegian health surveys. Health surveys have a long tradition in Norway in the studies of major health problems such as tuberculosis and cardiovascular illnesses. Recently, mental disorders have received status as a major health problem in society, and, therefore, measurements of anxiety and depression have become a major goal of the national health surveys (1).

4.1. ANXIETY, DEPRESSION AND PUBLIC HEALTH

4.1.1. Prevalence

Anxiety disorders and depression are among the most frequently occurring mental disorders in the general population. However, prevalence estimates vary markedly in different studies. In the Epidemiologic Catchment Area Study (ECA) (2) the 12-month prevalence of a major depressive episode was 5.8%, compared to 10.3% in the National Comorbidity Study (NCS) (3), and 7.3% in a recent study from Oslo, Norway (4). The 12-month prevalence of any anxiety disorder in ECA was 12.7%, and in NCS 17.2%. In the Oslo study the overall prevalence of anxiety disorders was

not reported, but the prevalence of the separate anxiety disorders were lower than in NCS. Although this may reflect real differences geographically or historically, the main explanation is probably differences in assessment instruments and their relation to different classification systems. ECA used the Diagnostic Interview Schedule (DIS) (5) which gave diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) (6). In contrast, the Composite International Diagnostic Interview (CIDI) (7) was used in NCS and the Oslo study, giving diagnoses according to DSM-III-R (8) and the International Classification of Diseases, version 10 (ICD-10) (9). The sampling procedures also differed; while ECA was a multi-site study, NCS included a nationally representative sample, and the Oslo study included a locally representative sample.

The findings of a relatively high prevalence of mental disorders, e.g. 29% of any one-year DSM-III-R mental disorder in NCS, have questioned the clinical significance of the diagnoses achieved in such studies (10). This issue has recently been considered in a re-analysis of ECA and NCS (11), where clinical significant symptoms had to be related to self-reported use of health services, medication, or impairment. By this approach the prevalence of the anxiety disorders and major depression generally decreased, and the revision concluded with a one-year prevalence of any anxiety disorder of 11.8% and major depressive episode of 4.5%. The one-year prevalence of the anxiety disorders differed considerably, the most prevalent was simple phobias (4.3%), followed by posttraumatic stress disorder (3.6%), social phobia (3.2%), generalised anxiety disorder (2.8%), agoraphobia (2.1%), obsessive-compulsive disorder (2.1%), and panic disorder (1.4%). Dysthymic disorder (low-grade, chronic depression) and bipolar disorder (I/II) (recurrent depressive and manic/hypomanic episodes) had a one-year prevalence of 0.7% and 1.7%, respectively. Since the one-year prevalence of having any of these mental disorders was 14.9%, the public health impact of depression and anxiety disorders should be evident.

4.1.2. Impact on public health, costs and need for research

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) by the Global Burden of Disease Study (GBD) (12) and was predicted to advance to the second most

important cause by year 2020 (13). The role of anxiety disorders was not addressed in the GBD, but analyses from the NCS estimated the annual costs of anxiety disorders (panic disorder, posttraumatic stress disorder, agoraphobia, social phobia, simple phobia and generalised anxiety disorder) to be 54 % of the total costs due to treatment for somatic illness, and 31 % of the costs due to treatment for mental illness (14). The total cost of affective disorders (major depression, dysthymia and bipolar disorder) was very similar to the total cost of anxiety disorders.

Measures to prevent these widespread, deteriorating, and costly disorders should be of great interest to society. However, much is still unknown about the etiology and prevention of anxiety disorders and depression. Population-based epidemiological studies collecting comprehensive information on both mental and somatic health as well as characteristics of personal environment, lifestyle, use of health services, and biological measures, are warranted to identify modifiable risk factors. Such studies have not been abundant, but in Norway some have been performed during the last two decades. Data from three of these health surveys are the basis of the studies included in this dissertation.

4.2. ASSESSMENT OF ANXIETY AND DEPRESSION

Mental disorders are assessed by registration of subjective symptoms, behavioural patterns, and impairment during a specified period, either through interviews or questionnaires. However, there is a controversy about which features should characterise the constructs of anxiety and depression, and whether these conditions should be considered as categorical diagnoses or continuous phenomena. Both approaches, therefore, are used in this dissertation . However, before the assessment methods are presented, different approaches to the understanding of anxiety and depression will be reviewed.

4.2.1. What is anxiety and depression?

Anxiety is usually described as the emotion of fear involving feelings of tension, worry, apprehension, and dread for something considered dangerous in the future (15). Depression is associated with the emotion of sadness, in addition to feelings of sorrow, hopelessness, gloom, lack of energy, and anhedonia (16). These symptoms are sometimes considered as normal psychological responses, equivalent to physical pain, on a continuous scale from being absent to a maximum intensity. This

approach is often described as dimensional (17). In contrast, the categorical approach views anxiety and depression as discrete psychopathological entities, or disorders. Such disorders are classified as being present or not according to a threshold for specific diagnostic criteria (17). Figure 1 is illustrating the difference between the two approaches.

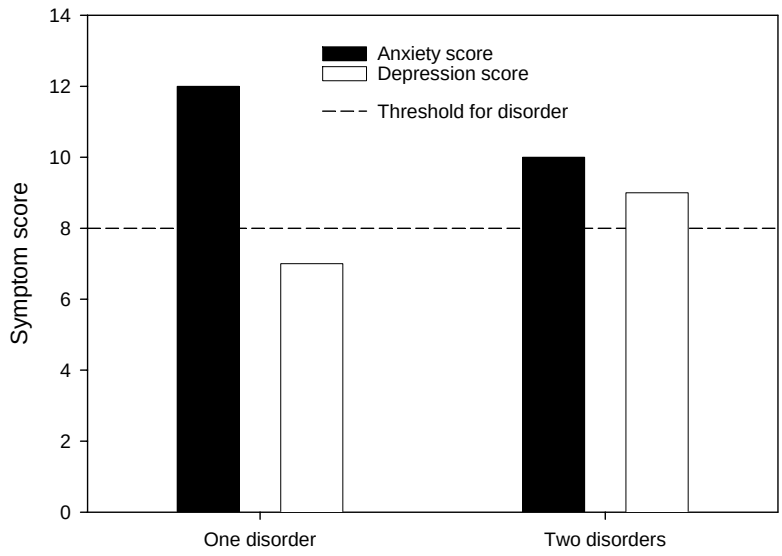


Figure 1: Categorical versus dimensional approach to anxiety and depression. The categorical approach applies the rating scale score as a test for the disorder defined by a cut-off value, and in this example two different subjects with the same sum score have one versus two disorders. The dimensional approach applies the rating scale score to describe the contribution from both anxiety and depression.

4.2.2. The categorical approach

From a public health and clinical point of view it is necessary to identify individuals suffering from anxiety disorders and depression in order to make decisions about planning of health services and treatment. Researchers also address anxiety and depression by the categorical approach in order to get a reliable description of their samples. The classification is based upon distinctive symptoms, such as panic or depressed mood, and their impact, most often on functional impairment, as well as their duration. The validity of categorical diagnoses can be

settled by converging data from clinical, family, population–based, and laboratory studies (the Washington University criteria) (18, 19).

A syndrome is defined by the presence of a set of co-occurring symptoms, and may be considered as a valid diagnosis if it has a predictable clinical course, treatment response, and pattern of familial aggregation (20). Accordingly, the current classification systems, DSM-IV (21) and ICD-10 (9), are meant to be atheoretical, solely describing the characteristic of the diagnoses, mainly without consideration of etiology or hierarchical organisation of the disorders. Moreover, in the expanding revision of DSM-III-R (8), which aimed to include all kinds of psychopathology, there was "no assumption that each mental disorder is a discrete entity with sharp boundaries (discontinuity) between it and other mental disorders" (p. xxii).

In both ICD-10 and DSM-IV anxiety is classified as different anxiety disorders, while depression is mainly classified as unipolar or bipolar disorder with a variety of subtypes.

4.2.3. The dimensional approach

A limitation of the categorical approach is the need to define sharp, clear-cut thresholds between normality and pathology. Sub-threshold conditions of depression as well as of anxiety disorders have been found to have significant clinical impact in terms of functional impairment, mortality, treatment, and prognosis (22-27). However, simply lowering the diagnostic threshold does not solve the problem of categorisation (28). Thus, it has been suggested that anxiety and depression are dimensional phenomena with no thresholds between pathology and normality (29). Hence, the use of symptom scores opposed to categorical diagnoses has been proposed for research addressing anxiety and depression (17).

4.2.3.1. Models for underlying dimensions

By use of latent trait analyses of GHQ scores from primary care patients, Goldberg and colleagues (30) identified the highly correlated dimensions of anxiety and depression underlying the common mental illnesses presented in these patients. Later, Goldberg proposed a dimensional model for common mental disorders, including anxiety, depression and somatisation (31). Other similar models of non-psychotic psychopathology have been developed, such as Krueger's model (32) that

identified an externalising and an internalising dimension, the latter encompassing the anxious-misery and fear sub-dimensions.

After having reviewed nearly 400 studies addressing symptoms of anxiety and depression among patients and non-patients, Clark and Watson (33) suggested *a tripartite model.* First, the model contains a common factor for anxiety and depression consisting of general distress or Negative Affect including both anxious and depressed mood, insomnia, and poor concentration. Second, a specific factor for anxiety, consisting of tension and anxious arousal manifested as shortness of breath, dizziness or light-headedness, and dry mouth was described. Third, the depression factor was described as anhedonia and absence of Positive Affect, i.e. loss of interest and feeling that nothing is interesting or enjoyable. However, subsequent testing of this model failed in confirming such a simple concept. Hence, Mineka, Watson and Clark (34) proposed an *integrative hierarchical model* of anxiety and depression, not very different from the original tripartite model, but where each individual anxiety disorder and depression had their own unique component that differentiated them from all the others. Later, Watson has suggested more specific factors for the various anxiety disorders (35).

4.2.4. Assessment of anxiety and depression in epidemiological studies

In epidemiological studies focusing mainly on mental health, standardised interviews performed by trained lay people have been the gold standard. As described in section 4.1.1., in the ECA, DIS was used, while CIDI was used in the NCS and the Oslo study. Such interviews are suitable for collecting comprehensive information as to a variety of mental symptoms, and yield categorical diagnoses according to the ICD-10 and DSM-IV classification systems. However, in large-scale health surveys the diagnostic information is mostly obtained from short questionnaires, resulting in a limited number of data on each topic.

4.2.5. Rating scales

Rating scales are widely used for clinical as well as scientific purposes. They yield scores that may be used as continuous measures (dimensional approach), or they may be used as diagnostic tests to identify cases by defined cut-off values (categorical approach). Several questionnaires that assess anxiety and depression are applicable in many settings due to their low cost. In epidemiologic studies the following

instruments are mostly used: Center for Epidemiological Studies of Depression Scale (CES-D) (36); Beck's Depression Inventory (BDI) (37); Spielberger State-Trait Anxiety Inventory (STAI) (38); Hopkins Symptom Check List (HSCL) (39); General Health Questionnaire (GHQ) (40); and Hospital Anxiety and Depression Scale (HADS) (41). Some assess both anxiety and depression (HADS, HSCL, GHQ) while others assess only anxiety (STAI) or depression (CES-D; BDI).

4.2.6. The Hospital Anxiety and Depression Scale (HADS)

Due to its briefness (14 items) and subscales for both anxiety and depression HADS is a feasible rating scale to be applied in health surveys. The subscales consist of seven items for anxiety (HADS-A) and seven for depression (HADS-D), each scored from 0 (not present) to 3 (maximally present) on a Likert scale formulated in readily understandable language (41). To increase acceptability and to preclude that individuals feel tested for mental disorders, symptoms of severe psychopathology are not included. HADS-A contains items mainly concerned with restlessness and worry, as in generalised anxiety disorder, plus one item on panic attacks. HADS-D focuses mainly on the reduced pleasure response aspect (anhedonia) of depression, as well as psychomotor retardation and depressed mood.

The reported characteristics of a rating scale may vary depending on the sample on which it is applied as well as on the external validity criterion employed. Hence, to avoid such bias a number of studies addressing case-finding and other psychometric properties should be reviewed. The state of the art in doing so is the *systematic review* (42) hallmarked by the application of strategies, which are documented in the materials and methods section, to avoid bias in location and selection of studies (43, 44). Sources of such bias include limiting the search to one database, inclusion of studies published in English only, or not applying inclusion criteria (43).

In a somewhat methodologically less stringent examination of studies applying HADS published until May 1996, Herrmann (45) concluded that "HADS is a reliable and valid instrument for assessing anxiety and depression in medical patients". Hermann reported the following psychometric data on HADS (definitions of the psychometric measures, see section 3): Test-retest reliability after two weeks was high ($r > 0.80$ for both subscales), but decreased to 0.70 after six weeks. Internal consistency was reported from four studies, and varied from 0.80 to 0.93 for HADS-

A, and from 0.81 to 0.90 for HADS-D. Factor analysis was reported from five studies giving most support for two separate dimensions, at least in the English and German versions, mainly corresponding to the two subscales. Discriminant validity was reported from 18 studies with an average of r = 0.63. In 17 studies of the English version the average sensitivity and specificity of both subscales at cut-off ≥ 8 were 0.8 or higher. In further nine "international" HADS versions comparable or slightly poorer results were found, while specificity of less than 0.5 was observed in three studies of Asian and Australian patients. The external criteria, or gold standards, for anxiety disorders or depression varied in the studies. However, these were not stated explicitly in the review. Likewise, the efficiency of HADS as a casefinder at different cut-off scores demonstrated by Receiver Operating Characteristics curves (ROC curves, see section 6.4.2., "Paper I") (46) was not reported. Finally, the concurrent validity of HADS was approved, however, no specific results were reported by Herrmann.

4.3. COMORBIDITY

The co-occurrence, or comorbidity, of two or more diseases is relatively common both in psychiatry and in somatic medicine, in particular in older age groups (47). Various combinations of diseases may occur simply by chance. However, the term comorbidity is usually applied when the risk (e.g. odds ratio) for a co-occurring disease is more than by chance (48). Some critics claim that comorbidity is simply an artefact of splitting nosological entities into separate classes. Hence, two disorders that have some common diagnostic criteria, are more prone to co-occur, which is called *diagnostic comorbidity* (49). Furthermore, when the co-occurring condition is a consequence of the other, e.g. when panic disorder is followed by agoraphobia, it has been referred as *pathogenic comorbidity* (49). As long as the diagnostic hierarchy with one main diagnosis introduced by Jaspers in 1913, was accepted, comorbidity was non-existing. The idea to make hierarchy-free diagnoses was suggested in 1984 (50), and was accepted in DSM-III-R in 1987, after which comorbidity ensued as an important issue. However, due to lack of consensus as to definition, the reported extent of comorbidity varies across studies (51).

4.3.1. Comorbidity between anxiety and depression

Varying degrees of comorbidity between anxiety disorders and depression have been reported in different studies. In NCS (52) the comorbidity between the 12 month prevalence of major depressive disorder (MDD) and any anxiety disorder was 51 %. In the international WHO Study on Psychological Disorders in Primary Health Care (53) the rates were somewhat lower. Among cases of depression 39% had an anxiety disorder, and among cases of anxiety disorder 44% had a depression. In a clinical sample panic disorder and generalised anxiety disorder were found to be more common in bipolar disorder than in MDD (54), while this pattern was not seen in a population-based study (55).

Comorbidity between anxiety disorders and depression has several consequences including increased symptom severity (56), impaired treatment response to antidepressive medication (57), impaired recovery rate from depression, increased time to recovery, decreased time to relapse (58, 59) as well as increased risk for suicide (60).

Studies addressing comorbidity have almost exclusively applied a categorical approach (61). Since the dimensional approach is seen as complementary to the categorical (62), it is paradoxical that the dimensional approach to anxiety and depression has hardly been applied when studying the causes or consequences of such comorbidity. In co-occurring anxiety and depression the contribution from each may vary from a minimum to a maximum of symptom load, resulting in an anxiety-depression ratio varying from zero to infinite (figure 2).

Although it is well known that anxiety and depression are highly correlated (34), a correlation coefficient alone cannot describe whether the relationship between the two is the same in the lower and upper parts of the symptom scales. The lower parts (i.e. few symptoms) are of special interest because sub-threshold conditions have been reported to be of clinical significance (22), and because most individuals have scores in that range.

The high correlation between anxiety and depression does not necessarily mean that they are similarly associated with other mental or somatic conditions, or with various risk factors. However, in studies addressing depression, comorbid anxiety disorders or co-occurring anxiety symptoms are frequently not accounted for, and vice versa for studies addressing anxiety disorders. Hence, it is not known whether the findings are mainly “caused” by the anxiety or the depression component.

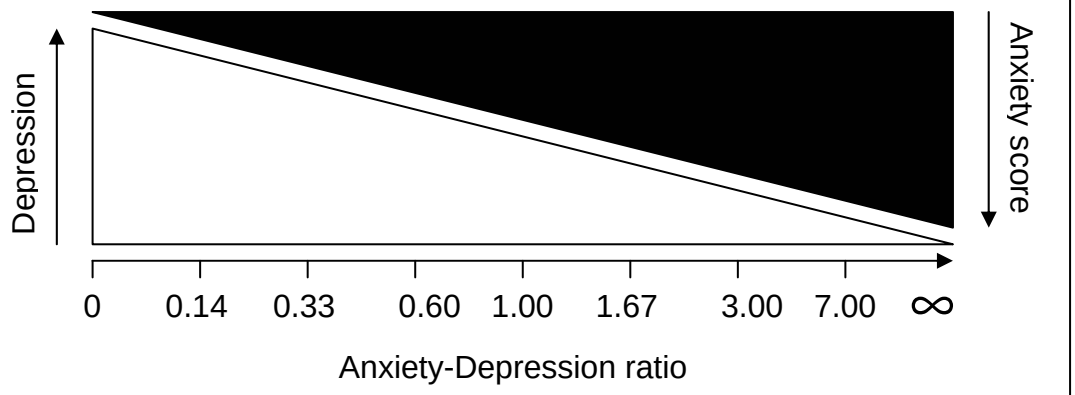


Figure 2: An illustration of how anxiety and depression as dimensional phenomena may co-occur in all possible combinations (*codimensionality* as a parallel to *comorbidity*). The Anxiety-Depresion ratio expresses the relative contribution from the anxiety and depression symptoms.

4.3.2. Comorbidity between anxiety and depression, and somatic disease

The prevalence of anxiety disorders and depression among individuals reporting somatic illness in the general population (63) or among patients in general practice (64, 65), is higher than the prevalence among somatically healthy individuals. The hospital stay of patients with such comorbidity has been reported to be significantly longer than for somatic patients without co-occurring anxiety or depression (66). In an international study the economic consequences of depression were influenced to a greater extent by the presence of somatic comorbidity than by depressive symptom severity alone (67).

The majority of studies have examined cardiovascular disease, such as myocardial infarction (68-73), stroke (74), and arterial stiffness (75), and found increased prevalence of depression. Increased prevalence of depression has been reported as well in diabetes (76, 77), Parkinson's disease (78), rheumatoid arthritis (79), and back pain (80). Increased prevalence of anxiety has been reported among patients with peptic ulcer (81). Among patients with functional gastrointestinal complaints (82), cancer (83-85), HIV-infection (86-88), and multiple sclerosis (89) the prevalence of both anxiety and depression is increased.

The mechanisms linking anxiety and/or depression with somatic disease are not known in part due to the presumed complexity of such mechanisms, as well as the

heterogeneity of both mental disorders and somatic diseases included in the various studies (90-92). In addition, there is a paucity of longitudinal studies and most of these have addressed depression only (47).

Three theoretical explanations for these associations have received some support. First, anxiety/depression may cause or aggravate somatic disease, second, somatic disease may cause or aggravate anxiety/depression, or, third, there may be some common pathophysiological mechanisms for both anxiety/depression and somatic disease (92). Some studies suggest a reciprocal relationship between depression and somatic health problems (93, 94) merging the two first theoretical alternatives. Common pathophysiological mechanisms may involve the effect of hormonal dysfunction, nutritional deficiencies, toxic agents, or neurodegenerative or inflammatory processes.

It is also possible that the observed comorbidity may be due to one or more uncontrolled confounding factors in the studies (95). These may include age or gender, as well as socioeconomic status, psychosocial factors or health behaviours (smoking, alcohol consumption, unhealthy dietary habits and lack of physical exercise). Finally, many studies have examined either anxiety or depression, and if they have included both, they usually have not accounted for the close association between the two. If the subjects studied have a depression with co-occurring anxiety (or vice versa) it may be hard to tease apart whether the association with a somatic disease is mainly due to the depression or the anxiety (20). We are aware of only one study (N=711) (96) addressing the occurrence of somatic illness in comorbid anxiety and depression. Hence, the patients with panic disorder and comorbid major depressive disorder were reported to have higher rates of somatic illness (peptic ulcer, angina pectoris, and thyroid disease) than patients with anxiety disorder without depression. However, the specific rates were not reported, nor tests of statistical difference between them.

4.4. RISK FACTORS

A risk factor may be defined as “An aspect of personal behaviour or life-style, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiological evidence, is known to be associated with health-related condition(s) considered important to prevent” (97). However, the term is frequently

inconsistently and imprecisely used (98), and should be differentiated into e.g. risk markers, determinants and modifiable risk factors (97).

In the social sciences intermediate factors in a causal pathway from e.g. socioeconomic status (SES) to e.g. anxiety and/or depression, are often denoted "mediators" (99). However, to identify a mediator, a longitudinal study design with at least two follow-up points is necessary to establish the causal direction between various factors (100). In a cross-sectional study, or when there is only one follow-up, it might be difficult to decide whether a factor is a mediator or a confounder. Contrary to a mediator, a confounder should not be caused by the exposure (101), which is difficult to prove without three consecutive measurements as well.

Specific risk factors may be difficult to identify when the validity of the outcome is questionable, e.g. due to extensive comorbidity (see section 4.3.1.) or overlapping criteria with other outcomes. In the search for risk factors in mental disorders, strong associations are therefore not to be expected. Alternatively, other phenotypes of neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological (including configured self-report data) nature, called endophenotypes, have been suggested (102).

Different theoretical approaches to mental disorders have emphasised their unique etiological models. Hence, research addressing biological, psychological, as well as social risk factors has been conducted. These different perspectives are, however, artificially separated, and an explicit integrated biopsychosocial model acknowledging the multifactorial diathesis of disease in general, and mental disorders in particular, was proposed by Engel (103) and has been implemented to a certain extent. Our knowledge of neurobiological and psychosocial risk factors is incomplete, as well as how they interplay in precipitating mental disorders (104). In the following sections some of these factors will be reviewed as to current status and unanswered questions.

4.4.1. Biological factors

4.4.1.1. Genetics

A meta-analysis including twin studies of anxiety disorders has revealed a heritability between 30-40% (105), while another meta-analysis of major depressive disorder found 37% heritability (106). However, the limited reliability of life-time diagnosis in, for example, major depression (107) is likely to cause too low estimates

of the heritability due to overestimation of the individual specific environmental factors (108). The genetic factor in bipolar disorder is assumed to be even stronger than in major depression (109).

There is some evidence for common etiologic factors for anxiety and depression. Female twin studies have shown that the genetic factors of MDD and generalised anxiety disorder seemed identical (110), while the association between the genetic factors of MDD and other anxiety disorders was modest (111). Obsessive compulsive disorder seemed to be genetically unrelated to depression or other anxiety disorders (112), but related to Tourette's syndrome (113).

Some studies have shown associations between a single nucleotide polymorphism in the promotor region of the serotonin transporter gene and neurotisism (114), anxiety (115) and depression (116), but others have not (117). Moreover, a study using functional magnetic resonance imaging demonstrated an association between this polymorphism and an increased response in amygdala, (the neurophysiological substrate for normal and abnormal fear behaviour) to fearful stimuli (118).

4.4.1.2. Neurobiology

Most studies examining neurobiological factors in mental disorders compare clinical samples to healthy controls. To measure such factors expensive and sometimes unpleasant or painful procedures are necessary, limiting the sample size and the chance of participation at follow-up assessments. Accordingly, in the paucity of longitudinal population-based studies, it may be difficult to decide whether the factors identified in cross-sectional association studies are determinants or only markers of the disorder. Hence, frequently short-cuts are made directly from clinical cross-sectional observations to randomised clinical trials (RCT).

In mental disorders neurotransmission is compromised in various ways, which has lead to the development of drugs influencing receptors and transport mechanisms for neurotransmitters. Benzodiazepines binding to the gamma amino butyric acid – benzodiazepine receptor complex have a tranquillising effect on anxiety (119), while different drugs inhibiting the serotonin reuptake in the synapses have a relatively good effect on depression and anxiety as well (120).

The hypothalamic-pituitary-adrenal (HPA) axis is affected in both anxiety and depression. Anxiety is characterised by hypocortisolemia, supersuppression after

dexamethasone, and increased number of glucocorticoid receptors. In contrast, depression is characterised by hypercortisolemia, non-suppression after dexamethasone and decreased glucocorticoid receptors (121).

Abnormal regulation of sex-hormones (122), thyroid hormones (123, 124), and melatonin (125, 126) is observed in patients with anxiety disorder and depression. Elevated levels of cytokines, as seen in some infections and immunotherapy of cancer and hepatitis, may induce depression and possibly anxiety as well (127).

4.4.1.3. B-vitamins and depression

Deficiency of nutritional factors, such as fatty acids (128), tryptophan (129), folic acid, and cobalamin have all been associated with depression. The evidence for folic acid and cobalamin will be reviewed more closely in this section.

Folate is a B-vitamin of major importance for methylation processes (one-carbon metabolism) in the brain. By transferring a methyl group from 5-methyl-tetrahydrofolate (5mTHF), the cobalamin dependent methionine synthetase converts homocysteine into methionine (figure 3). Folate deficiency may be caused by an inadequate dietary intake, increased metabolic demands due to cancer, or certain drugs (130), or due to a single nucleotide polymorphism of methylenetetrahydrofolate reductase gene (MTHFR 677C→T) reducing the availability of 5mTHF (131). Cobalamin deficiency may also be caused by an inadequate intake (e.g. among strict vegetarians) as well as gastrointestinal disease (in particular atrophic gastritis among elderly) (130). Low levels of both folate (132) and cobalamine (133) are associated with elevated levels of serum homocysteine .

Four decades ago Victor Herbert (134) treated successfully his self-induced folate deficiency symptoms of insomnia, irritability, and impaired memory by folate supplementation. However, our understanding of the role of folate, and one-carbon metabolism in general, in mental disorders is still insufficient. Most studies on folate and depression are cross-sectional and compare folate status in depressed patients with the status in patients with other mental disorders or in healthy subjects. These studies suggest that low folate status is associated with depression, especially with more severe forms, prolonged episodes and weak treatment response (135). The limitations of these studies are related to lack of longitudinal design, small sample size, highly selected patients and lack of adequate control groups. Notably, two

population-based studies (136, 137) controlling for possible confounders demonstrated no association between folate status and depression.

Indications that folate deficiency increases the risk for depression, have been obtained mainly from biochemical and in vitro studies, but also from a recent study of dietary habits (138). Folate metabolism is linked to biopterin-dependent neurotransmitter synthesis (139) (figure 4) and methylation of biogenic amines and phospholipids in the central nervous system (CNS) (140).

Only two studies (141) have shown an association between serum total homocysteine and depression, while other studies have not (137, 142, 143). Homocysteine, or its metabolites, may have a direct excitotoxic effect on the N-methyl-D-aspartate glutamate receptors in the CNS, or may inhibit the S-adenosylmethionine (SAM)-dependent methylation via S-adenosylhomocysteine (140).

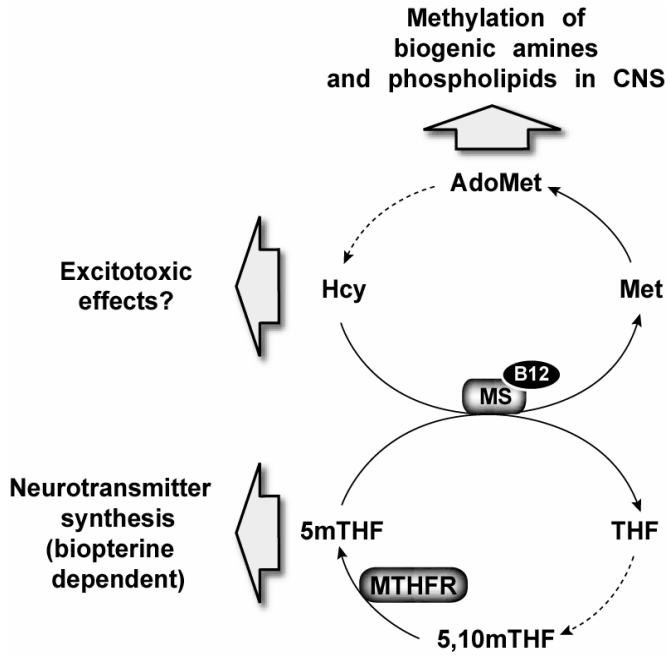
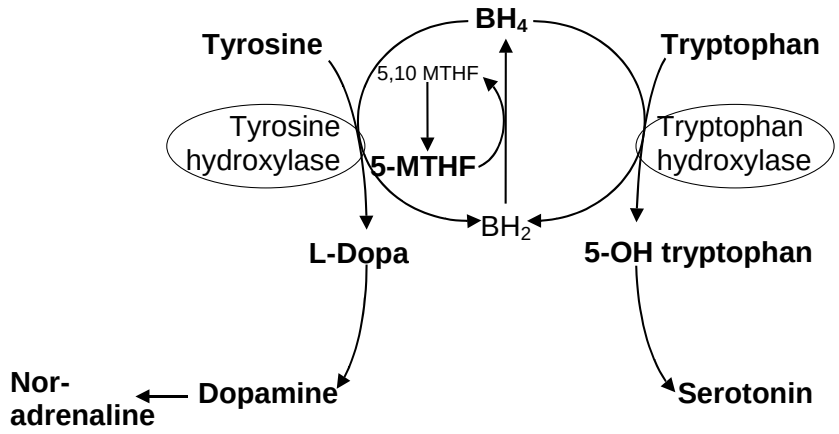


Figure 3: Components of one-carbon metabolism and central nervous system functions. **SAM,** S-adenosylmethionine; **Hcy,** homocysteine; **Met**, methionine; **B12,** cobalamin; **MS**, methionine synthetase; **5mTHF,** 5-methyl-tetrahydrofolate; **5,10mTHF**, 5,10-methylene-tetrahydrofolate; **THF**, tetrahydrofolate; **MTHFR**, methylenetetrahydrofolate reductase

Some smaller clinical trials suggest that SAM is superior to placebo in the treatment of depression (144).

Investigations on a possible role of cobalamin status in neuropsychiatric disorders have been motivated by the central nervous system damage caused by overt or subtle cobalamin deficiency (145, 146). Data regarding the association between serum cobalamin levels and depression are ambiguous (137, 143, 147-149). Elevated levels of the cobalamin marker, methylmalonic acid, have been found among depressed physically disabled older women in a population-based study (137). Moreover, higher baseline serum cobalamin has been associated with a better outcome in treated depressed outpatients (150). Cobalamin is a co-factor in the methylation of homocysteine to methionine, which in turn affects the levels of both homocysteine and SAM figure 3).



Figur 4: The possible role of folate in neurotransmitter synthesis. 5-methyl-tetrahydrofolate (5-MTHF) reduces dibiopterine (BH2) to tetrahydrobiopterine (BH4), which is a cofactor for tyrosine hydroxylase and tryptophan hydroxylase in their synthesis of dopamine and serotonin, respectively. **5,10 MTHF**, 5,10-methylene-tetrahydrofolate.

MTHFR 677C→T affects MTHFR activity and thus folate distribution and homocysteine remethylation (131). Inconsistent results on the association between depression and the MTHFR 677C→T polymorphism have been obtained (151, 152). In case such a relation can be confirmed, it will support the hypothesis that altered folate status may precede the onset of depression.

Despite our incomplete understanding of the relation between methylation and mood, several clinical trials examining the effect of folate in antidepressant treatment have been conducted. The results are promising, though the samples are small, and in only four of the studies were patients randomised to folate or placebo (153-156). The largest (n=127) and best designed study (154) showed a significant beneficial effect only in women. The lack of significance in men could be due to the small sample size or an insufficient dosage of folate. Still, we do not know which patients should be supplemented with folate, the duration of treatment, the dosage (135) or the safety of high dosage folate supplementation (157).

In spite of the extensive comorbidity between depression and anxiety (52, 53), we have found no more than three studies (148, 158, 159) addressing the possibility of impaired one carbon metabolism in anxiety disorders. Only one of theses suggests such an association, namely between low cobalamin and anxiety (148).

4.4.2. Psychosocial factors

Environmental influences are strong and pervasive on mental health (160). Since World War II various kinds of stress have been addressed as determinants of anxiety and depression (161). Childhood adversities, such as loss of a parent, parental psychopathology, parental aggression, physical or sexual abuse, or life-threatening accidents, are associated with later anxiety and depression (162, 163). Likewise, adverse life events in adulthood, such as unemployment, homelessness, violence, breakdown of a relationship, loneliness, and lack of social support, have been observed to have similar effects on anxiety and depression (161, 164). Psychosocial factors have been associated with a worsened prognosis in bipolar disorder, however the relationship between such factors and bipolar disorder is more ambiguous (109).

In the Islington study from London, some common environmental risk factors for developing both anxiety and depression in women were found (165). These were parental indifference and physical and sexual abuse in childhood. In adults, loss (of a person, a position or resources) and lack of social support predicted depression, while danger or threats (of a future loss, or a serious threat to life), predicted anxiety. The combination of loss and threat predicted comorbid anxiety and depression. A common feature of many of these adversities is their association with social inequalities (166), in that individuals belonging to the lower social classes have higher risk for being exposed to such unfortunate influences.

4.4.2.1 Socioeconomic status

Socioeconomic status (SES), which most often is characterised by length of completed education, household's annual income, and/or occupation, has consistently been associated with poor somatic and mental health (166, 167). However, due to differences in study design, use of indicators for SES, and assessment of mental status, the relationship between SES and anxiety and depression is still ambiguous. Moreover, despite the role of psychosocial factors in both SES and mental health, the mechanisms causing this relationship are unknown.

A meta-analysis

In a recent meta-analysis Lorant et al found compelling evidence for socioeconomic inequalities in depression (168). Low-SES individuals had a significantly higher risk of being depressed (OR=1.81) compared to high-SES individuals in the 51 cross-sectional studies, where a dose-response relation was observed both for education and income. In the few longitudinal studies (n=7) similar socioeconomic inequalities in depression were observed: a slight association in the incidence studies (OR=1.24) and a moderate to strong association in the persistence studies (i.e. persistence of depression from baseline to follow-up) (OR=2.06). However, after excluding the studies not addressing education, the most frequently used SES indicator, the results of the studies on incidence (169, 170) and persistence (170-172) were inconsistent. The discrepancy may be due to differences in sample size and follow-up period between the studies. Moreover, only one of the studies that examined SES included education as the main predictor of depression (169).

Differences in indicators of SES and anxiety and depression

The indicators of SES usually vary from study to study, and despite being only moderately intercorrelated, such indicators are seldom addressed specifically. Likewise, the assessment of anxiety and depression varies between studies, however, according to Dohrenwend the use of different measures for mental health is welcomed in this field, because "…until diagnosis is less dependent on interviews, it is important to use a variety of methods…" (166).

Although anxiety disorders are closely related to depression (52, 53), we are not aware of longitudinal studies of their relation to education.

Causation or selection?

The association between SES and depression is not fully understood. In contrast to e.g. schizophrenia, there is most evidence that depression is a consequence, rather than a cause, of low SES, at least in women (168, 173). However, some studies (174, 175) support the selection theory; (176) that is, depression may be an obstacle to upward social mobility, and may promote downward social mobility.

Mechanisms – mediators

Assuming SES is a determinant, little is known about *how* SES influences the development of new cases or the maintenance of chronic cases of depression. The effect on depression of measures of SES other than education has been explained by work characteristics (SES measure: occupational grade) (177), health behaviours (SES measure: economic situation) (178), and psychosocial factors (SES measure: income) (170). In longitudinal studies the effect of education has mainly been explained by depressive symptoms at baseline (171, 172) and prior to baseline (172).

5. AIMS OF THE STUDY

The inclusion of the Hospital Anxiety and Depression Scale (HADS) in two recent large scale Norwegian health surveys has enabled further epidemiological research addressing anxiety and depression in an array of interesting health related questions. However, because the properties of HADS had been somewhat loosely evaluated, we felt the need to review its characteristics more thoroughly.

The use of HADS made it possible to define various anxiety/depression categories by the combination of certain cut-off values of the two subscales. However, because HADS basically is a continuous measure of anxiety and depression symptom load, a dimensional approach to the HADS scores was obvious. Due to the paucity of research addressing the dimensional approach in co-occurring anxiety and depression, we wanted to use the HADS-A and HADS-D scores to compare a dimensional and categorical approach to anxiety and depression.

Despite the increased focus on co-occurring anxiety and depression during the last two decades, anxiety and depression are usually addressed separately in studies relating them to other somatic diseases or complaints. Hence, we wanted to compare the associations, or comorbidity, between various anxiety/depression combinations and somatic health problems.

Combining HADS data with results from blood sample analyses gave opportunity for analyses as to biological markers and determinants of anxiety or depression. Affiliation to Locus of Homocysteine and Related Vitamins at the University of Bergen made it possible to investigate the role of anxiety and depression in disturbed folate metabolism.

There is a paucity of longitudinal studies addressing the association between socioeconomic status (SES) and depression. Moreover, anxiety, separately or comorbid with depression, has got even less research attention than depression. The combination of the two health studies of Nord-Trøndelag County, HUNT 1 (1984-86) and HUNT 2 (1995-97) made it possible to design a cohort study with a follow-up period of 11 years examining the role of SES, measured by educational level, as a predictor for anxiety and depression.

The specific aims of this dissertation are:

1. To review the literature and to update information regarding:
   A. the factor structure, discriminant validity and the internal consistency of HADS. (Paper I)
   B. the case finding performance of HADS for anxiety disorders and depression. (Paper I)
   C. to what extent HADS agrees with other self-rating instruments (concurrent validity). (Paper I)

2. To examine the relation between HADS anxiety and depression scores in the general population. (Paper II)

3. To examine how co-occurring anxiety and depression is associated with impairment due to chronic mental health problems according to the dimensional approach compared to the categorical one. (Paper II)

4. To investigate the associations between comorbid anxiety disorders and depression (in contrast to the pure conditions) and somatic diseases and symptoms. (Paper III)

5. To examine whether key components of the folate metabolism are associated with anxiety disorders and/or depression. (Paper IV)

6. To examine whether low education is a predictor of new and chronic cases of anxiety disorder, depression and comorbid disorder, (Paper V)

7. and if so, whether these relationships may be explained by somatic illness, use of health services, health behaviours, psychosocial status, and sociodemographic or work characteristics. (Paper V)

6. MATERIALS AND METHODS

6.1. DATA SOURCES

6.1.1. The literature review (Paper I)

The Medline (179), ISI (180), and PsycINFO (181) databases were searched until May 2000. All papers containing the terms “Hospital” and “Anxiety” and “Depression”, or “HAD”, or “HADS” in the title or abstract were identified. This procedure identified 1403 abstracts which were inspected in order to ascertain whether they contained information about the psychometrics or case-finding abilities of HADS. The abstracts indicated 747 studies for closer review for relevant issues, and based on this examination 71 papers were identified for the review. Only studies where diagnoses were made by a structured interview were considered for sensitivity and specificity measures.

6.1.2. The other studies (Paper II-V)

The three health surveys were performed by the National Health Screening Service (SHUS), today a part of The Norwegian Institute of Public Health, in collaboration with HUNT Research Centre and the administration of Nord-Trøndelag County (HUNT 1 and HUNT 2); the Faculty of Medicine, the Norwegian University of Science and Technology (NTNU) (HUNT 2); the University of Bergen (HUSK); and regional health services (all surveys). All surveys were carried out in a two-stage sequence: First, all individuals in the source populations were invited to participate by a posted letter including the first questionnaire (Appendix I, III, V). The invitation file was created from periodically updated census data from Statistics Norway. At attendance the questionnaire was handed over to the survey staff who checked the questionnaire for completeness. The participants then underwent a brief physical examination, which was performed by two teams visiting each municipality of the county. All clinical examinations were performed indoors at comfortable room temperature. The team surveying the largest municipalities used more extensive standard office facilities; the other team working in the smaller municipalities used a large, well-equipped trailer with efficient temperature regulation and other modern facilities. In HUNT 1 a chest x-ray was taken as well, and in HUNT 2 and HUSK blood samples were drawn and stored. The participants were given a second

questionnaire (Appendix II, IV, VI) which they could fill in and deliver on the spot or bring home for completion before returning it by prepaid mail.

6.1.2.1. The Nord-Trøndelag Health Study 1984-86 (HUNT 1)

HUNT 1 (182) was the first health study in Nord-Trøndelag County, primarily designed to cover four areas, i.e. on hypertension, diabetes, lung diseases and quality of life. All 87,285 inhabitants $\geq$ 20 years were invited to take part, of these 74,599 individuals participated, yielding a participation rate of 88%.

6.1.2.2. The Nord-Trøndelag Health Study 1995-97 (HUNT 2)

HUNT 2 (1) was both a follow-up of HUNT 1, with identical or similar questions and assessments of hypertension, diabetes and quality of life, but in addition HUNT 2 was much more comprehensive collecting more data on each participant covering an extensive range of topics. Of 92,100 eligible individuals aged 20-89 years, 65,648 (71%) participated.

6.1.2.3. The Hordaland Health Study 1997-99 (HUSK)

In HUSK all individuals in Hordaland county born 1953-57 (N=29,400) were invited. A total of 8,598 men and 9,983 women participated, yielding a participation rate of 57% for men and 70% for women. The study also included 2,291 men and 2,558 women born 1950-51 and 1,868 men and 2,470 women born 1925-27, who had participated in an earlier study in 1992-93 (the homocysteine cohort). Participation rates in these groups were 73%, 81%, 79%, and 76%, respectively.

6.2. STUDY POPULATIONS

This dissertation includes four study populations, those in Paper II and III were almost identical:

Paper II: The study population was sampled from HUNT 2: Among the 65,648 participants those with both valid HADS-A and HADS-D ratings (N = 61,216; 47% males) were selected.

Paper III: The study population was sampled from HUNT 2: Among the 65,648 participants the 60,869 individuals who had valid ratings of HADS as well as of the somatic variables in question were selected.

Paper IV: The study population was sampled from the homocysteine cohort in HUSK consisting of 7,072 participants (77% of those invited).

Paper V: Individuals participating in both HUNT 1 (baseline) and HUNT 2 (follow-up) with valid scores of mental distress (Anxiety-Depression Index-12, ADI-12, see section 6.3.1.2.) at baseline, and valid information on educational level were selected (N=36,150). The sample was further divided into two cohorts by the 80^{th} percentile of ADI-12 at baseline: The incident cohort (N=29,463) was selected by ADI-12 $\leq$ the 80^{th} percentile; the persistent cohort (N=6,687) was selected by ADI-12 > the 80^{th} percentile. The selection procedure is illustrated in figure 5.

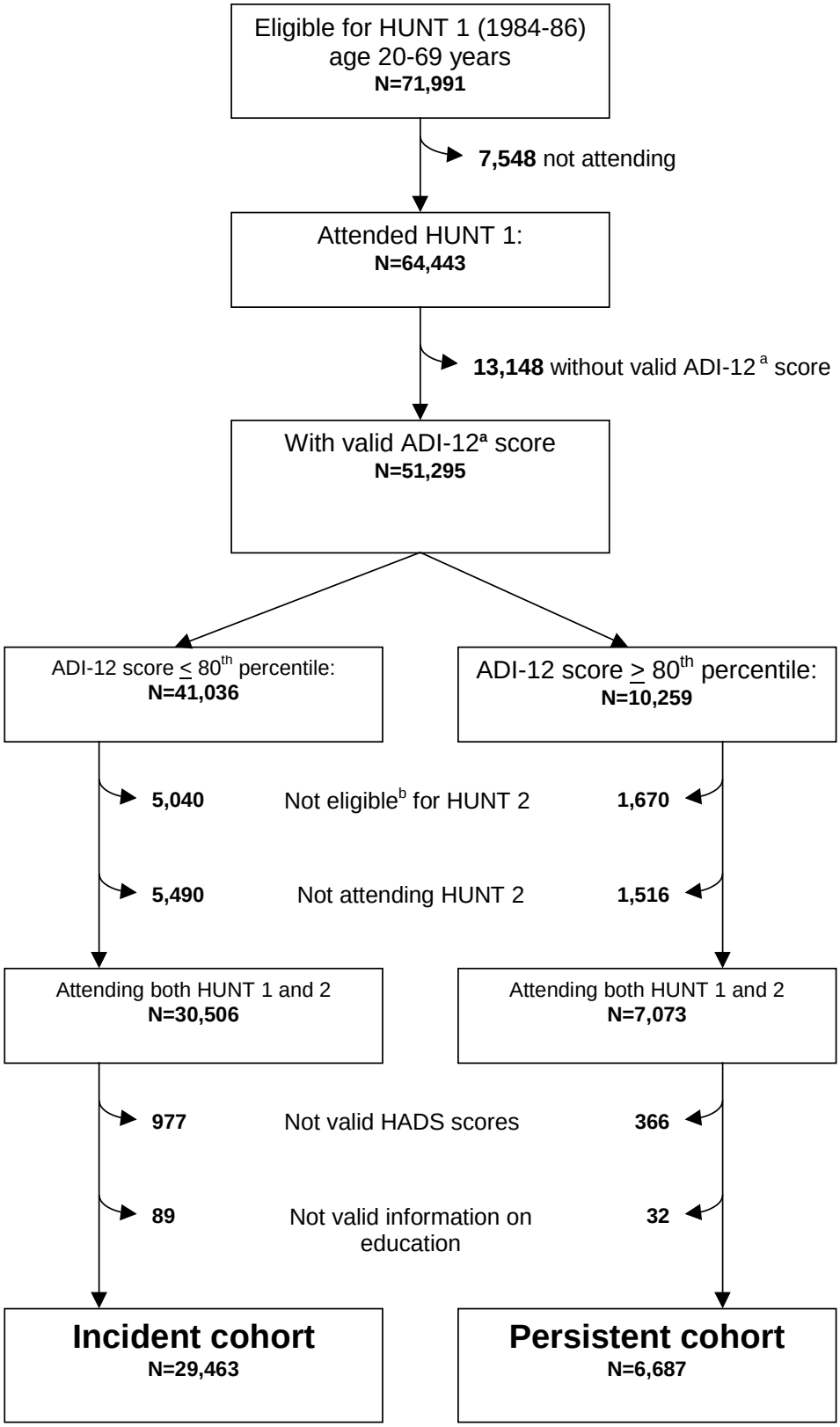


Figure 5:The selection procedure for the study population in Paper V.

[a] Anxiety-Depression Index-12, see section 6.3.2.

[b] Deceased or moved out of the county during the follow-up period.

6.3. VARIABLES

6.3.1. The Hospital Anxiety and Depression Scale (HADS) (All papers)

HADS is described in section 4.2.6. and the examination of its psychometric and case-finding properties is the objective of Paper I. However, its application in the other studies will be described here.

When applied as continuous measures the anxiety and depression subscales (HADS-A and HADS-D) were used without consideration to each other in the analyses (Paper II). However, when defining anxiety-depression categories, the other scale was most often taken into consideration (Paper II-V). Hence, "pure" anxiety disorder was defined as HADS-A $\geq$ 8 restricting HADS-D < 8, and vice versa. To evaluate the influence of the other subscale score even in the < 8 range, it was included as a covariate in a set of the analyses as well (Paper II and V). Comorbid anxiety disorder and depression (or only "comorbid disorder") was defined by scores $\geq$ 8 for both HADS-A and HADS-D. To illustrate the impact of not considering the other subscale a set of analyses was performed on anxiety disorder and on depression, respectively, without restrictions of the other subscale (Paper II and V). The differences in the resulting estimates in analyses wit or without consideration of the other subscale, is illustrated in figure 8 and in figure 4 in Paper II. The relation between anxiety and depression symptoms was expressed by the ratio between HADS-A and HADS-D, the Anxiety-Depression ratio, as illustrated in figure 2 and in figure 1 in Paper II.

While anxiety and depression were the outcome in most analyses, in Paper II they were treated as exposure variables.

6.3.2. The Anxiety Depression Index 12 (ADI-12) (Paper V)

In HUNT 1 there was no direct measure of anxiety and depression included. In order to get an evaluation of these symptoms, the Anxiety-Depression Index (ADI-12) was composed out of 12 questions in HUNT 1 addressing different aspects of anxiety, depression, life satisfaction, and personality (Appendix I, II). Individuals having answered at least eight of the 12 questions were given valid ADI-12 scores. These were calculated as the mean of the z-scores of the 12 ADI questions, which had been weighted by their correlation with the one factor extracted from a principal component analysis. In a follow-up study of 6,380 participants four years after HUNT 1 where these 12 questions were repeated, the ADI-12 scores predicted 67% of the

variance of the Hopkins Symptom Checklist (SCL-25) scores (183). ADI-12 was, therefore, considered a valid measure to divide the cohort in HUNT 1into a mentally healthy sample (the incident cohort) by ADI-12 score $\leq$ the 80th percentile and a sample with more symptoms of mental distress (the persistent cohort) by ADI-12 score > the 80th percentile. ADI-12 was also used to adjust for mental distress level at baseline within each of the two cohorts.

6.3.3. Impairment due to chronic health problems (Paper II-III)

In HUNT 1 and 2 (Questionnaire 1, Appendix I, III) the participants were asked whether they had any chronic (lasting at least one year) physical or mental disease or injuries that impaired their daily life functioning. Subjects checking "no" (n = 56,992) were categorised as not being impaired. Those who checked "yes" were further required in the questionnaire to rank their impairment into "little", "moderate" or "much" due to impairment of either movement, reduced sight, reduced hearing, somatic disease, or mental health problems. Subjects checking "moderate" or "much" due to mental health problems in HUNT 2 (Paper II) were categorised as being impaired due to mental health problems. Those who checked "little" were categorised as not being impaired. Impairment due to chronic somatic illness in HUNT 1 (Paper V) was categorised by an identical procedure.

6.3.4. Educational level (Paper III and V)

In paper V the level of education was the main variable of exposure. Considering that not all participants had finished their education at the time of HUNT 1, we composed a common educational level variable for HUNT 1 and HUNT 2, by choosing the highest level from the two if there was a discrepancy. Although educational level was divided into eight categories in HUNT 1 and five in HUNT 2 (Appendix II, III) we could combine the categories into three common levels: Primary school (< 10 years), high school (10-12 years) and college or university (> 12 years). When information of education was missing at HUNT 1 the reported level from HUNT 2 was substituted, and *vice versa*. Further, a variable that identified individuals reporting a higher level of education at HUNT 2 than at HUNT 1 (from primary to high school, or from high school to college or university) was used to examine the relation between level of mental distress at HUNT 1 and additional educational attainment during the follow-up period.

As a proxy for socioeconomic status (SES) the educational level was included as a covariate to adjust for possible confounding in paper IV. There were six educational categories in HUSK (Appendix V), which were combined to three main categories (< 10; 10-12; > 12 years) similar to the categories used in paper V.

6.3.5. Somatic health and health behaviours (Paper III)

In the HUNT 2 questionnaire (Appendix III) somatic diseases were defined as: "Do you have or have you ever had the following disease?". Several somatic diseases were addressed in the questionnaire. However, the aim of the study was not to make an exhaustive examination of them all, but rather to illustrate the associations between comorbid anxiety/depression and somatic health problems. Hence, these five were included in the paper: *myocardial infarction, stroke, diabetes, migraine, and fibromyalgia*. Some other somatic symptoms, health behaviours, and measurements were included as well. *Musculoskeletal symptoms* were reported as pain and/or stiffness in muscles of at least 3 months duration in the last year, and *cardiovascular symptoms* implied report of palpitations or breathlessness the last year. *Impairment due to somatic illness* was entirely based on the subjective reports of the respondents (see section 6.3.3.). *Smoking* was defined as daily consumption of any number of cigarettes. *Low physical activity* was defined as neither easy nor hard leisure time physical activity. *Alcohol problems* (Appendix IV) implied positive response to at least one of the five items of the CAGE screening instrument (184). *High Body Mass Index (BMI)* was defined as $\geq$ 30kg/m^2. *Hypertension* was defined as systolic blood-pressure > 140 mmHg and/or diastolic blood-pressure > 90 mmHg, based on the mean of the second and the third measurement at the HUNT 2 examination.

6.3.6. Variables related to folate metabolism (Paper IV)

Plasma total homocysteine (tHcy) was analysed by High Performance Liquid Chromatography (HPLC) and fluorescence detection (185) and divided into four categories (< 9.0 µmol/L [reference], 9.0 - 11.9 µmol/L, 12.0-14.9 µmol/L, $\geq$ 15.0 µmol/L) (186), which corresponded approximately to the 0-30th, 30th-5th , 75th-90th and 90th-100th percentiles.

Plasma folate was determined by a *Lactobacillus casei* microbiological assay (187) and divided into four categories corresponding to the 0-10th, 10th-25th, 25th-70th

and 70^{th}-100^{th} percentiles: < 3.80 nmol/L, 3.80-4.99 nmol/L, 5.00-8.49 nmol/L, ≥ 8.50 nmol/L (reference).

Plasma cobalamin was determined by a *L. leichmannii* microbiological assay (188) and divided into four categories similar to the folate percentiles: < 230.0 pmol/L, 230.0-279.9 pmol/L, 280.0-414.9 pmol/L, ≥ 415.0 pmol/L (reference). Both the folate and cobalamin assays were adapted to a microtiter plate formate and carried out by a robotic workstation (Micro-lab AT plus 2; Hamilton Bonaduz).

Genotyping of the methylenetetrahydrofolate reductase (MTHFR) 677C→T polymorphism into the CC, CT and TT variants was performed by a real-time polymerase chain reaction (PCR) (189).

6.3.7. Potential mediators for the education – anxiety/depression association (Paper V)

HUNT 1 included self-reported information on somatic health, use of health services, health behaviours, psychosocial factors, and sociodemographic and work characteristics (Appendix I, II). These characteristics might be assumed to be consequences of educational level or SES, and if associated with anxiety or depression at follow-up, they would be intermediate variables, or mediators. However, they might be assumed as confounders as well (100), and, therefore, they were denoted "potential mediators". No matter what, we included them in the analyses to examine their effect on the associations.

At baseline, current or former diabetes, myocardial infarction, angina pectoris and stroke were reported. The three latter were combined to denote cardiovascular disease. Daily impairment due to chronic physical illness or injury was dichotomised into "Not impaired" and "Impaired". Use of analgesics was defined as daily or weekly use during the last month. Having visited a general practitioner or other physician during the last 12 months and having been hospitalised during the last five years, were the two measures for use of health services. Problems with falling asleep or other sleep disturbances frequently or almost every night were characterised as "Sleep problems". Calculation of Body Mass Index was based on data from the clinical examinations and categorised by two cut-offs, ≥ 25kg/m^2 and ≥ 30kg/m^2. Physical exercise was defined as at least weekly practising. Daily smoking was compared to less frequent smoking/not smoking. High alcohol consumption was defined as use of alcohol ten of the 14 last days. Psychosocial factors included whether the respondents

felt lonely, or had available social support in case of long-lasting illness requiring bed rest. Sociodemographic characteristics included whether they were living alone and/or were separated or divorced. Work characteristics included dichotomised variables as to whether the respondents considered their job to be stressful, whether the job allowed influence on the planning of one's work, whether they were satisfied with their job, and whether they were unemployed.

6.3.8. Age (Paper II-V)

Age was somewhat differently categorised in the various studies: In paper II and III age (20-89 years) was categorised into seven ten-year groups, and in paper V into three HUNT 1 age groups (20-34, 35-49, 50-69 years). In paper IV the age groups of the homocysteine cohort (46-49 70-74 years) were kept unchanged.

6.3.9. Other covariates (Paper IV)

Smoking status in HUSK was dichotomised separating daily smokers from non-smokers similarly to the procedure for the smoking variable in HUNT 1 and HUNT 2.

Coffee consumption was tricotomised into the following categories: 0, 1-5, > 5 cups per day.

Physical exercise was categorised somewhat differently in HUSK than in HUNT 2, namely at least one hour easy or some hard exercise weekly outside job.

Body Mass Index was divided into the following categories: < 20.0, 20.0-24.9, 25.0-29.9, $\geq$ 30 kg/m^2.

As in HUNT 1 and 2 somatic diseases were asked for in the HUSK questionnaire (Appendix V) by the standard formulation: "Do you have or have you ever had the following disease?". Individuals checking "Yes" for myocardial infarction, angina pectoris, or stroke were categorised as having cardiovascular disease.

In the HUSK questionnaire the respondents were asked whether they had taken any medicines or vitamin supplements "yesterday", and if "Yes", they were asked to write down their names (Appendix V). All individuals who were taking any B-vitamin supplement, tranquilliser or antidepressant, were categorised as their respective users. These variables were added as covariates to the multivariate models estimating the association between the folate-related compounds and anxiety or

depression. Use of B-vitamin supplements was additionally examined as a “predictor” for anxiety or depression.

6.4. STATISTICAL ANALYSES

6.4.1. General considerations

To adjust for possible confounding we chose statistical multivariate approaches allowing for simultaneous adjustment of several covariates. The choice of statistical methods was also influenced by our approach to anxiety and depression, which mainly was categorical defining anxiety disorder, depression and comorbid disorder by certain cut-off values of HADS-A and HADS-D scores (see section 6.3.1.).

The categorical approach was considered to be the more appropriate when studying possible risk factors (Paper IV-V) for two reasons: First, we were interested in clinically relevant outcomes and, second, we would give priority to an effect measure that could be easily interpreted. However, considering the possible confounding effect of co-occurring depression when addressing anxiety, and vice versa, “pure” anxiety or “pure” depression and combined categories were explicitly defined (see section 6.3.1). The effect measure from the categorical approach applying logistic regression models was odds ratio (OR) with a corresponding 95% confidence interval for being a case when increasing the value of the explanatory variable by one unit, or when having a value of the explanatory variable (indicator variable) compared to its reference value . The representation of covariates as indicator variables was used to allow for assessment of non-linear dose-response relationships while a linear (1 df) representation was used to test for linear trends (Paper IV and V). In general, adjustments for age and gender were included in all models. Likewise, interaction terms were added separately to all models to evaluate effect modification of age and gender. In all analyses, except those in paper III, binary logistic regression models were applied. In contrast to binary, multinomial regression models allowed the outcome variable to have more than two values. The interpretation of the ORs was similar to binary logistic regression.

When studying the relation between anxiety and depression (Paper II) a dimensional approach was also applied, which implied exploration of the whole range of scores. For that purpose we used generalised logistic regression, which is based on the generalised additive model (GAM) (190). GAM is helpful when exploring the

dose-response relation between a continuous measure, e.g. HADS scores, and a categorical outcome measure adjusting for covariates. The outcome is presented as a plot ("GAM curves") of ORs on a log scale where the reference value (OR = 1.00) corresponds to the mean value of the explanatory variable.

The precision of the OR estimates in the logistic regression analyses was expressed with 95% confidence intervals. A two-sided p-value < 0.05 was chosen to indicate statistical significance. The statistical analyses were conducted using the software package of S-Plus 6.0 (GAM-curves) and SPSS 11.0-11.5 (all other analyses).

6.4.2. Analyses applied in the separate papers

Paper I. In studies reporting pairs of sensitivity and specificity at several cut-off values of HADS-A and HADS-D, Receiver Operating Characteristics (ROC) curves were plotted by us. ROC curves may guide the decision of the cut-off score that yields the optimal balance between sensitivity and specificity (46). The ROC method produces an overall measure of the efficiency of the test defined by the *Area Under the Curve* (AUC). Approximations of AUC were calculated by summarising the areas of trapeziums occurring between two sequential cut-off points on the curve (the trapezium rule) (191). An AUC value of 0.50 is reflecting a test that is unable to discriminate between cases and non-cases, while a value of 1.00, means perfect sensitivity and specificity at all cut-off values. In order to summarise the findings, optimal cut-off values as well as sensitivity and specificity from each study were weighted by their respective numbers of subjects, and means were calculated.

Paper II. Associations between anxiety and depression as dimensional quantities and impairment due to chronic mental health problems were examined by a dose-response approach (GAM-curves) adjusting for age and gender. The "effect" of anxiety on impairment was evaluated in individuals with HADS-D scores < 8 and $\geq$ 8, respectively. Likewise, the dose-response "effect" of depression was evaluated in the corresponding anxiety categories. ORs (95% CI) for impairment due to chronic mental health problems were estimated for five different anxiety/depression categories (see section 6.3.1.), compared to a non-anxiety/depression category, using logistic regression models adjusting for age and gender. To examine the effect of co-occurring below-threshold depressive symptoms (HADS-D < 8) in pure anxiety

disorder, and *vice versa*, two models adjusting for HADS-D and HADS-A scores, respectively, were added.

Paper III. Logistic regression analysis was used to estimate ORs between the somatic health variables and the categories of anxiety and depression.

Paper IV. Logistic regression analyses were used to estimate ORs for being a case comparing each category to the reference category of the metabolites and the MTHFR polymorphism. Two logistic regression models were used, one with adjustment for age and gender (Model 1) and one with additional adjustments for smoking status and educational level (Model 2). The effects of other possible confounders, such as coffee consumption, physical exercise, Body Mass Index, and self-reported cardiovascular disease, were examined by adding these one by one to model 2. Possible effect modification of B-vitamin supplementation or tranquilliser or antidepressant use was evaluated by stratification. To examine whether use of B-vitamin supplements was associated with anxiety or depression logistic regression analyses were used to estimate the OR for being a case comparing non-users with users, after adjusting for age, gender, smoking status and educational level. GAM-curves adjusted for age, gender, smoking status, and educational level were used to provide graphical representations of the dose-response relations of plasma folate, cobalamin, and tHcy to anxiety or depression.

Paper V. Logistic regression analyses were used to estimate ORs for being a case of the various anxiety/depression categories at follow-up, comparing the two lower educational levels separately to the highest. Most analyses were performed separately for the incident and persistent cohorts. Two logistic regression models were used, one with adjustment for age and gender (Model 1) and one with additional adjustment for mental distress (ADI-12 score) at baseline (Model 2). The latter aimed to adjust for the variation in ADI-12 score within the cohorts. To examine whether co-occurring low-score depression symptoms (HADS < 8) in anxiety disorder would influence the association between educational level and anxiety disorder, the HADS-D score was added to the model, and vice versa regarding low-score anxiety symptoms (HADS-A < 8) in depression. Moreover, to evaluate possible effect modification of age and gender, product terms between these variables and

educational level were added separately to Model 2. The effect of the potential mediators was examined by logistic regression analyses performed in three steps. First, all the mediator variables were added one by one separately to Model 2 for all the three anxiety/depression outcome variables. Second, those mediators reducing the OR for being a case at the lowest versus the highest educational level with at least 5%, were included in the analyses to evaluate the combined effect of all the mediators. However, to examine the individual effect of the identified mediators in the combination, each variable was added to the model after the other(s) were already in. Third, the mediators still reducing the OR were included in the final model. One aspect of the selection hypothesis was tested by examining whether a high mental distress (ADI-12) score at baseline was associated with subsequent less educational attainment during the follow-up period in the youngest age group. Hence, a logistic regression analysis adjusting for age and gender, which estimated the OR for an unchanged educational level at follow-up for individuals in the high-ADI-12 group compared to the low ADI-12 group was performed as well. Contrary, the causation hypothesis could be supported if lower educational attainment during the observational period was associated with anxiety/depression at follow-up. Hence, a logistic regression analysis adjusting for age, gender, and ADI-12 score was performed, estimating the OR for being a case at follow-up among those with unchanged educational level between baseline and follow-up compared to those with an increased level.

7. RESULTS OF THE PAPERS

7.1. PAPER I: The validity of the Hospital Anxiety and Depression Scale. An updated literature review .

After a review of 747 papers found by a literature search in MEDLINE, ISI and PsychINFO we examined published reports on HADS regarding factor structure, discriminant validity, and the internal consistency, how HADS performed as a case-finder for anxiety disorders and depression, and how HADS agreed with other self-rating instruments used to rate anxiety and depression.

HADS performed as a bidimensional test, although the factors were not absolutely consistent with the subscales of anxiety and depression. Among the 19 studies reporting factor analysis of HADS, eleven studies (total N=14,588) achieved a two-factor structure, five studies (total N=3,459) a three-factor structure and two studies (total N=235) a four-factor structure. Two studies from the general population both reported a two-factor structure (total N= 6,017). One of these found that the two-factor solution was stable across different age groups from the general population and in different clinical samples. The other found the same two-factor structure for both males and females.

21 studies reported the Pearson correlation coefficient between HADS-A and HADS-D (mean 0.56). In seven studies of non-patient samples the correlations varied between 0.49 and 0.74 (mean 0.59). In 12 studies of somatic patient samples the correlations varied between 0.40 and 0.64 (mean 0.55). The two studies of psychiatric patients both achieved a correlation of 0.56.

Cronbach's coefficient alpha of internal consistency was reported in 15 studies and varied for HADS-A from 0.68 to 0.93 (mean 0.83), and for HADS-D from 0.67 to 0.90 (mean 0.82).

In most studies an optimal balance between sensitivity and specificity was achieved when caseness was defined by a score of 8 or above on both HADS-A and HADS-D. The weighted means of cut-offs were 8.01 for HADS-A and 8.04 for HADS-D. The sensitivity and specificity for HADS-A were 0.79 and 0.83, respectively, and for HADS-D 0.76 and 0.83, respectively, which was similar to the sensitivity and specificity achieved by the GHQ. Figure 6, which is taken from the paper of elRufaie and Absood (192), illustrates how ROC curves for HADS-D and HADS-A demonstrated the screening properties at various cut-off values. In that study AUC was calculated to 0.86 for both subscales. Correlations between HADS

and other commonly used questionnaires (Beck's Depression Inventory, GHQ, Clinical Anxiety Scale, Spielberger's State-Trait Anxiety Inventory, Symptom Check List-90, Montgomery Asberg Depression Rating Scale) were in the range 0.49 - 0.83.

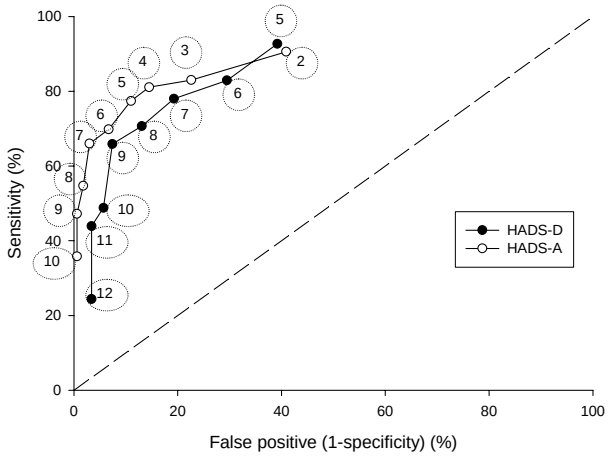


Figure 6: Receiver Operating Characteristics (ROC) curves showing the case-finding properties of HADS-D and HADS-A in a sample of 217 primary care patients (192). Numbers in circles are cut-off values (≥).The external criteria were anxiety disorders and major depression according to DSM-III (Clinical Interview Schedule).

7.2. PAPER II: A dimensional versus a categorical approach to co-occurring anxiety and depression: The HUNT study

Data from 61,216 individuals aged 20 to 89 years in HUNT 2 with valid ratings of HADS were analysed to explore the occurrence of anxiety and depression as *codimensions* and to examine how co-occurring anxiety and depression was associated with impairment in a dimensional approach compared to a categorical one.

We found that mean anxiety scores in general exceeded mean depression scores in both genders, however, less markedly by increasing age, which was demonstrated by the mean AD ratio (figure 1 in paper II). In general, women achieved higher anxiety scores, and marginally lower depression scores than men. The relation between anxiety and depression scores was close to linear.

The dimensional approach revealed a dose-response relation between anxiety symptoms and impairment in the high-score as well as in the low-score depression categories. A similar relation was seen between depression symptoms and impairment in the anxiety categories.

The categorical approach demonstrated that all the anxiety/depression categories were associated with chronic subjective impairment, more in younger than older age groups. The two anxiety categories were more strongly associated with impairment than the depression categories and the comorbid category more than the others.

The dimensional approach demonstrated the impact of co-occurring symptoms in the entire range of scores, even in the lower part. This finding indicates that the categorical analyses should be performed and interpreted with caution. Our results showed that depression without any anxiety restriction was more than twice as strongly associated with impairment as pure depression. Hence, ignoring the degree of co-occurring anxiety would induce a significant bias. Even in pure depression the co-occurring sub-threshold anxiety symptoms contributed as much as the depression itself to the association with impairment.

7.3. PAPER III: Anxiety and depression in individuals with somatic health problems. The Nord-Trøndelag Health Study (HUNT)

To examine the relationship between anxiety disorders and depression and various somatic health problems in the general population we used data from 60,869 individuals aged 20-89 years in HUNT 2.

Among those reporting somatic health problems, about one-third also had anxiety disorder and/or depression. Subjective impairment due to somatic symptoms as well as myocardial infarction, diabetes, migraine, fibromyalgia, musculoskeletal symptoms, cardiovascular symptoms, smoking, and low physical activity were all more strongly associated with comorbid anxiety disorder and depression than with pure anxiety disorder and pure depression, in both genders. The strongest associations were seen for cardiovascular symptoms, fibromyalgia, musculoskeletal symptoms, and impairment due to somatic symptoms. There were, however, some few exceptions: Stroke and high BMI were more strongly associated with pure depression than the comorbid condition, and alcohol problems were more strongly associated with pure anxiety disorder. High BMI and little physical exercise were more strongly associated with pure depression than pure anxiety, while the opposite was seen for musculoskeletal symptoms, smoking, alcohol problems, and cardiovascular symptoms.

7.4. PAPER IV: Folate, cobalamin, homocysteine and the MTHFR 677C→T polymorphism in anxiety and depression. The Hordaland Homocysteine study.

We investigated the association between key components of folate metabolism and anxiety disorders and depression in a cohort of 7,072 subjects.

The strongest relationship was observed between the TT MTHFR genotype and depression, and the association was present for both cut-off levels of depression (HADS-D ≥ 8: OR = 1.69 [95% CI 1.09-2.62]; HADS-D ≥ 11: OR=2.75 [95% CI 1.20 - 6.32]). Significant associations were observed between hyperhomocysteinemia (plasma total homocysteine ≥ 15.0 μmol/L) and depression (OR = 1.90 [95% CI 1.11-3.25]) and between the lowest level of cobalamin (< 230.0 pmol/L) and depression with high cut-off (HADS-D ≥ 11) (OR=2.39 [95% CI 1.07 - 5.36]). Borderline significant associations were found between depression and low folate levels (< 3.80 nmol/L) (OR=3.05 [95% CI 0.96- 9.65]) among middle-aged women. No significant relations were seen between anxiety disorder, or comorbid anxiety disorder and depression, and tHcy, folate, cobalamin or MTHFR genotype.

7.5. PAPER V: Education as predictor for anxiety and depression. A population-based cohort study.

In a study of 36,150 individuals aged 20-69 years from HUNT 1 we examined whether educational level in those with low and high levels of mental distress at baseline was associated with anxiety and depression after a follow up period of 11 years, assessed in HUNT 2. We also wanted to identify mediators if significant associations were found.

There was a strong association between ADI-12 scores at baseline and HADS categories at follow-up (figure 7).

Educational level was inversely associated with depression and comorbid disorder at follow-up, in both the incident and persistent cohorts, and, among younger women with anxiety disorder in the incident cohort. A significant gradient ($p < 0.001$), demonstrated by the trend tests, was found from the highest to the lowest educational level. The associations were only modestly affected by the potential mediators (table 1). Adjusting for HADS-D and HADS-A scores at follow-up in the analyses of anxiety disorder and depression, respectively, resulted in a markedly reduction in the ORs for the lowest educational level for anxiety disorder in the

incident cohort. The other outcome categories were less affected. An illustration of the ORs for being a case at follow-up among individuals in the lowest compared to the highest educational group is presented in figure 8.

A high mental distress (ADI-12) score at baseline was inversely but weakly associated with unchanged educational level during the follow-up period. Additional educational attainment during the observation period was not significantly associated with anxiety/depression at follow-up.

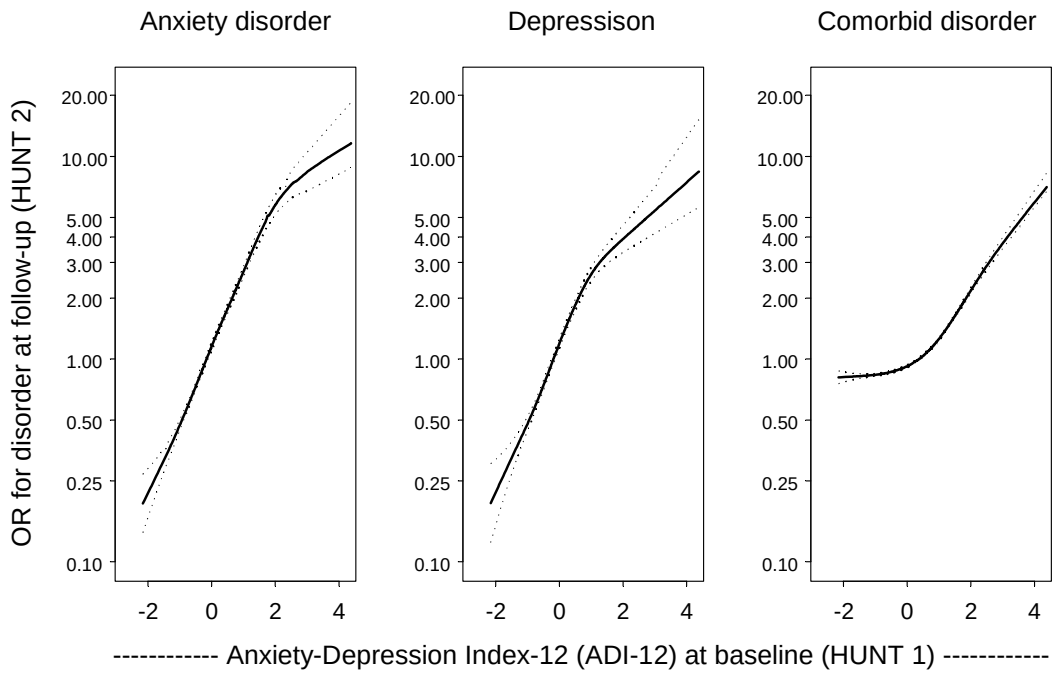


Figure 7: Dose-response relationships between ADI-score at baseline and HADS categories at follow-up 11 years later. The ORs that constitue the curves are estimated by a generalised additive model (GAM), which has adjusted for age and gender. Dotted lines represent pointwise 95% confidence intervals.

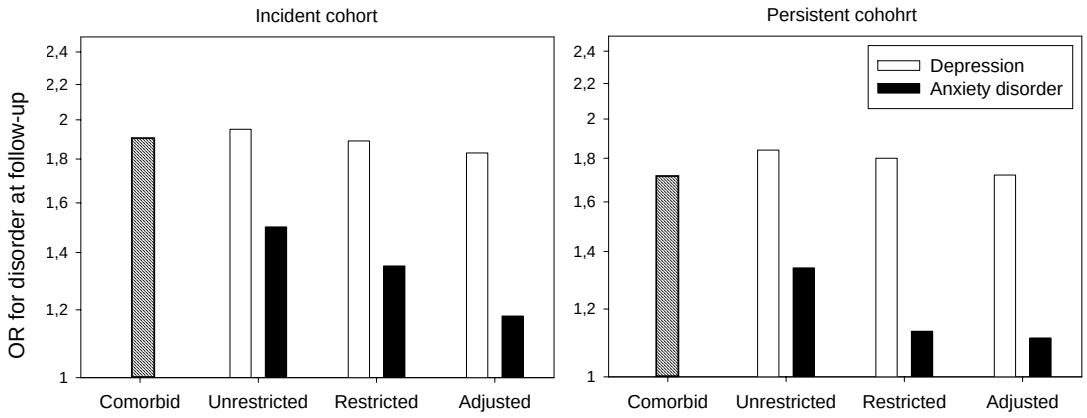


Figure 8: Risk (OR) for being a case of various categories of anxiety disorder and depression at follow-up among individuals in the lowest educational group compared to the highest educational group. **Comorbid**, HADS-A $\geq$ 8 and HADS-D $\geq$ 8; **Unrestricted,** HADS-A $\geq$ 8 or HADS-D $\geq$ 8; **Restricted**, HADS-A $\geq$ 8 and HADS-D < 8, or HADS-D $\geq$ 8 and HADS-A < 8; **Adjusted,** Restricted adjusted by HADS-D or HADS-A score.

Table 1: Adjusted[a] ORs for being a case in the lowest (primary school) educational group compared to the highest (college/university) before and after introduction of the various identified mediators[b] in the models.

Identified mediators	Model without mediators		Model with identified mediators	
	OR	95% CI	**OR**	95% CI
INCIDENT COHORT				
Anxiety disorder: Daily smoking	**1.34**	1.16-1.55	**1.28**	1.11-1.49
Depression: Low physical activity	**1.86**	1.54-2.25	**1.81**	1.49-2.19
Comorbid disorder: Daily smoking, low physical activity	**1.97**	1.59-2.44	**1.88**	1.51-2.33
PERSISTENT COHORT				
Anxiety disorder: Daily smoking, impaired due to somatic disease, use of analgesics, unemployment	**1.17**	0.92-1.50	**1.15**	0.89-1.48
Depression: Lack of social support	**1.80**	1.32-2.44	**1.75**	1.29-2.38
Comorbid disorder: Daily smoking, use of analgesics	**1.69**	1.33-2.15	**1.62**	1.28-2.07

[a] Before introduction of the mediators, the models were adjusted for age, gender and ADI-12 score, the latter due to its variation within each cohort.

[b] Mediators reducing the risk for being a case at the lowest educational level compared to the highest with at least 5 percent (mediators that did not contribute to a reduction in OR when introduced into the model after the other mediators, were excluded)

8. GENERAL DISCUSSION

The scope of this dissertation covers several areas of investigation. The common feature is, however, how anxiety and depression can be examined in epidemiological studies. Such observational studies have limitations as to design and potential biases in terms of systematic errors regarding selection of participants, information obtained, and confounding factors. These limitations will be discussed in the following sections. Further, the findings from our studies will be compared to those of others, and discussed in more detail.

8.1. METHODOLOGICAL CONSIDERATIONS

8.1.1. Study design

In analytic epidemiology, aiming to test hypotheses, a longitudinal study design is necessary to observe the influence of exposures on health over time. Cross-sectional health surveys are, however, designed for more descriptive purposes such as estimating prevalence of different health related problems. All but one of our studies had a cross-sectional design, nevertheless, their aims were beyond solely prevalence estimates. By examining associations between anxiety and depression, and other measures, new hypotheses could be generated, which might be subject for later testing in longitudinal studies. However, in cross-sectional studies an element of longitudinal information may be achieved by collecting information retrospectively, which was done in all the current surveys. Moreover, in studies examining the effects of genetic factors by DNA analyses (Paper IV) a cross-sectional design would be appropriate because such factors are not modified by environmental influence.

By combining data from consecutive health surveys in the same population a longitudinal design can be achieved, which was done by linking the data sets from HUNT 1 and HUNT 2, (Paper V). However, in order to evaluate the incidence of the outcome to be studied at follow-up, the occurrence of the same variable, or a proxy for it, must be known at baseline. The questionnaire used in HUNT 1 did not contain the HADS items, nevertheless, there were items on various aspects of relevance to mental health. Hence, it was possible to establish an index for mental distress, ADI-12 (see section 6.3.2). The ADI-12 score was used primarily to define a cohort that was mainly mentally healthy (incident cohort) at baseline by excluding the upper quintile of ADI-12 scores. The upper quintile (persistent cohort) was examined to address the chronicity of mental distress. Self-report of educational level at both baseline and

follow-up enabled analyses of educational attainment during the observational period as well.

8.1.2. Selection bias

When the association between the two factors to be examined is different in the participants and the non-participants, the selection of participants has resulted in a systematic error, or a selection bias (101). Information about differences between participants and non-participants is helpful when considering such bias, and such information will be discussed in this section.

In HUNT 1 and 2 there was a characteristic pattern as to participation rates (1): the younger and older age groups were under-represented, and among the younger and middle aged groups (up to 50 years in HUNT 1 and 60 years in HUNT 2) men were under-represented (figure 9). Further, the proportion of missing data for various variables increased in older age. The proportions missing varied between the different variables, possibly due to differences in how easily the questions and their corresponding answer alternatives could be understood. In the homocysteine cohort of HUSK the participation rates were lowest in the youngest age group (46-49 years) and among men.

In 1997 a 2.5% random sample of non-participants (n=685) in HUNT 2 were selected shortly after the data collection for a non-participant study (193). Non-participants were contacted and asked to give their reasons for not participating (table 2). Information was obtained from 291 individuals (42%). In the youngest age group (20-44 years) the most common reasons were having moved out of the county (31%), lack of time (22%), or they had forgotten the invitation, or had no reason (19%). Among the oldest ($\geq$ 70 years), reasons included being under the care of a physician/hospital (thus, no need to participate in a health study) (29%), having moved out of the county (21%), or being immobilised by disease (21%). Generally, the participation rate was better in HUNT 1 than in HUNT 2 (figure 9).

In the cohort study of participants in HUNT 1 re-examined in HUNT 2 (Paper V), the baseline differences between participants and non-participants in HUNT 2 (20-69 years at baseline) were examined (table 3). The non-participant group included significantly more men, more individuals in the youngest and oldest age groups, as well as people with less education and higher ADI-12 scores. Non-participants had significantly more unfavourable characteristics with regard to somatic health, health

behaviours, and sociodemographic characteristics, with the exception of a lower proportion reporting a stressful job and having little influence on the planning of their work.

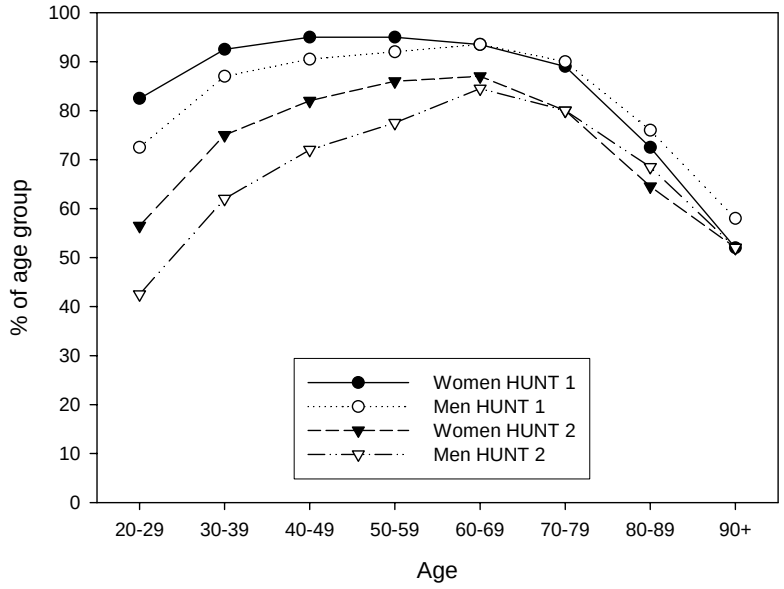


Figure 9: Participation rates in various age and gender groups in HUNT 1 and HUNT 2 (1).

Table 2: Reasons for non-participation in HUNT 2 (193)

	20-44 years		**45-69 years**		**≥70 years**		**Total**	
Reasons for non-participation	n	(%)	n	(%)	n	(%)	n	(%)
Follow-up by physician/hospital	11	(5.8)	10	(13.7)	8	(28.6)	29	(10.0)
Long waiting at screening site	8	(4.2)	4	(5.5)	0	(0.0)	12	(4.1)
Busy at job	42	(22.1)	18	(24.7)	2	(7.1)	62	(21.3)
Immobilised by disease	16	(8.4)	6	(8.2)	6	(21.4)	28	(9.6)
Moved, or long time absent	59	(31.1)	10	(13.7)	6	(21.4)	75	(25.8)
Forgot/no reason/other	36	(18.9)	21	(28.8)	3	(10.7)	60	(20.6)
Unnecessary/unwilling	18	(9.5)	4	(5.5)	3	(10.7)	25	(8.6)
Total	190	(100.0)	73	(100.0)	28	(99.9)	291	(100.0)

Table 3: A comparison between attendees [a] and nonattendees [b] in HUNT 1 and HUNT 2.

	Attended HUNT 1 and HUNT 2		Attended HUNT 1 but not HUNT 2	
	n	(%) [c]	n	(%) [d]
Men	17,706	(47.1)	7,866	(57.3)**
20-34 years	10,757	(28.6)	4,582	(33.4)**
35-49 years	13,211	(35.2)	3,131	(22.8)**
50-69 years	13,611	(36.2)	6,003	(43.8)**
Primary school	16,059	(42.9)	7,275	(54.5)**
High school	15,536	(41.5)	4,521	(33.9)**
College/university	5,863	(15.7)	1,554	(11.6)**
ADI-12 score [e] > the 80th percentile	30,506	(81.2)	10,530	(76.8)**
Cardiovascular disease [f]	972	(2.6)	1,031	(7.5)**
Diabetes	368	(1.0)	399	(2.9)**
Impaired due to somatic disease	2,265	(6.9)	1,399	(12.1)**
Use of analgesics	2,800	(7.7)	1,397	(10.1)**
Visit to a physician, last year	28,739	(76.5)	10,347	(75.)4*
Hospital admission, last five years	12,394	(33.1)	4,777	(34.9)**
Low physical activity	14,798	(40.0)	5,700	(42.6)**
Sleep problems	2,277	(6.1)	1,130	(8.4)**
BMI $\geq$ 25 kg/m^2	16,119	(42.9)	6,192	(45.3)**
BMI $\geq$ 30 kg/m^2	3,249	(8.7)	1,560	(11.4)**
Daily smoking	12,686	(34.3)	5,986	(44.6)**
High alcohol consumption [g]	1,081	(2.9)	491	(3.7)**
Separated or divorced	1,131	(3.0)	693	(5.1)**
Living alone	2,556	(6.9)	1,771	(13.1)**
Lack of social support	6,330	(17.0)	2,782	(20.5)**
Loneliness	2,005	(5.4)	1,062	(7.8)**
Stressful job	15,766	(49.2)	4,668	(48.7) [ns]
Low job control	10,673	(33.2)	3,112	(32.3) [ns]
Job dissatisfaction	1,232	(3.6)	591	(5.4)**
Unemployment	2,393	(7.0)	1,091	(9.1)**

[ns] non-significant difference between attendees and non-attendees

* $p < 0.05$ for the difference between attendees and non-attendees

** $p < 0.001$ for the difference between attendees and non-attendees

[a] Participated in HUNT 1 and HUNT 2 (age 20-69 years at HUNT 1)

[b] Participated in HUNT 1, but not in HUNT 2 (age 20-69 years at HUNT 1)

[c] % within the attendees

[d] % within the nonattendees

[e] Anxiety-Depression Index-12 score measured at HUNT 1

[f] Self-reported present or previous angina pectoris, myocardial infarction, or stroke

[g] Use of alcohol at least ten of the last 14 days

There is some evidence that the non-participants could be divided into two main groups; (I) men in the younger age groups who were too busy to participate, and (II) elderly individuals of both genders with poor health. Both groups possibly had less favourable health behaviours, psychosocial status, and sociodemographic work characteristics. Non-participants in another Norwegian health survey have been reported to have a higher prevalence of mental disorders (194), the same was also found in an analysis of non-participants in the ECA (195) and in the Swedish Survey of Living Conditions (196), but not in a health survey of the elderly in Australia (197). Hence, the mental and somatic health status in our study populations probably was better than the true health status in the total population of same age groups. Likewise, the risk factors we examined in Paper IV and V were probably more prevalent in the total population. These differences do not necessarily imply that the findings in our studies would be different with a higher participation rate. However, the "under-representation" of both the risk factors and outcomes (HADS anxiety/depression) in question, could have attenuated the associations.

8.1.3. Information bias

Information regarding exposure or outcome may be subject to information bias resulting in systematic error (101). Such information bias is often called misclassification if the variable is measured categorically, and the error leads to a person being placed in an incorrect category. If the misclassification of an exposure variable is related to the outcome, or the misclassification of an outcome variable is related to the exposure, the misclassification is differential. Otherwise, the misclassification is non-differential. Differential misclassification will either strengthen or attenuate the association studied, while non-differential misclassification always will have an attenuating effect.

In studies where most of the information collected is self-reported, there will always be some degree of non-differential misclassification. This can be illustrated by comparing data from HUNT 1 with HUNT 2 in individuals participating in both surveys (the study population in Paper V). In HUNT 2, 12% of the individuals reported a higher educational level than in HUNT 1 (from primary school to high school, or from high school to college or university). However, another 5% of the individuals reported a lower educational level, which must be due to misclassification. There were probably misclassified individuals among those reporting a higher

educational level as well. Hence, the estimated associations between educational level and the anxiety and depression categories at follow-up in Paper V were probably attenuated, as were the associations between additional educational attainment during the observational period and anxiety/depression level at baseline or anxiety/depression categories at follow-up. Similar non-differential misclassifications probably also occurred for other self-reported variables, due to inaccurate checking of answer options, impaired memory, or misreading. Some of the residual confounding might be due to such information bias.

The use of HADS as a screening instrument for DSM-IV or ICD-10 diagnoses of anxiety disorders or major depressive disorder may be viewed as another source of non-differential misclassification. Using a cut-off of ≥ 8 for both sub-scales will most often result in sensitivities and specificities of approximately 0.8. In a population with a prevalence of any anxiety disorder of 10%, only 31% of the HADS-A identified cases would have such an disorder (table 4). If the prevalence of major depressive disorder was 5%, only 17% of the HADS-D identified cases would be correctly classified. However, simple rating scales are not expected to have any better positive predictive value in populations with a relatively low prevalence of the disorder in question. In section 8.2.1. the question as to what HADS really is measuring is discussed. Generally, dimensional rating scales not covering the whole syndrome of the disorder, but rather some core feature of it, may be as appropriate as conventional categorical diagnoses in analytic epidemiological research (102). The estimated associations reported in the various papers of this thesis support the notion that cases identified by HADS-D cover some central aspects of depression.

Finally, differential misclassification may have occurred in the studies as well. Information from individuals reporting high levels of anxiety or depression might be biased. A high anxiety score might be associated with a stronger awareness, sensitivity, and worry about somatic symptoms such as pains, palpitations, and gastrointestinal, or respiratory symptoms. In Paper III such information bias might have resulted in too strong associations between somatic health problems and anxiety disorder or comorbid disorder (198). Accordingly, anxiety disorder was not associated with the physically measured health problems (high BMI and hypertension), or two of the more definite organic diagnoses reported (myocardial infarction and diabetes).

Table 4: HADS as a screening test in a hypothetical population (N=1000) with a prevalence of any anxiety disorder of 10% and major depressive disorder of 5%, given that both HADS-A and HADS-D cut-offs of ≥ 8 result in sensitivities and specificities of 0.8.

	Anxiety disorder					Major depressive disorder				
Test result	Cases	Non-cases	Total	PPV	NPV	Cases	Non-cases	Total	PPV	NPV
Positive (n)	80	180	260	0.31		40	190	230	0.17	
Negative (n)	20	720	740		0.97	10	760	380		0.99
Total (n)	100	900	1000			50	950	1000		
Sensitivity	0.80					0.80				
Specificity		0.80					0.80			

PPV Positive predictive value (proportion of true cases among the test-positive subjects)

NPV Negative predictive value (proportion of true non-cases among the test-negative subjects)

8.1.4. Confounding

Confounding implies that the effect of an exposure is mixed together with the effect of another variable, leading to bias (101). Hence, the confounder must be imbalanced between the exposure groups to be compared (i.e. associated with the exposure), and associated with the outcome (either as a cause or as a proxy for the cause of the outcome). However, the confounder should not be an effect of the exposure or the outcome.

The effect of a specific confounder can be prevented by selecting individuals to a study with restricted values on that variable. Epidemiological studies, however, usually aim to select representative population samples, without making such restrictions. Hence, in observational studies attempts are made to reduce the effect of selected confounders by stratification or by use of various multivariate statistical techniques (e.g. regression models). The challenge is, nevertheless, to identify the appropriate confounders. Some characteristics, such as age and gender, are well known to confound associations between a variety of exposures and outcomes. Hence, they are almost routinely adjusted for in observational studies, including the studies of this dissertation. Life-style factors, or health behaviours, such as smoking, alcohol

intake, and coffee consumption, as well as physical exercise, are often associated with both other exposures under investigation and various diseases or health problem outcomes. In our studies these variables were included as confounders in the regression analyses in the "risk factor studies" (Papers IV and V). However, as defined above, a confounder should not be caused by the exposure or the outcome. To rule out such a possibility, a longitudinal design with measurements of the variables involved at a minimum of three different times with adequately intervals, is required (100). What comes first, low educational level or smoking? In studies addressing human behaviour and social phenomena, the sequence of factors is not always obvious. Hence, factors associated with both exposure and outcome are often considered as mediating the effect of the exposure, rather than confounding it (99, 100). This problem is addressed in Paper V where the covariates are referred to as "potential mediators" suggesting that they might just as well act as intermediate variables as confounders. The covariates did, however, not markedly influence the association between educational level and anxiety or depression, simplifying the interpretation regarding the main results. In that study the covariates were reported at baseline, and could therefore not have been caused by the outcome assessed at follow-up. In the cross-sectional study in Paper IV, however, the health behaviours considered as confounders and adjusted for in the analyses (smoking status, coffee-consumption, and physical exercise), might be the consequence, rather than the cause of the outcome (HADS anxiety and depression). If so, some of the associations should be minimally stronger (more deviation from the null hypothesis) than reported because the adjustments had a minor attenuating effect.

In paper II and V the HADS scores were included in some additional analyses as covariates (HADS-D when anxiety was the exposure [Paper II] or outcome [Paper V], and HADS-A when depression was the exposure or outcome). The general prerequisite that a confounder should be associated with both the exposure and the outcome, was fulfilled (an association between anxiety and depression, and an association between anxiety or depression, and impairment, or educational level). However, as illustrated in figure 10, when anxiety or depression is "caused" by the exposure or the outcome (indicated by "Yes" in the figure), they are doubtful confounders. It is likely that anxiety leads to depression, probably mediated by impairment (199, 200). Anxiety disorders due to depression are less probable (200). The main finding of Paper V was that low educational level predicted depression (and

possibly anxiety disorder), but not the other way round. Hence, the adjustments were solely suggestive, and intended not to rule out true confounding.

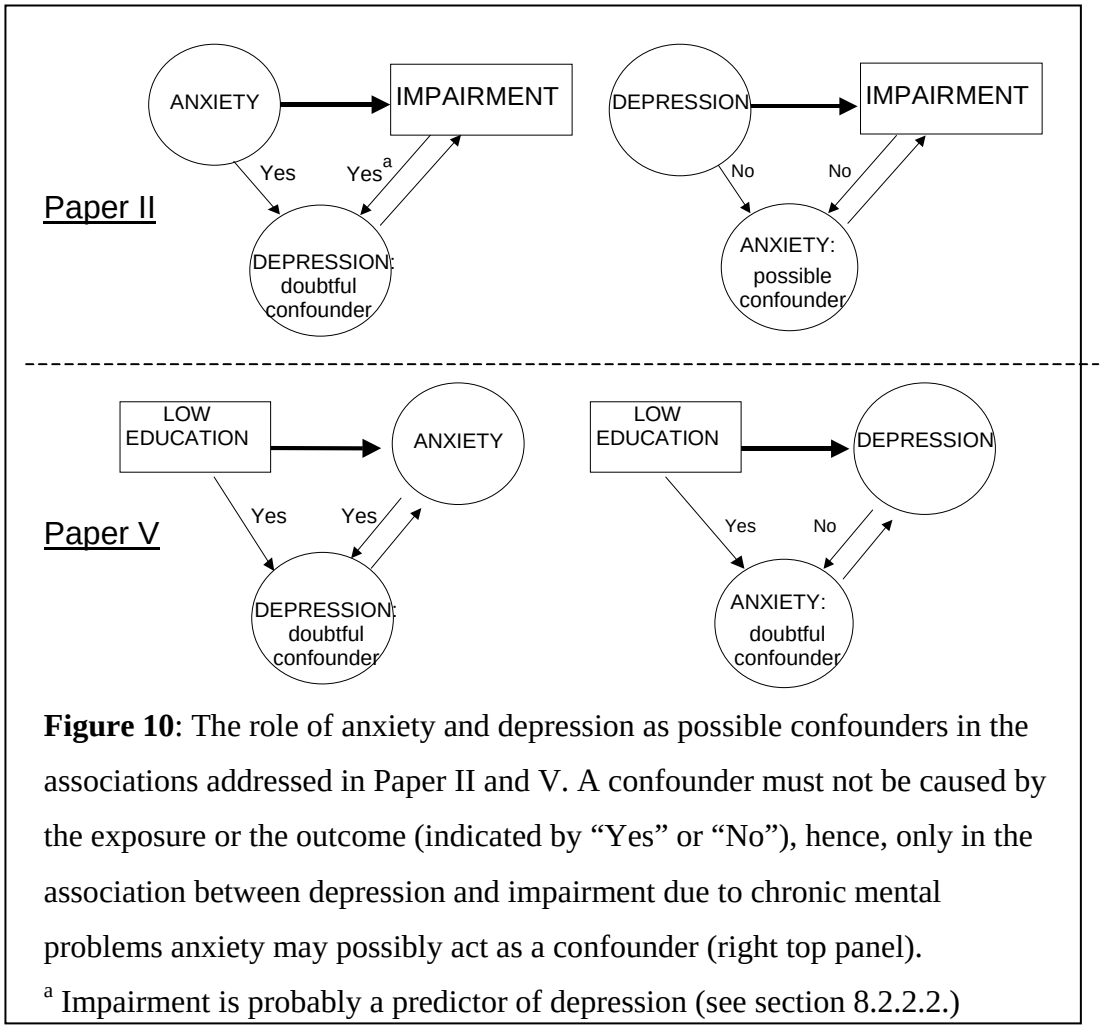


Figure 10: The role of anxiety and depression as possible confounders in the associations addressed in Paper II and V. A confounder must not be caused by the exposure or the outcome (indicated by "Yes" or "No"), hence, only in the association between depression and impairment due to chronic mental problems anxiety may possibly act as a confounder (right top panel).

[a] Impairment is probably a predictor of depression (see section 8.2.2.2.)

8.2. DISCUSSION OF SPECIFIC RESULTS

8.2.1. Assessment of anxiety and depression (Paper I and II)

The use of HADS in the current three health surveys will be mainly discussed regarding its characteristics as a rating scale reviewed in Paper I, but also as to what constructs of anxiety and depression it is reflecting (Paper II).

Our systematic review of HADS essentially confirmed the findings in Herrmann's paper (45). The majority of studies that applied factor analyses, including the largest one with a general population sample, concluded that a two-factor solution achieved the better fit. Hence, there is evidence that HADS really is measuring two different, though correlated, underlying factors or dimensions of mental distress, probably closely related to some core features of anxiety and depression. The

identified factors were not completely consistent with the subscales, however, in a factor analysis of HUNT 2 (201) the two factors were identical with the subscales in most age and gender strata. The mean correlation between the subscales in our review (r = 0.56) was somewhat lower than in Herrmann's (r = 0.63), but similar to HUNT 2 (r = 0.55) (201). Other self-report measures of anxiety and depression have been correlated with coefficients in the 0.45 to 0.75 range (16). Some authors (202) have argued that the correlation between any valid and reliable measure of anxiety and depression should be at the 0.70 level, not because of shared symptoms between anxiety and depression, but because of a common causal factor. However, other authors (16) have claimed that a low correlation between the two measures of anxiety and depression is a hallmark of good discriminant validity of a bidimensional test.

The properties of HADS as a screening test for anxiety disorders or major depressive disorder were similar in our and Herrmann's review. Zigmond and Snaith's original recommendations of a cut-off value of scores $\geq$ 8 for both subscales to identify "possible" cases (41) were confirmed as the cut-off resulting in an optimal balance between sensitivity and specificity of approximately 0.8. A similar result was achieved in a recent Norwegian study of primary care patients (N=1781) examining the screening properties of HADS against DSM-IV major depressive disorder (measured by the General Anxiety Screening Questionnaire – GASQ) and generalised anxiety disorder (measured by the Depression Screening Questionnaire – DSQ) (Ingrid Østby-Deglum, personal communication, 2004). Receiver Operating Characteristics (ROC) curves resulted in a very good Area Under Curves (AUC) of 0.93 and 0.89 for HADS-A and HADS-D, respectively. However, the usefulness of a test in a specific population is dependent on the actual prevalence of the condition to be identified. As illustrated in section 8.1.3., the positive predictive value is only 17% if the prevalence of the disorder is 5%, and 31% if the prevalence is 10%. Hence, the properties of HADS as a case finder of anxiety disorders or major depressive disorder as defined by ICD-10 or DSM-IV in health surveys of the general population, is questionable. Other brief self-report rating scales assessing anxiety and depression do not, however, exhibit better case-finding properties (see section 7.1). Still, in studies addressing risk factors, some core features of anxiety disorders or depression (variants of endophenotypes) may be just as, or even more appropriate outcomes, than the whole syndromes (see section 4.4.).

Considering the content of the various items in the two subscales (face validity) gives a clue of what HADS is measuring: The items of HADS-A are mainly reflecting restlessness and worry, as in generalised anxiety disorder, while the items of HADS-D are concerned with the reduced pleasure response (anhedonia), which is but one of several core diagnostic criteria of major depressive episode in both ICD-10 and DSM-IV. Anhedonia is by some authors (16, 203) considered to be the most characteristic feature of depression, while it has been difficult to identify such a common feature for the anxiety disorders (34) Mineka et al). Possibly HADS-A is reflecting generalised anxiety disorder more specifically, or mental distress more generally. In HUNT 2 there were seven questions addressing general mental distress; the CONOR Mental Health Index (CONOR-MHI) (Appendix III), the first seven question in the section "Hvorledes føler du deg?"). Correlation coefficients corrected for attenuation between CONOR-MHI and HADS-A and HADS-D were 0.91 and 0.76, respectively (204) supporting the notion that HADS-A is assessing mental distress more generally.

In contrast to other epidemiological studies (205) there was no female, but rather a minor male preponderance of depression in HUNT 2 (206) (and HUSK). Hence, HADS-D may possibly reflect a gender non-specific depression component. Accordingly, in NCS there were only minimal gender differences in depression when cases with "somatic" depression were excluded, while the prevalence of the latter category was twice as high in women than in men (207). The somatic component of depression, consisting of disturbances of sleep, appetite, and weight, were not included in HADS in order to avoid diagnostic comorbidity when used in patients with somatic illness (41). This feature is specific for HADS and may explain some of the similarity in prevalence between genders.

Even if anxiety and depression may be best characterised and understood as dimensional disorders, which were supported by Paper II, a categorical approach was applied in the current studies addressing comorbidity with somatic health problems (Paper III) and risk factors (Paper IV and V). In epidemiological studies, both descriptive and analytical, the outcome usually is a disease entity that can be classified as being present or not, which is the prerequisite for quantities such as prevalence, incidence, persistence, sensitivity, specificity, and various measures assessing risk. The challenge when using a rating scale like HADS is, however, to define appropriate cut-off points for anxiety and depression categories. By elevating

the cut-off for caseness the specificity and the PPV would increase, and thus reduce the number of false positives. Hence, in Paper IV analyses with cut-off of ≥ 11 on both HADS sub-scales were performed resulting in stronger associations compared to when cut-offs ≥ 8 were used. However, elevating the cut-off value reduces number of cases, and thereby the statistical power.

Another challenge of categorisation is how to manage co-occurring anxiety and depression. For example, in the group with HADS-A ≥ 8 there were individuals with HADS-D scores in the whole range of the distribution, and vice versa among those with HADS-D ≥ 8 (figure 11). By classifying all cases with scores ≥ 8 on both subscales in a comorbid disorder category, the anxiety disorder and depression categories were made relatively "pure". However, as illustrated in figure 11, there were still considerable co-occurring symptoms (bars to the left of the dotted lines in the figure) that probably are of some clinical significance (Paper II). With this categorisation the prevalence of anxiety disorder was 11.5%, of depression 4.8%, and comorbid disorder 5.2% in the homocysteine cohort (Paper IV), which was very close to the revised prevalence estimates from ECA and NCS (comorbidity was not addressed in the revised study) (11) (see section 4.1.1.).

Despite the domineering role of the categorical approach in the current studies, the dimensional approach proved to be appropriate when examining the (probable) consequences of anxiety or depression, demonstrated by a precise indication of the dose-response relationship between HADS-A or HADS-D scores and reported impairment due to chronic mental problems (Paper II). Hence, these two approaches are not contradictory, but can rather be viewed as complementary (62).

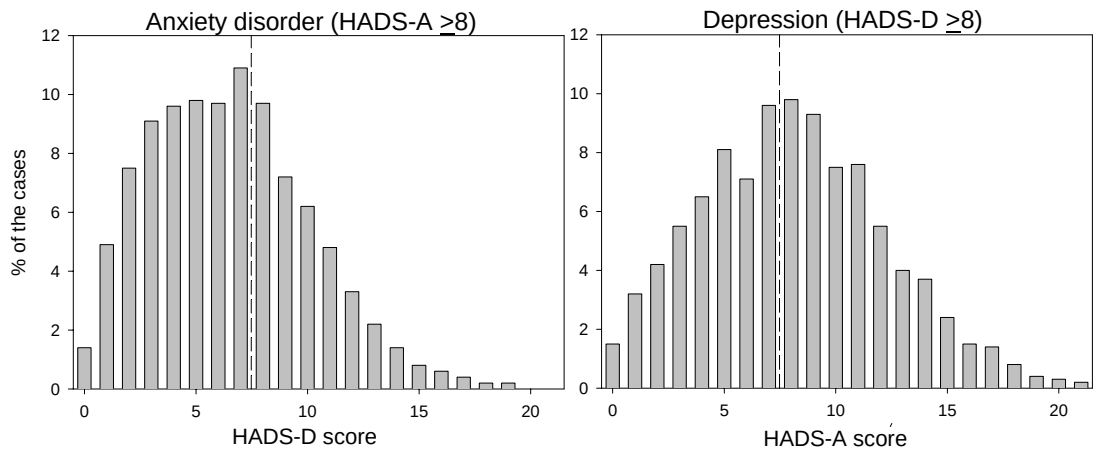


Figure 11: Distribution of depression symptoms (HADS-D scores) in the anxiety disorder category (HADS-A ≥8) (left panel), and distribution of anxiety symptoms (HADS-A scores) in the depression category (HADS-D ≥8) (right panel).

8.2.2. Comorbidity (Paper II and III)

In the introduction to the HADS questionnaire the respondents were invited to report their feelings during the last week, thus yielding point prevalence estimates of anxiety disorder and depression and their comorbidity. However, the associations between various measures of anxiety and depression, categorical or dimensional, and impairment due to *chronic* mental health problems reported in Paper II, were strong. Assumed that these chronic health problems were reflected by the HADS-scores, this finding indicates that the reported symptoms of anxiety and depression may have been long lasting. The period for report of the various health problems was *life time* for alcohol problems and diagnosed diseases, the *last year* for impairment due to somatic health problems, symptoms of cardiovascular and musculoskeletal symptoms, and physical exercise, and *current* for smoking. Hence, the estimates of comorbidity between the various anxiety and depression categories and health problems might differ according to the different time periods covered. Such potential patterns were, however, not possible to investigate in these data.

8.2.2.1. Anxiety and depression (Paper II)

Comorbidity defined by the categorical approach was a frequent finding in HUNT 2. Among 9,493 cases of anxiety disorder 3,639 (38%) had a depression as well, and among the 6,671 cases of depression 3,032 (55%) had an anxiety disorder. These figures are higher than those reported in NCS (see section 4.3.1.), which probably is due to different methods of measuring anxiety disorders and depression, and a wider age range in HUNT 2 than in NCS. The pattern regarding the preponderance of comorbid anxiety disorder in depression compared to the opposite, was, however, seen in both studies.

When viewing the co-occurrence of anxiety and depression as the ratio between HADS-A and HADS-D scores (AD-ratio) a very distinct pattern appeared (figure 1 in Paper II). The generally higher mean AD-ratio level in women reflects the discrepancy in gender differences between HADS-A and HADS-D, with higher HADS-A levels in women, but (minimally) higher HADS-D levels in men. The decreasing AD-ratio with increasing age in both genders similarly reflects the discrepancy in age trends between HADS-A and HADS-D, with a continuous increase in HADS-D with increasing age, but a more stable, though somewhat lowered levels of HADS-A in the older age groups (figure 12). Assuming no historical effects, the

age distribution of the AD-ratio may reflect the temporal pattern with anxiety disorders preceding depression, which is observed in other studies as well (52). Such a pattern is observed already in childhood (figure 13) (200). The fact that anxiety predicts depression does not necessarily imply that anxiety causes depression. The association could be due to common risk factors causing anxiety first, then depression (see section 4.4.1.1 and 4.4.2.). However, the chronic course and major impairment associated with many of the anxiety disorders are suggested to increase the risk for depression (199, 208, 209).

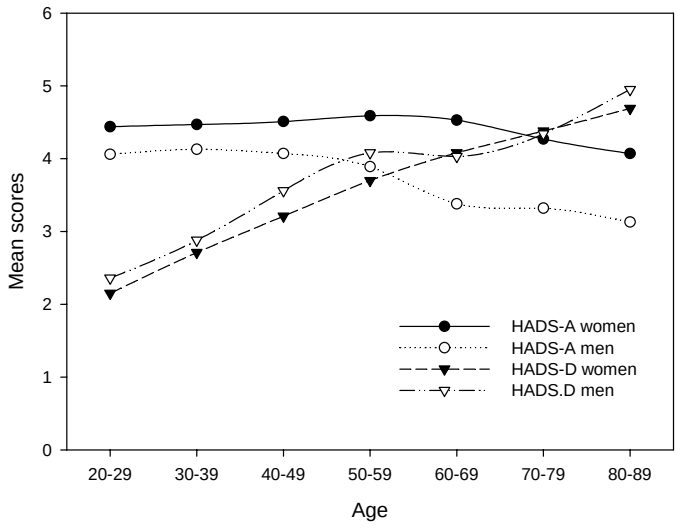


Figure 12: Age and gender distribution of mean HADS-A and HADS-D scores in HUNT 2.

The presence of a continuous measure of anxiety or depression achieved by a rating scale does not necessarily infer that they should be regarded as dimensional disorders. If lower levels of e.g. anxiety was hardly associated with any impairment, while there was a sudden increase in impairment over a certain level of symptoms, that could indicate a natural threshold above which symptom levels cause impairment and become clinical relevant. However, we found no such break points when examining the symptom continuum of anxiety or depression related to impairment. Others have found similar gradients when examining various sub-threshold categories of anxiety and depression (22, 26, 27, 210), but we are not aware of any studies having examined these relationships with a generalised additive model, which gives point-wise estimates along the symptom scales.

The close relationship between anxiety/depression and impairment is supported by other studies addressing the impact on public health and costs (see section 4.1.2.). Moreover, findings from the Australian National Survey of Mental Health and Well-Being suggest that the combination of affective (depression and dysthymia) and anxiety disorders was more predictive of disability and service utilisation than any other combinations of mental disorders (211). Consistently with our results, a systematic review concluded that there was some evidence that anxiety disorders have a worse outcome than depressions (212).

The possible moderating effect of age on the association between anxiety/depression and impairment was somewhat surprising, and we have not found any studies addressing this issue. This is probably due to smaller sample sizes and narrower age ranges in most previous studies. A possible explanation of our finding is an increase in competent emotion regulation across the life span (213-215).

The close relationship between anxiety and depression symptoms throughout the whole scale, combined with the strong dose-response relationships between anxiety or depression and impairment, suggests that the use of the categorical approach has some limitations, in particular when not considering the co-occurrence of anxiety and depression symptoms.

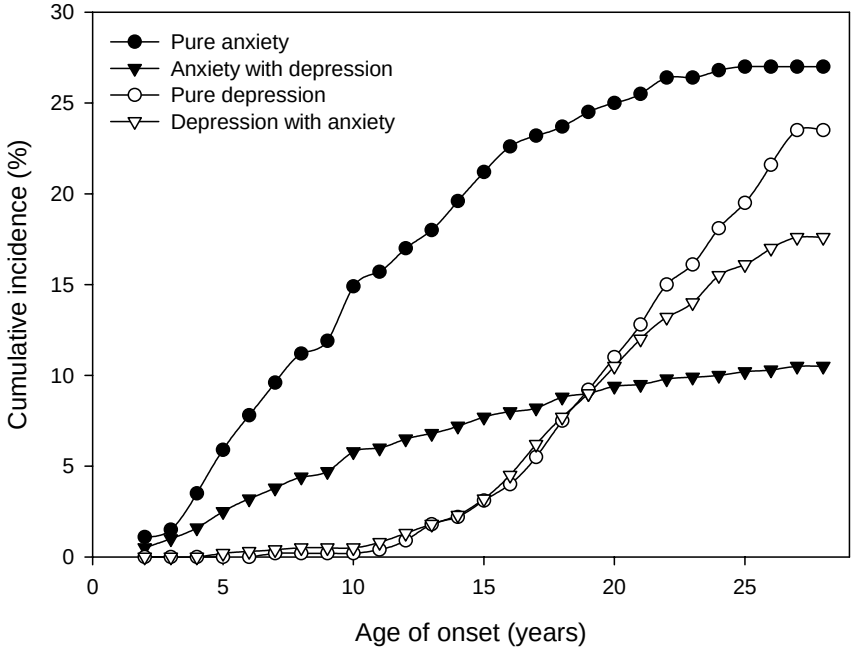


Figure 13: Cumulative incidence of anxiety and depression in childhood, adolescence, and early adulthood (200).

8.2.2.2. Somatic health problems (Paper III)

Comorbidity between various somatic health problems and the anxiety/depression categories was common in HUNT 2, an expected finding on the basis of the review of relevant studies (section 4.3.2.). In our study comorbid anxiety disorder and depression was positively associated with all the somatic health problem outcomes, except hypertension, and the associations were in general stronger than those between pure anxiety disorder or pure depression and somatic health problems. Hence, despite the predominant attention to depression in this field, as revealed in our review of the literature (section 4.3.2.), anxiety disorders may play a more prominent role than previously assumed. The role of anxiety is probably different from that of depression as to the question of cause or consequence, and what kind of somatic health problem to be examined. Accordingly, anxiety symptoms and disorders have in particular been associated with gastrointestinal symptoms (82, 216) and diseases (81, 216), associations that have also been found in HUNT 2 (217, 218). While some authors suggest that gastrointestinal complaints solely reflect an unspecific concomitant vegetative disturbance common to anxiety (82), others propose that anxiety related stress has a deteriorating influence on somatic health via the hypothalamic-pituitary-adrenal (219, 220) axis. Hence, generalised anxiety disorder, which may be assumed to be a marker of chronic stress, has demonstrated a dose-response relationship with gastric ulcer (81). However, as suggested in section 8.1.3., a high anxiety score might also be related to a stronger awareness, sensitivity, and worry about bodily symptoms, resulting in stronger associations between somatic health problems and anxiety disorder alone or comorbid with depression (198).

Somatic comorbidity has been associated with late, in contrast to early life onset depression (221). In HUNT 2 the prevalence of depression increased with age in both genders (206). However, the increased risk for depression in older age groups was mainly explained by impairment due to somatic illness or disabilities as well as somatic diagnoses and symptoms (222) (figure 13). While late onset depression has been associated with neurobiological brain changes in particular (90), early onset depression has been associated with anxiety (221). In a study of patients with secondary depression (N=401) those who were secondary to other mental disorders, had an earlier onset of their depression, were more often suicidal, had less treatment response and higher relapse rate, and had more often family members with alcohol

problems compared to patients with depression secondary to somatic illness, who more often had memory problems (223).

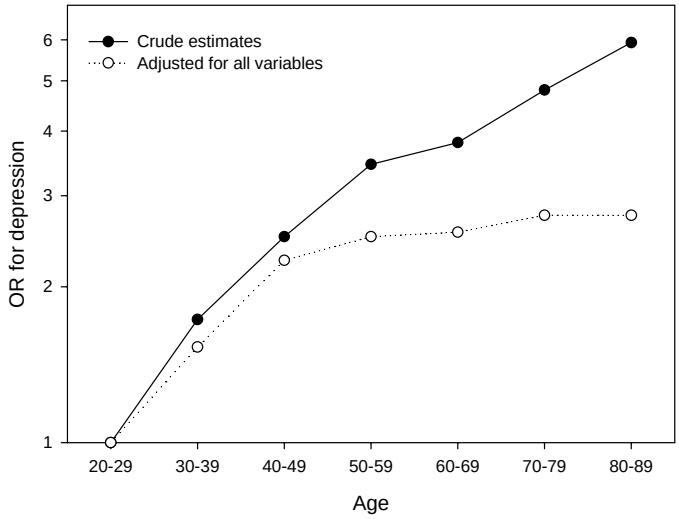


Figure 13: Crude and adjusted ORs for having depression in various age and gender groups is HUNT 2 (222). Adjustments were made for impairment due to somatic disease/disabilities, sociodemographic characteristics, health behaviours, somatic diagnoses, somatic symptoms, and physical measurements in a logistic regression analysis.

Hence, it is possible that depression most often is secondary to somatic illness. In the analyses from HUNT 2 (222) impairment due to somatic illness or disability was the main predictor of late life depression, indicating that depression might be a psychological reaction to physical impairment. Common pathophysiological factors for both the somatic disease and the depression, such as nutrient deficiency or toxic agents, can, however, not be ruled out. Likewise, cytokines from inflammatory processes may induce depression (127). The role of anxiety disorders in most somatic diseases still remains equivocal, mainly due to the paucity of studies considering co-occurring anxiety in depression. Accordingly, in Stordal and colleagues' study from HUNT 2 (222) depression was defined as HADS-D $\geq$ 8 without considering the co-occurring HADS-A scores, which were considerable in the older age groups as demonstrated in Paper II.

8.2.3. Risk factors (Paper IV and V)

Both the biological (Paper IV) and the social (Paper V) risk factors addressed seemed to be more related to depression than to anxiety disorder. By considering the age distribution of mean HADS-A versus mean HADS-D (figure 12) there might be some indication that anxiety is less influenced by various factors accumulating throughout life than depression. However, the anxiety/depression outcome categories represented not only new cases in Paper V (incident and persistent cohorts) and in Paper IV.

8.2.3.1. Folate metabolism (Paper IV)

The strongest association was found between the MTHFR 677C→T polymorphism and depression, and this was the first study addressing this relation in a large population sample. The results from two smaller case-control studies, (152) (N=32) and (151) (N=71), are contradictory. Having applied DSM-III-R or DSM-IV criteria for major depressive disorder, these studies differed from our study also regarding diagnostic criteria for depression.

Another common polymorphism in the MTHFR is the 1298A→C substitution (224). The 1298CC variant also affects enzyme activity and homocysteine levels, but to a lesser degree than the TT variant of the 677C→T polymorphism (225). Some data suggest that heterozygosity for this polymorphism combined with heterozygosity for the MTHFR 677C→T polymorphism is associated with increased risk of neural tube defects (226) and increased (227) or decreased (228, 229) risk of cancer diseases. Its association with psychiatric disorders has previously not been reported. Hence, we made an additional analysis of the MTHFR 1298A→C polymorphism in our sample to examine a possible association with anxiety and depression. Contrary to the analyses of the MTHFR 677C→T polymorphism (Paper IV), we found no association between the CC variant of the 1298A→C polymorphism and depression. We also investigated the combined effect of the MTHFR 677C→T and 1298A→C polymorphisms, but neither of the combinations were associated with increased risk for anxiety disorder or depression (data not shown).

Our findings of only weak associations between plasma levels of folate and depression, contrasted somewhat to earlier findings of impaired folate status in depressed patients (230). However, those findings are mainly from clinical case-

control studies that are more prone to selection bias than a population-based study. Nevertheless, there might have been a selection bias (see section 8.1.2.) in our sample as well, due to a possible better folate status and less severe depression in participants versus non-participants.

None of the other folate related factors were associated with anxiety disorder. Hence, out data suggest that impaired folate metabolism is related to the sub-group of depression without comorbid anxiety. Depression may be a more secondary phenomenon than anxiety and, thus, is influenced by more risk factors (see section 8.2.2.1. and 8.2.2.2.). Moreover, if HADS-A is more an indicator of general mental distress than HADS-D (see section 8.2.1.), associations with specific risk factors, such as those related to folate metabolism, might be less probable.

Although the design of the study of Paper IV was cross-sectional, the association between the MTHFR 677C→T polymorphism is suggestive of a causal relationship between impaired folate metabolism and depression. The associations between deficiency of folate or cobalamin and depression could be due to depression related impaired dietary habits. However, the MTHFR 677C→T polymorphism is not affected by mental status or environmental factors.

8.2.3.2. Educational level (Paper V)

During a follow-up period of 11 years significant gradients from the lowest to the highest educational level were observed in the association with depression, with or without comorbid anxiety disorder, in both the incident and the persistent cohorts. A similar association was seen with anxiety disorder among the youngest women in the incident cohort.

Our findings for depression are in accordance with the results of Kaplan et al (170) who followed 4,864 individuals for nine years. The ORs for being depressed at follow-up in the lowest compared to the highest educational groups were 1.6 (95% CI: 1.2-2.1) in both the incident and the persistent cohort. However, findings from the three other longitudinal studies were inconsistent with our results: After a 15 years follow-up period Eaton et al (169) did not find such an association in their incident cohort (N=693). In a persistent cohort (N=2,223) Bracke (171) reported an association between low educational level and depression after three years follow-up in men only, but after adjustment for baseline depression severity, the association was not present. Likewise, Sargeant et al (172) estimated a significant effect of low educational level

on depression after one year in a persistent cohort (N=423), however after adjustments for the number and length of former depressive episodes and symptom severity at baseline, the association was no longer significant. In our study adjustments for mental distress level at baseline (ADI-12 score) were performed in both cohorts, without influencing the associations markedly.These inconsistent findings may be due to differences in assessment of depression. Kaplan et al. used the Human Population Laboratory Depression Index (231), while the samples of Sargeant et al and Eaton et al were from the ECA using DSM-III criteria for major depression, and Bracke used a modified version of the global depression scale in the Health and Daily Living Form (232). The inconsistencies might as well be due to differences in sample size, sample characteristics, observational time, and/or covariates included in the analyses.

Educational level was just as strongly associated with pure depression as depression comorbid with anxiety disorder (comorbid disorder) in both cohorts. This finding along with the limited effect of educational level on pure anxiety disorder indicates that educational level mainly affects depression and to a lesser degree anxiety. The markedly attenuating effect of adjusting for even low-score depression (HADS-D at follow-up) on the association between educational level and anxiety disorder supports this notion.

By studying a mentally healthy cohort at baseline (incident cohort) the effect of educational level on anxiety and depression could be examined without the possible confounding effect of mental distress. The participants in the persistent cohort (high mental distress level at baseline) had lower educational levels at baseline compared to the incident cohort (table 1 and 2 in Paper V), and the association between educational level and depression at follow-up, therefore, could be biased by baseline mental distress. However, neither stratification nor adjustments with ADI-12 score within the strata did mainly influence the associations between educational level and depression. In other words, in both cohorts educational level independently predicted depression during the observational period of 11 years.

The selection theory (176) claims that health problems may be an obstacle to upward and promote downward social mobility, would be supported if a high level of mental distress at baseline was associated with a lack of additional educational attainment during the observational period. However, the opposite was surprisingly found, namely that a high, compared to a low level of mental distress at baseline was

modestly associated with additional educational attainment. A possible interpretation is that individuals with a high level of mental distress at baseline actually have delayed their education. Moreover, there were no effects of additional educational attainment on the anxiety/depression outcome categories (HADS) at follow-up. Hence, the factor(s) inherent to lower educational level that predicts depression is probably established relatively early in life, which might be a vulnerable personality trait or belonging to a lower social class. Hence, to test the theories of causation and selection theories properly, an inter-generational (233) or inter-ethnicity (173) study design is recommended

Length of education is the most frequently used measure of SES, probably because it is a robust variable that does not change much during adult life and is easy to categorise, contrary to households' annual income and occupation. Opposed to income, which reflects material resources, education may reflect personal resources, such as knowledge and competence. Moreover, education probably influences important choices in early adult life and might even serve as a "vaccination" against the effect of later adverse incidents. Accordingly, contrary to educational level, the effect of income on depression at follow up disappeared after adjusting for other psychosocial variables in the study of Kaplan et al (170). In a natural experiment moving parts of a population out of poverty, the raise in income did not affect symptoms of anxiety and depression in children (234).

In our analyses the associations between educational level and depression were only modestly influenced by adjustments for a variety of covariates including somatic illness, use of health services, health behaviours, psychosocial status, and sociodemographic and work characteristics. Hence, our study did not add new information as to the mechanisms of the observed associations. Other authors have made efforts to reveal potential mechanisms as well, but mainly addressing other indicators of SES than education. In a cross-sectional study (177) using occupational grade as a proxy for SES, work characteristics, including skill discretion and decision authority, explained most of the SES-depression gradient. Physical disease has been suggested (166), but was not found to play a mediating role in a study using economic situation as the measure of SES (178). Health behaviours have been proposed (235) as possible mediators, and adjusting for smoking, alcohol consumption, physical activity, and Body Mass Index reduced the SES (economic hardship)-depression association in a longitudinal study (178). However, psychological functioning was

assessed only at follow-up, and the different behaviours were not evaluated separately. Personality traits such as optimism, coping style, personal control, and sense of mastery have been suggested to influence the SES-health relation (167). Moreover, social support has been associated with higher SES and less depression (236), partly as a mediator, partly as a moderator (or effect modifier) buffering the effect of low SES on depression.

A comprehensive concept that integrate vulnerability factors such as genetic predisposition, developmental experiences, health behaviours, and physiological responses to acute and, in particular, chronic stress, called “allostatic load”, has been proposed by McEwen (220). Allostatic load is meant to reflect the resulting “wear and tear” of an elevated physiologic activation due to the many events of daily life and is suggested to be related to SES (237), anxiety, and depression (162).

A low social position is suggested to cause feelings of shame, social anxiety, and depression (238) more directly. The health gradients associated with SES have mainly been independent of average income in the population, but rather to the range of inequalities in income (239), indicating the significance of social hierarchy for health. Social anxiety is characterised by a fear of being devaluated and ridiculed, which may be more pronounced among individuals belonging to lower social classes. Depression has been suggested as well to be an adaptation in response to situations dominated by others where the consequences of opposition could be harmful (240), equivalent to the lower position in the social hierarchy.

9. CONCLUSIONS AND INTEGRATION OF THE FINDINGS

The issues in this dissertation cover a broad scope, which hopefully has illustrated the complex aspects of anxiety and depression in both mental and somatic health issues. Although HADS is a brief self-rating instrument, our systematic review showed that HADS performed well in assessing some core aspects of these mental syndromes (Paper I). To simplify our main findings and our interpretation of these in light of previously reported studies, an illustration will be presented for each paper. Finally, an attempt will be made to merge the findings in an integrated model (figure 14).

1. The basic model states that anxiety and depression are related, and that they are influenced by genetic and environmental (non-genetic) factors. Certain genetically determined personality traits may influence what environmental factors that an individual will be exposed to as well (104, 108, 241).

2. In Paper II the strong relationship between anxiety, depression and impairment is best described by the dimensional approach. We suggest a causal relationship from anxiety to depression, at least among younger adults, and in agreement with findings from other studies.

3. Paper III demonstrates an extensive comorbidity between somatic disease and various combinations of anxiety and depression. Most evidence is for depression as a consequence of somatic disease, which probably is the most important determinant of depression in older age. However, the relationship between somatic diseases and anxiety is less clear.

4. Paper IV contributes further evidence that impaired folate metabolism may be a determinant of depression, but probably not of anxiety. A genetic vulnerability (the MTHFR 677C→T polymorphism) combined with low folate intake probably gives the highest risk for depression.

5. In Paper V low educational level is suggested to be a determinant for depression, and to a smaller degree for anxiety. Low educational level may be considered as a

proxy for some vulnerability associated with living conditions in the lower social strata, or less personal or network resources which can buffer the effect of stress. Factors related to somatic health, use of health services, health behaviours, psychosocial status, or sociodemographic or work characteristics explained only a small part of the observed association between low educational level and depression.

6. Finally, the integrated model converges our findings with those of others. Findings from studies suggesting that low education is related to somatic illness (167) and low folate intake (242), and that impaired folate metabolism is associated with somatic illness (243-249), are included in order to complete the model. Although the model is by no means comprehensive, it illustrates the complexity of the relationship between anxiety and depression, and biological and psychosocial factors. Furthermore, in such a complex network of associations, the various subtypes of anxiety and depression may show different associations. The model is in accordance with the biopsychosocial model of mental disorders (103).

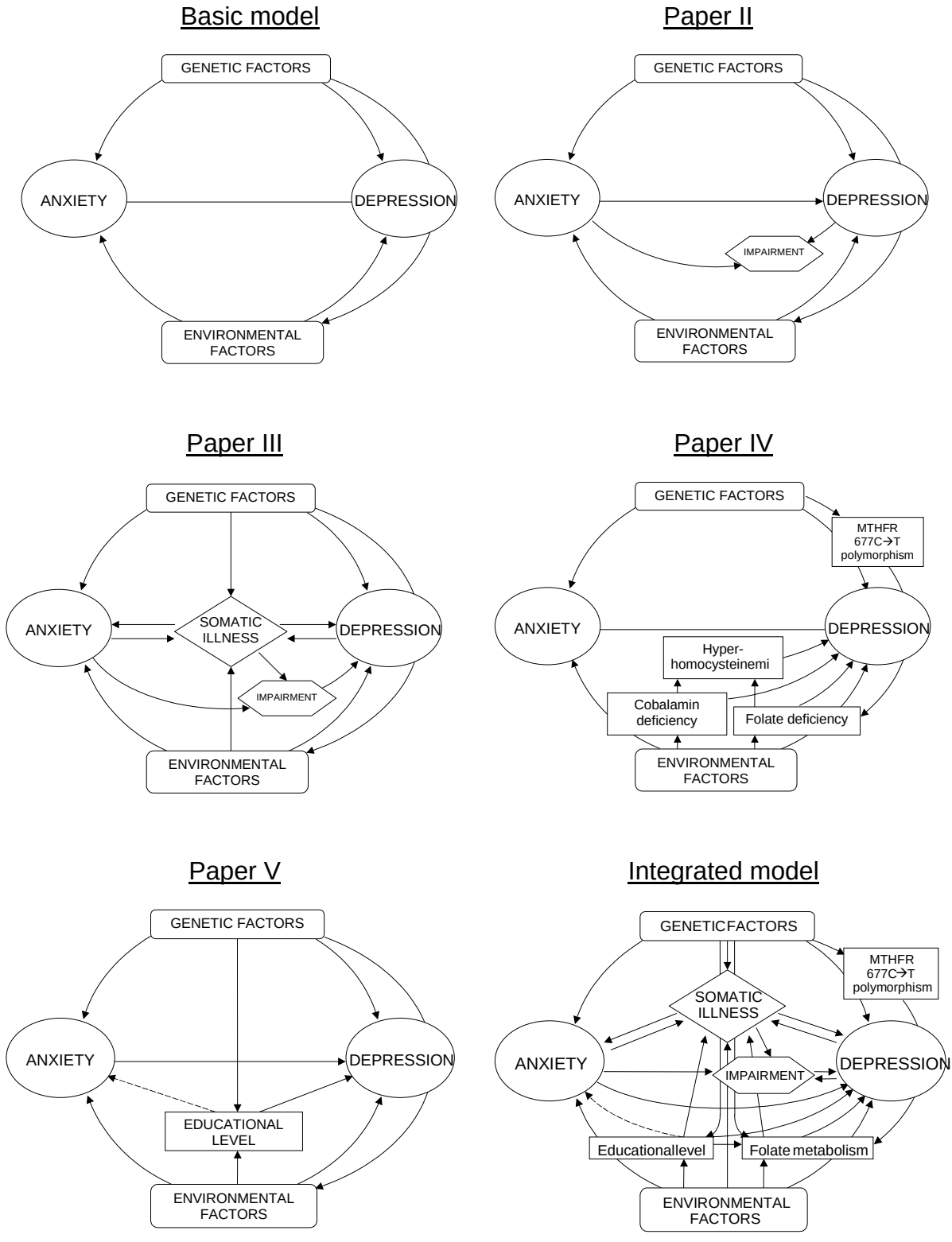


Figure 14: Models of the relation between anxiety and depression including the findings from the papers in the dissertation. The final model (right bottom panel) attempts to integrate these findings and results from other studies as well.

10. IMPLICATIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH

Generally. Anxiety and depression are common and costly public health problems. As demonstrated in this dissertation, much is still unknown regarding causes and efficient preventive measures. Hence, increased resources not only for the treatment of mental disorders, but for research as well, are welcomed. Large scale, representative epidemiological studies that include information regarding various biopsychosocial aspects are needed to study these complex phenomena. According to their relative impact on public health, items addressing mental health problems have been under-represented in general health surveys in Norway.

Assessment. For both clinical and research purposes HADS can be recommended as an efficient screening tool to identify possible anxiety disorder and depression. In the health services further assessment of the screen-positive subjects must, however, be made in order to ascertain clinically significant cases. In epidemiological studies supplementary scales that might identify other subtypes of anxiety and depression, suitable for both a categorical and a dimensional approach, could be included. Some measure of clinical significance related to symptom scores should be included, such as impairment, use of health services, and medication.

Comorbidity. It is a challenge for clinicians as well as researchers to identify the extensive co-occurrence of anxiety, depression, and somatic health problems, and consider the deteriorating effect of such comorbidity. However, while much is known of the co-occurrence of various mental disorders and somatic diseases, less is known about the possible mechanisms of this phenomenon. Most probably there are different mechanisms for different variants of comorbidity. A longitudinal design is necessary to settle the temporal relationship between the disorders. To avoid information bias, somatic disease should be ascertained by objective measures or information from a physician or a hospital.

Risk factors. There is still not irrefutible evidence that folate should be recommended in prevention and treatment of depression. However, folate and cobalamin are both inexpensive and non-toxic agents, which might be supplemented in patients with a deficiency of those vitamins and perhaps in patients with a treatment restistent depression.

Whether a generally increased level of education in the population, which actually has taken place after World War II, would prevent depression, is highly questionable. Most probably the education-depression gradient reflects social inequalities in general, which rather should be addressed, a challenge that is more a political than a health care issue.

Cohort studies with comprehensive measurements at baseline and regular follow-ups will be of great value in further examination of risk factors. One such study, the Mother and Child Study (Den Norske Mor & Barn Undersøkelsen) (250) by the Norwegian Institute of Public Health, has by February 2004 recruited 35,000 pregnant women who will be followed up several times during the pre-, peri- and neonatal period. The relationship between folate metabolism and mental health, in particular pregnancy related depression, may be examined. Detailed information regarding dietary habits and intake of vitamin supplements is collected, as well as blood samples and assessment of anxiety and depression at both baseline and follow-up. The children will be followed up during their childhood enabling examination of developmental aspects of their mental health. Such aspects will be addressed in another cohort study as well, the Bergen Child Study (Barn i Bergen) (251). Preliminary results regarding the relation between neurodevelopmental (attention deficit and hyperactivity, obsessive compulsive symptoms, language problems, autism, and clumsy motor behaviour) and emotional problems (anxiety and depression) have already been presented (252).

It may also be possible to link data from health surveys to various other data sources, such as the Norwegian Medical Birth Registry, the Cancer Registry of Norway, and Statistics Norway. Linkage to bio banks will enable examination of genetic risk factors, such as single nucleotide polymorphisms, and other biological markers.

Statistical methods. Due to the complex network of mediators, moderators, and independent, overlapping, and proxy risk factors (100) associated with anxiety and depression, statistical techniques that can model such intricate relationships are recommended. While conventional regression models are useful, other techniques such as generalised linear latent and mixed models (GLLAMM) (253) including structural equation modelling (SEM) (254), may better attend to the complexity of these relationships.

11. REFERENCES

1. Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen T, Bratberg G, Vatten L, Lund-Larsen P. The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation. Norsk Epidemiologi 2003;13:19-32.
2. Regier DA, Myers JK, Kramer M, Robins LN, Blazer DG, Hough RL, Eaton WW, Locke BZ. The NIMH Epidemiologic Catchment Area program. Historical context, major objectives, and study population characteristics. Arch Gen Psychiatry 1984;41:934-41.
3. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8-19.
4. Kringlen E, Torgersen S, Cramer V. A Norwegian psychiatric epidemiological study. Am J Psychiatry 2001;158:1091-8.
5. Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. Arch Gen Psychiatry 1981;38:381-9.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition. Washington, DC: American Psychiatric Association, 1980.
7. Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, Farmer A, Jablenski A, Pickens R, Regier DA, et al. The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 1988;45:1069-77.
8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association, 1987.
9. World Health Organisation. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. Geneva, Switzerland: WHO, 1992.
10. Regier DA, Kaelber CT, Rae DS, Farmer ME, Knauper B, Kessler RC, Norquist GS. Limitations of diagnostic criteria and assessment instruments for mental disorders. Implications for research and policy. Arch Gen Psychiatry 1998;55:109-15.
11. Narrow WE, Rae DS, Robins LN, Regier DA. Revised prevalence estimates of mental disorders in the United States: using a clinical significance criterion to reconcile 2 surveys' estimates. Arch Gen Psychiatry 2002;59:115-23.
12. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349:1436-42.
13. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997;349:1498-504.
14. Greenberg PE, Sisitsky T, Kessler RC, Finkelstein SN, Berndt ER, Davidson JR, Ballenger JC, Fyer AJ. The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry 1999;60:427-35.

15. Stein MB, Hollander E. Textbook of Anxiety Disorders. Washington, DC: The American Psychiatric Publishing, 2002.
16. Watson D, Weber K, Assenheimer JS, Clark LA, Strauss ME, McCormick RA. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. J Abnorm Psychol 1995;104:3-14.
17. Goldberg D. Plato versus Aristotle: categorical and dimensional models for common mental disorders. Compr Psychiatry 2000;41:8-13.
18. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry 1970;126:983-7.
19. Feighner JP, Robins E, Guze SB, Woodruff RA, Jr., Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry 1972;26:57-63.
20. Maser JD, Cloninger CR. Comorbidity of Anxiety and Mood Disorders: Inroduction and Overview. In: Maser JD, Cloninger CR, eds. Comorbidity of Mood and Anxiety Disorders. Washington, DC: American Psychiatric Press, 1990:3-12.
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association, 1994.
22. Angst J, Merikangas KR, Preisig M. Subthreshold syndromes of depression and anxiety in the community. J Clin Psychiatry 1997;58:6-10.
23. Angst J, Sellaro R, Merikangas K. Depressive Spectrum Diagnoses. Comprehensive Psychiatry 2000;41:39-47.
24. Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey [see comments]. Jama 1990;264:2524-8.
25. Johnson J, Weissman MM, Klerman GL. Service utilization and social morbidity associated with depressive symptoms in the community. Jama 1992;267:1478-83.
26. Maier W, Gansicke M, Weiffenbach O. The relationship between major and subthreshold variants of unipolar depression. J Affect Disord 1997;45:41-51.
27. Rapaport MH, Judd LL. Minor depressive disorder and subsyndromal depressive symptoms: functional impairment and response to treatment. J Affect Disord 1998;48:227-32.
28. Helmchen H, Linden M. Subthreshold disorders in psychiatry: clinical reality, methodological artifact, and the double-threshold problem. Compr Psychiatry 2000;41:1-7.
29. Schotte K, Cooper B. Subthreshold affective disorders: a useful concept in psychiatric epidemiology? Epidemiologia e Psichiatria Sociale 1999;8:255-61.
30. Goldberg DP, Bridges K, Duncan-Jones P, Grayson D. Dimensions of neuroses seen in primary-care settings. Psychol Med 1987;17:461-70.
31. Goldberg D. A dimensional model for common mental disorders. Br J Psychiatry 1996;(Suppl 30):44-9.
32. Krueger RF. The structure of common mental disorders. Arch Gen Psychiatry 1999;56:921-6.
33. Clark LA, Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. J Abnorm Psychol 1991;100:316-36.

34. Mineka S, Watson D, Clark LA. Comorbidity of anxiety and unipolar mood disorders. Annual Review of Psychology 1998;49:377-412.
35. Watson D. Dimensions underlying the anxiety disorders: a hierarchical perspective. Current opinion in Psychiatry 1999;12:181-6.
36. Radloff L. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Measurement 1977;1:385-401.
37. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
38. Spielberger C, Gorsuch RL, Luschene R. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press, 1970.
39. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. Behav Sci 1974;19:1-15.
40. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. Psychol Med 1979;9:139-45.
41. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
42. Egger M, Smith GD. Meta-Analysis. Potentials and promise. Bmj 1997;315:1371-4.
43. Egger M, Smith GD. Bias in location and selection of studies. Bmj 1998;316:61-6.
44. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. Bmj 1998;316:140-4.
45. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale - a review of validation data and clinical results. J Psychosom Res 1997;42:17-41.
46. Murphy JM, Berwick DM, Weinstein MC, Borus JF, Budman SH, Klerman GL. Performance of screening and diagnostic tests. Application of receiver operating characteristic analysis. Arch Gen Psychiatry 1987;44:550-5.
47. Krishnan KR, Delong M, Kraemer H, Carney R, Spiegel D, Gordon C, McDonald W, Dew M, Alexopoulos G, Buckwalter K, Cohen PD, Evans D, Kaufmann PG, Olin J, Otey E, Wainscott C. Comorbidity of depression with other medical diseases in the elderly. Biol Psychiatry 2002;52:559-88.
48. Batstra L, Bos EH, Neeleman J. Quantifying psychiatric comorbidity - lessions from chronic disease epidemiology. Soc Psychiatry Psychiatr Epidemiol 2002;37:105-11.
49. Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidity in evaluatin the outcome of diabetes mellitus. J Chronic Dis 1974;27:387-404.
50. Boyd JH, Burke JD, Jr., Gruenberg E, Holzer CE, 3rd, Rae DS, George LK, Karno M, Stoltzman R, McEvoy L, Nestadt G. Exclusion criteria of DSM-III. A study of co-occurrence of hierarchy-free syndromes. Arch Gen Psychiatry 1984;41:983-9.
51. Wittchen HU. Critical issues in the evaluation of comorbidity of psychiatric disorders. Br J Psychiatry 1996;(Suppl 30):9-16.
52. Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. Br J Psychiatry 1996;(Suppl 30):17-30.

53. Sartorius N, Ustun TB, Lecrubier Y, Wittchen HU. Depression comorbid with anxiety: results from the WHO study on psychological disorders in primary health care. Br J Psychiatry 1996;(Suppl 30):38-43.
54. Simon NM, Smoller JW, Fava M, Sachs G, Racette SR, Perlis R, Sonawalla S, Rosenbaum JF. Comparing anxiety disorders and anxiety-related traits in bipolar disorder and unipolar depression. J Psychiatr Res 2003;37:187-92.
55. Rihmer Z, Szadoczky E, Furedi J, Kiss K, Papp Z. Anxiety disorders comorbidity in bipolar I, bipolar II and unipolar major depression: results from a population-based study in Hungary. J Affect Disord 2001;67:175-9.
56. Sherbourne CD, Wells KB. Course of depression in patients with comorbid anxiety disorders. J Affect Disord 1997;43:245-50.
57. Brown C, Schulberg HC, Madonia MJ, Shear MK, Houck PR. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. Am J Psychiatry 1996;153:1293-300.
58. Hayden EP, Klein DN. Outcome of dysthymic disorder at 5-year follow-up: the effect of familial psychopathology, early adversity, personality, comorbidity, and chronic stress. Am J Psychiatry 2001;158:1864-70.
59. Coryell W, Endicott J, Winokur G. Anxiety syndromes as epiphenomena of primary major depression: outcome and familial psychopathology. Am J Psychiatry 1992;149:100-7.
60. Angst J. Comorbidity of anxiety, phobia, compulsion and depression. Int Clin Psychopharmacol 1993;8 (Suppl 1):21-5.
61. Maser JD, Patterson T. Spectrum and nosology: implications for DSM-V. Psychiatr Clin North Am 2002;25:855-85.
62. Blashfield R. Comorbidity and Classification. In: Maser JD, Cloninger CR, eds. Comorbidity of Mood and Anxiety Disorders. Washington, DC: American Psychiatric Press, 1990:61-82.
63. Wells KB, Golding JM, Burnam MA. Psychiatric disorder in a sample of the general population with and without chronic medical conditions. Am J Psychiatry 1988;145:976-81.
64. Kisely SR, Goldberg DP. Physical and psychiatric comorbidity in general practice. Br J Psychiatry 1996;169:236-42.
65. Maier W, Falkai P. The epidemiology of comorbidity between depression, anxiety disorders and somatic diseases. Int Clin Psychopharmacol 1999;14 (Suppl 2):1-6.
66. Fulop G, Strain JJ, Vita J, Lyons JS, Hammer JS. Impact of psychiatric comorbidity on length of hospital stay for medical/surgical patients: a preliminary report. Am J Psychiatry 1987;144:878-82.
67. Chisholm D, Diehr P, Knapp M, Patrick D, Treglia M, Simon G. Depression status, medical comorbidity and resource costs. Evidence from an international study of major depression in primary care (LIDO). Br J Psychiatry 2003;183:121-31.
68. Welin C, Lappas G, Wilhelmsen L. Independent importance of psychosocial factors for prognosis after myocardial infarction. J Intern Med 2000;247:629-39.
69. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. Jama 1993;270:1819-25.
70. Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, van Tilburg W. Depression and cardiac mortality: results from a community-based longitudinal study. Arch Gen Psychiatry 2001;58:221-7.

71. Aromaa A, Raitasalo R, Reunanen A, Impivaara O, Heliovaara M, Knekt P, Lehtinen V, Joukamaa M, Maatela J. Depression and cardiovascular diseases. Acta Psychiatr Scand 1994;(Suppl):77-82.
72. Schleifer SJ, Macari-Hinson MM, Coyle DA, Slater WR, Kahn M, Gorlin R, Zucker HD. The nature and course of depression following myocardial infarction. Arch Intern Med 1989;149:1785-9.
73. Watkins LL, Schneiderman N, Blumenthal JA, Sheps DS, Catellier D, Taylor CB, Freedland KE. Cognitive and somatic symptoms of depression are associated with medical comorbidity in patients after acute myocardial infarction. Am Heart J 2003;146:48-54.
74. Rao R. Cerebrovascular disease and late life depression: an age old association revisited. Int J Geriatr Psychiatry 2000;15:419-33.
75. Tiemeier H, Breteler MM, van Popele NM, Hofman A, Witteman JC. Late-life depression is associated with arterial stiffness: a population-based study. J Am Geriatr Soc 2003;51:1105-10.
76. Carnethon MR, Kinder LS, Fair JM, Stafford RS, Fortmann SP. Symptoms of depression as a risk factor for incident diabetes: findings from the National Health and Nutrition Examination Epidemiologic Follow-up Study, 1971-1992. Am J Epidemiol 2003;158:416-23.
77. Eaton WW. Epidemiologic evidence on the comorbidity of depression and diabetes. J Psychosom Res 2002;53:903-6.
78. Aarsland D, Karlsen K. Neuropsychiatric aspects of Parkinson's disease. Curr Psychiatry Rep 1999;1:61-8.
79. Pincus T, Griffith J, Pearce S, Isenberg D. Prevalence of self-reported depression in patients with rheumatoid arthritis. Br J Rheumatol 1996;35:879-83.
80. Joukamaa M. Depression and back pain. Acta Psychiatr Scand 1994;(Suppl):83-6.
81. Goodwin RD, Stein MB. Generalized anxiety disorder and peptic ulcer disease among adults in the United States. Psychosom Med 2002;64:862-6.
82. Hochstrasser B, Angst J. The Zurich Study: XXII. Epidemiology of gastrointestinal complaints and comorbidity with anxiety and depression. Eur Arch Psychiatry Clin Neurosci 1996;246:261-72.
83. Stark DP, House A. Anxiety in cancer patients. Br J Cancer 2000;83:1261-7.
84. Razavi D, Delvaux N, Farvacques C, Robaye E. Screening for adjustment disorders and major depressive disorders in cancer in-patients. Br J Psychiatry 1990;156:79-83.
85. McDaniel JS, Musselman DL, Porter MR, Reed DA, Nemeroff CB. Depression in patients with cancer. Diagnosis, biology, and treatment. Arch Gen Psychiatry 1995;52:89-99.
86. Morrison MF, Petitto JM, Ten Have T, Gettes DR, Chiappini MS, Weber AL, Brinker-Spence P, Bauer RM, Douglas SD, Evans DL. Depressive and anxiety disorders in women with HIV infection. Am J Psychiatry 2002;159:789-96.
87. Dickey WC, Dew MA, Becker JT, Kingsley L. Combined effects of HIV-infection status and psychosocial vulnerability on mental health in homosexual men. Soc Psychiatry Psychiatr Epidemiol 1999;34:4-11.
88. Atkinson JH, Grant I. Natural history of neuropsychiatric manifestations of HIV disease. Psychiatr Clin North Am 1994;17:17-33.
89. Mohr DC, Cox D. Multiple sclerosis: empirical literature for the clinical health psychologist. J Clin Psychol 2001;57:479-99.

90. Alexopoulos GS, Buckwalter K, Olin J, Martinez R, Wainscott C, Krishnan KR. Comorbidity of late life depression: an opportunity for research on mechanisms and treatment. Biol Psychiatry 2002;52:543-58.
91. Maier W, Falkai P. The epidemiology of comorbidity between depression, anxiety disorders and somatic diseases. Int Clin Psychopharmacol 1999;14 (Suppl 2):1-6.
92. Dew M. Psychiatric Disorder in the Context of Physical Illness. In: Dohrenwend B, ed. Adversity, Stress, and Psychopathology. New York, NY: Oxford University Press, 1998:177-218.
93. Bruce ML, Hoff RA. Social and physical health risk factors for first-onset major depressive disorder in a community sample. Soc Psychiatry Psychiatr Epidemiol 1994;29:165-71.
94. Meeks S, Murrell SA, Mehl RC. Longitudinal relationships between depressive symptoms and health in normal older and middle-aged adults. Psychol Aging 2000;15:100-9.
95. Charlson M, Peterson JC. Medical comorbidity and late life depression: what is known and what are the unmet needs? Biol Psychiatry 2002;52:226-35.
96. Rogers MP, White K, Warshaw MG, Yonkers KA, Rodriguez-Villa F, Chang G, Keller MB. Prevalence of medical illness in patients with anxiety disorders. Int J Psychiatry Med 1994;24:83-96.
97. Last. A Dictionary of Epidemiology. New York, NY: Oxford University Press, 2001.
98. Kraemer HC, Kazdin AE, Offord DR, Kessler RC, Jensen PS, Kupfer DJ. Coming to terms with the terms of risk. Arch Gen Psychiatry 1997;54:337-43.
99. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173-82.
100. Kraemer HC, Stice E, Kazdin A, Offord D, Kupfer D. How do risk factors work together? Mediators, moderators, and independent, overlapping, and proxy risk factors. Am J Psychiatry 2001;158:848-56.
101. Rothman K. Epidemiology. An Introduction. New York, NY: Oxford University Press, 2002.
102. Gottesman, II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003;160:636-45.
103. Engel GL. The need for a new medical model: a challenge for biomedicine. Science 1977;196:129-36.
104. Rutter M. Nature, nurture, and development: from evangelism through science toward policy and practice. Child Dev 2002;73:1-21.
105. Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am J Psychiatry 2001;158:1568-78.
106. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000;157:1552-62.
107. Foley DL, Neale MC, Kendler KS. Reliability of a lifetime history of major depression: implications for heritability and co-morbidity. Psychol Med 1998;28:857-70.
108. Kendler KS, Kessler RC, Walters EE, MacLean C, Neale MC, Heath AC, Eaves LJ. Stressful life events, genetic liability, and onset of an episode of major depression in women. Am J Psychiatry 1995;152:833-42.

109. Rush AJ. Toward an understanding of bipolar disorder and its origin. J Clin Psychiatry 2003;64 (Suppl 6):4-8.
110. Kendler KS. Major depression and generalised anxiety disorder. Same genes, (partly)different environments - revisited. Br J Psychiatry 1996; (Suppl 30):68-75.
111. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Major depression and phobias: the genetic and environmental sources of comorbidity. Psychol Med 1993;23:361-71.
112. Pauls DL, Leckman JF, Cohen DJ. Evidence against a genetic relationship between Tourette's syndrome and anxiety, depression, panic and phobic disorders. Br J Psychiatry 1994;164:215-21.
113. Pauls DL. The genetics of obsessive compulsive disorder and Gilles de la Tourette's syndrome. Psychiatr Clin North Am 1992;15:759-66.
114. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Muller CR, Hamer DH, Murphy DL. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 1996;274:1527-31.
115. Melke J, Landen M, Baghei F, Rosmond R, Holm G, Bjorntorp P, Westberg L, Hellstrand M, Eriksson E. Serotonin transporter gene polymorphisms are associated with anxiety-related personality traits in women. Am J Med Genet 2001;105:458-63.
116. Lesch KP, Mossner R. Genetically driven variation in serotonin uptake: is there a link to affective spectrum, neurodevelopmental, and neurodegenerative disorders? Biol Psychiatry 1998;44:179-92.
117. Flory JD, Manuck SB, Ferrell RE, Dent KM, Peters DG, Muldoon MF. Neuroticism is not associated with the serotonin transporter (5-HTTLPR) polymorphism. Mol Psychiatry 1999;4:93-6.
118. Hariri AR, Weinberger DR. Imaging genomics. Br Med Bull 2003;65:259-70.
119. Atack JR. Anxioselective compounds acting at the GABA(A) receptor benzodiazepine binding site. Curr Drug Target CNS Neurol Disord 2003;2:213-32.
120. Nutt DJ, Forshall S, Bell C, Rich A, Sandford J, Nash J, Argyropoulos S. Mechanisms of action of selective serotonin reuptake inhibitors in the treatment of psychiatric disorders. Eur Neuropsychopharmacol 1999;9 (Suppl 3):81-6.
121. Boyer P. Do anxiety and depression have a common pathophysiological mechanism? Acta Psychiatr Scand 2000;(Suppl):24-9.
122. Almeida OP, Barclay L. Sex hormones and their impact on dementia and depression: a clinical perspective. Expert Opin Pharmacother 2001;2:527-35.
123. Musselman DL, Nemeroff CB. Depression and endocrine disorders: focus on the thyroid and adrenal system. Br J Psychiatry 1996; (Suppl 30):123-8.
124. Simon NM, Blacker D, Korbly NB, Sharma SG, Worthington JJ, Otto MW, Pollack MH. Hypothyroidism and hyperthyroidism in anxiety disorders revisited: new data and literature review. J Affect Disord 2002;69:209-17.
125. Pacchierotti C, Iapichino S, Bossini L, Pieraccini F, Castrogiovanni P. Melatonin in psychiatric disorders: a review on the melatonin involvement in psychiatry. Front Neuroendocrinol 2001;22:18-32.
126. Rohr UD, Herold J. Melatonin deficiencies in women. Maturitas 2002;41 (Suppl 1):85-104.

127. Capuron L, Dantzer R. Cytokines and depression: the need for a new paradigm. Brain Behav Immun 2003;17 (Suppl 1):119-24.
128. Capuron L, Dantzer R. Cytokines and depression: the need for a new paradigm. Brain Behav Immun 2003;17 (Suppl 1):119-24.
129. Shaw K, Turner J, Del Mar C. Tryptophan and 5-hydroxytryptophan for depression. Cochrane Database Syst Rev 2002:CD003198.
130. Herbert V, Das K. Folic Acid and Vitamin B12. In: Shils M, Olson J, Shike M, eds. Modern Nutrition in Health and Disease. Malvern, PA: Lea & Febiger, 1994:402-25.
131. Ueland PM, Hustad S, Schneede J, Refsum H, Vollset SE. Biological and clinical implications of the MTHFR C677T polymorphism. Trends Pharmacol Sci 2001;22:195-201.
132. Carmel R. Folate Deficiency. In: Carmel R, Jacobsen D, eds. Homocysteine in Health and Disease. Cambridge, UK: Cambridge University Press, 2001:271-88.
133. Carmel R. Cobalamin Deficiency. In: Carmel R, Jacobsen D, eds. Homocysteine in Health and Disease. Cambridge, UK: Cambridge University Press, 2001:289-305.
134. Herbert V. Experimental Nutritional Folate Deficiency in Man. Trans Assoc Am Physicians 1961;75:307-20.
135. Alpert JE, Mischoulon D, Nierenberg AA, Fava M. Nutrition and depression: focus on folate. Nutrition 2000;16:544-6.
136. Lindeman RD, Romero LJ, Koehler KM, Liang HC, LaRue A, Baumgartner RN, Garry PJ. Serum vitamin B12, C and folate concentrations in the New Mexico elder health survey: correlations with cognitive and affective functions. J Am Coll Nutr 2000;19:68-76.
137. Penninx BW, Guralnik JM, Ferrucci L, Fried LP, Allen RH, Stabler SP. Vitamin B(12) deficiency and depression in physically disabled older women: epidemiologic evidence from the Women's Health and Aging Study. Am J Psychiatry 2000;157:715-21.
138. Tolmunen T, Voutilainen S, Hintikka J, Rissanen T, Tanskanen A, Viinamaki H, Kaplan GA, Salonen JT. Dietary folate and depressive symptoms are associated in middle-aged Finnish men. J Nutr 2003;133:3233-6.
139. Van Praag H. Neurotransmitters and CNS disease: depression. Lancet 1982;ii:1259-83.
140. Bottiglieri T, Hyland K, Reynolds EH. The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders. Drugs 1994;48:137-52.
141. Bottiglieri T, Laundy M, Crellin R, Toone BK, Carney MW, Reynolds EH. Homocysteine, folate, methylation, and monoamine metabolism in depression. J Neurol Neurosurg Psychiatry 2000;69:228-32.
142. Morris MS, Fava M, Jacques PF, Selhub J, Rosenberg IH. Depression and folate status in the US Population. Psychother Psychosom 2003;72:80-7.
143. Fava M, Borus JS, Alpert JE, Nierenberg AA, Rosenbaum JF, Bottiglieri T. Folate, vitamin B12, and homocysteine in major depressive disorder. Am J Psychiatry 1997;154:426-8.
144. Spillmann M, Fava M. S-Adenosylmethionine (Ademetionine) in Psychiatric Disorders. Historical Perspectives and Current Status. CNS Drugs 1996;6:416-25.
145. Allen RH, Stabler SP, Savage DG, Lindenbaum J. Metabolic abnormalities in cobalamin (vitamin B12) and folate deficiency. Faseb J 1993;7:1344-53.

146. Lindenbaum J, Healton EB, Savage DG, Brust JC, Garrett TJ, Podell ER, Marcell PD, Stabler SP, Allen RH. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 1988;318:1720-8.
147. Reynolds EH, Preece JM, Bailey J, Coppen A. Folate deficiency in depressive illness. Br J Psychiatry 1970;117:287-92.
148. Baldewicz TT, Goodkin K, Blaney NT, Shor-Posner G, Kumar M, Wilkie FL, Baum MK, Eisdorfer C. Cobalamin level is related to self-reported and clinically rated mood and to syndromal depression in bereaved HIV-1-super(+) and HIV-1-super(-) homosexual men. J Psychosom Res 2000;48:177-85.
149. Tiemeier H, Van Tuijl HR, Hofman A, Meijer J, Kiliaan AJ, Breteler MM. Vitamin b(12), folate, and homocysteine in depression: the rotterdam study. Am J Psychiatry 2002;159:2099-101.
150. Hintikka J, Tolmunen T, Tanskanen A, Viinamaki H. High vitamin B12 level and good treatment outcome may be associated in major depressive disorder. BMC Psychiatry 2003;3:17.
151. Kunugi H, Fukuda R, Hattori M, Kato T, Tatsumi M, Sakai T, Hirose T, Nanko S. C677T polymorphism in methylenetetrahydrofolate reductase gene and psychoses. Mol Psychiatry 1998;3:435-7.
152. Arinami T, Yamada N, Yamakawa-Kobayashi K, Hamaguchi H, Toru M. Methylenetetrahydrofolate reductase variant and schizophrenia/depression. Am J Med Genet 1997;74:526-8.
153. Passeri M, Cucinotta D, Abate G, Senin U, Ventura A, Stramba Badiale M, Diana R, La Greca P, Le Grazie C. Oral 5'-methyltetrahydrofolic acid in senile organic mental disorders with depression: results of a double-blind multicenter study. Aging (Milano) 1993;5:63-71.
154. Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. J Affect Disord 2000;60:121-30.
155. Goebel PN, Peter H, Mueller SK, Hand I. Neuroticism, other personality variables, and serum lipid levels in patients with anxiety disorders and normal controls. Int J Psychiatry Med 1998;28:449-62.
156. Coppen A, Chaudhry S, Swade C. Folic acid enhances lithium prophylaxis. J Affect Disord 1986;10:9-13.
157. Reynolds EH. Benefits and risks of folic acid to the nervous system. J Neurol Neurosurg Psychiatry 2002;72:567-71.
158. Edeh J, Toone BK. Antiepileptic therapy, folate deficiency, and psychiatric morbidity: a general practice survey. Epilepsia 1985;26:434-40.
159. Hermesh H, Weizman A, Shahar A, Munitz H. Vitamin B12 and folic acid serum levels in obsessive compulsive disorder. Acta Psychiatr Scand 1988;78:8-10.
160. Rutter M. Psychosocial influences: critiques, findings, and research needs. Dev Psychopathol 2000;12:375-405.
161. Dohrenwend B. Overview of Evidence for the Importance of Adverse Environmental Conditions in Causing Psychiatric Disorders. In: Dohrenwend B, ed. Adversity, Stress, and Psychopathology. New York, NY: Oxford University Press, 1998.
162. McEwen BS. Early life influences on life-long patterns of behavior and health. Ment Retard Dev Disabil Res Rev 2003;9:149-54.

163. Kessler RC, Davis CG, Kendler KS. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. Psychol Med 1997;27:1101-19.
164. Gilman SE, Kawachi I, Fitzmaurice GM, Buka SL. Family disruption in childhood and risk of adult depression. Am J Psychiatry 2003;160:939-46.
165. Brown GW, Harris TO, Eales MJ. Social factors and comorbidity of depressive and anxiety disorders. Br J Psychiatry 1996;(Suppl 30):50-7.
166. Dohrenwend BP. A psychosocial perspective on the past and future of psychiatric epidemiology. Am J Epidemiol 1998;147:222-31.
167. Taylor SE, Seeman TE. Psychosocial resources and the SES-health relationship. Ann N Y Acad Sci 1999;896:210-25.
168. Lorant V, Deliege D, Eaton W, Robert A, Philippot P, Ansseau M. Socioeconomic inequalities in depression: a meta-analysis. Am J Epidemiol 2003;157:98-112.
169. Eaton WW, Muntaner C, Bovasso G, Smith C. Socioeconomic status and depressive syndrome: the role of inter- and intra-generational mobility, government assistance, and work environment. J Health Soc Behav 2001;42:277-94.
170. Kaplan GA, Roberts RE, Camacho TC, Coyne JC. Psychosocial predictors of depression. Prospective evidence from the human population laboratory studies. Am J Epidemiol 1987;125:206-20.
171. Bracke P. The three-year persistence of depressive symptoms in men and women. Soc Sci Med 2000;51:51-64.
172. Sargeant JK, Bruce ML, Florio LP, Weissman MM. Factors associated with 1-year outcome of major depression in the community. Arch Gen Psychiatry 1990;47:519-26.
173. Dohrenwend BP, Levav I, Shrout PE, Schwartz S, Naveh G, Link BG, Skodol AE, Stueve A. Socioeconomic status and psychiatric disorders: the causation-selection issue. Science 1992;255:946-52.
174. Kessler RC, Foster CL, Saunders WB, Stang PE. Social consequences of psychiatric disorders, I: Educational attainment. Am J Psychiatry 1995;152:1026-32.
175. Johnson JG, Cohen P, Dohrenwend BP, Link BG, Brook JS. A longitudinal investigation of social causation and social selection processes involved in the association between socioeconomic status and psychiatric disorders. J Abnorm Psychol 1999;108:490-9.
176. West P. Rethinking the health selection explanation for health inequalities. Soc Sci Med 1991;32:373-84.
177. Stansfeld SA, Head J, Marmot MG. Explaining social class differences in depression and well-being. Soc Psychiatry Psychiatr Epidemiol 1998;33:1-9.
178. Lynch JW, Kaplan GA, Shema SJ. Cumulative impact of sustained economic hardship on physical, cognitive, psychological, and social functioning. N Engl J Med 1997;337:1889-95.
179. Entrez-Pubmed. National Library of Medicine 2000. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi.
180. ISI Web of Knowledge 2000. http://isi3.newisiknowledge.com/portal.cgi/wos.
181. PsychINFO. American Psychological Association 2000. http://www.apa.org/psycinfo/.
182. Helseundersøkelsen i Nord-Trøndelag (HUNT) 2004. http://www.hunt.folkehelsa.no/english/index.asp.

183. Tambs K, Moum T. Low genetic effect and age-specific family effect for symptoms of anxiety and depression in nuclear families, halfsibs and twins. J Affect Disord 1993;27:183-95.
184. Bush B, Shaw S, Cleary P, Delbanco TL, Aronson MD. Screening for alcohol abuse using the CAGE questionnaire. Am J Med 1987;82:231-5.
185. Fiskerstrand T, Refsum H, Kvalheim G, Ueland PM. Homocysteine and other thiols in plasma and urine: automated determination and sample stability. Clin Chem 1993;39:263-71.
186. Vollset SE, Refsum H, Tverdal A, Nygard O, Nordrehaug JE, Tell GS, Ueland PM. Plasma total homocysteine and cardiovascular and noncardiovascular mortality: the Hordaland Homocysteine Study. Am J Clin Nutr 2001;74:130-6.
187. Molloy AM, Scott JM. Microbiological assay for serum, plasma, and red cell folate using cryopreserved, microtiter plate method. Methods Enzymol 1997;281:43-53.
188. Kelleher BP, Broin SD. Microbiological assay for vitamin B12 performed in 96-well microtitre plates. J Clin Pathol 1991;44:592-5.
189. Ulvik A, Ueland PM. Single nucleotide polymorphism (SNP) genotyping in unprocessed whole blood and serum by real-time PCR: application to SNPs affecting homocysteine and folate metabolism. Clin Chem 2001;47:2050-3.
190. Hastie T, Tibshirani R. Generalized Additive Models. London: Chapman & Hall, 1990.
191. Altman DG. Practical Statistics for Medical Research. London, UK: Chapman & Hall/CRC, 1991.
192. el Rufaie OE, Absood GH. Retesting the validity of the Arabic version of the Hospital Anxiety and Depression (HAD) scale in primary health care. Soc Psychiatry Psychiatr Epidemiol 1995;30:26-31.
193. Langhammer A, Johnsen R, Holmen J, Gulsvik A, Bjermer L. Cigarette smoking gives more respiratory symptoms among women than among men. The Nord-Trondelag Health Study (HUNT). J Epidemiol Community Health 2000;54:917-22.
194. Hansen V, Jacobsen BK, Arnesen E. Prevalence of serious psychiatric morbidity in attenders and nonattenders to a health survey of a general population : the Tromso Health Study. Am J Epidemiol 2001;154:891-4.
195. Eaton WW, Anthony JC, Tepper S, Dryman A. Psychopathology and attrition in the epidemiologic catchment area surveys. Am J Epidemiol 1992;135:1051-9.
196. Allgulander C. Psychoactive drug use in a general population sample, Sweden: correlates with perceived health, psychiatric diagnoses, and mortality in an automated record-linkage study. Am J Public Health 1989;79:1006-10.
197. Jacomb PA, Jorm AF, Korten AE, Christensen H, Henderson AS. Predictors of refusal to participate: a longitudinal health survey of the elderly in Australia. BMC Public Health 2002;2:4.
198. Lydiard RB, Greenwald S, Weissman MM, Johnson J, Drossman DA, Ballenger JC. Panic disorder and gastrointestinal symptoms: findings from the NIMH Epidemiologic Catchment Area project. Am J Psychiatry 1994;151:64-70.
199. Alloy L, Kelly K, Mineka S, Clements C. Comorbidity of Anxiety and Depressive Disorders: A Helplessness-Hopelessness Perspective. In: Maser JD, Cloninger CR, eds. Comorbidity of Mood and Anxiety Disorders. Washington, DC: American Psychiatric Press, 1990:499-543.

200. Wittchen HU, Kessler RC, Pfister H, LIeb M. Why do people with anxiety disorders become depressed? A prospective-longitudinal community study. Acta Psychiatr Scand 2000;102 (Suppl):14-23.
201. Mykletun A, Stordal E, Dahl AA. The Hospital Anxiety and Depression Scale (HADS): Factor Structure, Item Analyses, and Internal Consistency in a Large Population. Br J Psychiatry 2001;179:540-4.
202. Burns DD, Eidelson RJ. Why are depression and anxiety correlated? A test of the tripartite model. J Consult Clin Psychol 1998;66:461-73.
203. Snaith P. Anhedonia: a neglected symptom of psychopathology. Psychol Med 1993;23:957-66.
204. Søgaard A, Bjelland I, Tell GS, Røysamb E. A comparison of the CONOR Mental Health Index to the HSCL-10 and HADS. Norsk Epidemiologi 2003;13:279-84.
205. Piccinelli M, Wilkinson G. Gender differences in depression. Critical review. Br J Psychiatry 2000;177:486-92.
206. Stordal E, Krüger MB, Dahl NH, Krüger Ø, Mykletun A, Dahl AA. Depression in relation to age and gender in the general population - the Nord-Trøndelag Health Study (HUNT). Acta Psychiatr Scand 2001;104:210-6.
207. Silverstein B. Gender difference in the prevalence of clinical depression: the role played by depression associated with somatic symptoms. Am J Psychiatry 1999;156:480-2.
208. Regier DA, Rae DS, Narrow WE, Kaelber CT, Schatzberg AF. Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders. Br J Psychiatry 1998;(Suppl):24-8.
209. Wittchen HU, Beesdo K, Bittner A, Goodwin RD. Depressive episodes - evidence for a causal role of primary anxiety disorders? Eur Psychiatry 2003;18:384-93.
210. Preisig M, Merikangas KR, Angst J. Clinical significance and comorbidity of subthreshold depression and anxiety in the community. Acta Psychiatr Scand 2001;104:96-103.
211. Andrews G, Slade T, Issakidis C. Deconstructing current comorbidity: data from the Australian National Survey of Mental Health and Well-Being. Br J Psychiatry 2002;181:306-14.
212. Emmanuel J, Simmonds S, Tyrer P. Systematic review of the outcome of anxiety and depressive disorders. Br J Psychiatry 1998;(Suppl):35-41.
213. Gross JJ, Carstensen LL, Pasupathi M, Tsai J, Skorpen CG, Hsu AY. Emotion and aging: experience, expression, and control. Psychol Aging 1997;12:590-9.
214. Lawton MP, Kleban MH, Rajagopal D, Dean J. Dimensions of affective experience in three age groups. Psychol Aging 1992;7:171-84.
215. Folkman S, Lazarus RS, Pimley S, Novacek J. Age differences in stress and coping processes. Psychol Aging 1987;2:171-84.
216. Drossman DA. Presidential address: Gastrointestinal illness and the biopsychosocial model. Psychosom Med 1998;60:258-67.
217. Haug TT, Mykletun A, Dahl AA. Are anxiety and depression related to gastrointestinal symptoms in the general population? Scand J Gastroenterol 2002;37:294-8.
218. Haug TT, Mykletun A, Dahl AA. The prevalence of nausea in the community: psychological, social and somatic factors. Gen Hosp Psychiatry 2002;24:81-6.
219. Drossman DA. The role of psychosocial factors in gastrointestinal illness. Scand J Gastroenterol 1996;(Suppl):1-4.

220. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med 1993;153:2093-101.
221. Baldwin RC, Tomenson B. Depression in later life. A comparison of symptoms and risk factors in early and late onset cases. Br J Psychiatry 1995;167:649-52.
222. Stordal E, Mykletun A, Dahl AA. The association between age and depression in the general population: a multivariate examination. Acta Psychiatr Scand 2003;107:132-41.
223. Winokur G, Black DW, Nasrallah A. Depressions secondary to other psychiatric disorders and medical illnesses. Am J Psychiatry 1988;145:233-7.
224. Weisberg I, Tran P, Christensen B, Sibani S, Rozen R. A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. Mol Genet Metab 1998;64:169-72.
225. Weisberg IS, Jacques PF, Selhub J, Bostom AG, Chen Z, Curtis Ellison R, Eckfeldt JH, Rozen R. The 1298A→C polymorphism in methylenetetrahydrofolate reductase (MTHFR): in vitro expression and association with homocysteine. Atherosclerosis 2001;156:409-15.
226. van der Put NM, Gabreels F, Stevens EM, Smeitink JA, Trijbels FJ, Eskes TK, van den Heuvel LP, Blom HJ. A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects? Am J Hum Genet 1998;62:1044-51.
227. Song C, Xing D, Tan W, Wei Q, Lin D. Methylenetetrahydrofolate reductase polymorphisms increase risk of esophageal squamous cell carcinoma in a Chinese population. Cancer Res 2001;61:3272-5.
228. Keku T, Millikan R, Worley K, Winkel S, Eaton A, Biscocho L, Martin C, Sandler R. 5,10-Methylenetetrahydrofolate reductase codon 677 and 1298 polymorphisms and colon cancer in African Americans and whites. Cancer Epidemiol Biomarkers Prev 2002;11:1611-21.
229. Skibola CF, Smith MT, Kane E, Roman E, Rollinson S, Cartwright RA, Morgan G. Polymorphisms in the methylenetetrahydrofolate reductase gene are associated with susceptibility to acute leukemia in adults. Proc Natl Acad Sci U S A 1999;96:12810-5.
230. Bjelland I, Ueland PM, Vollset SE. Folate and depression. Psychother Psychosom 2003;72:59-60.
231. Roberts RE. Prevalence of depressive symptoms among Mexican Americans. J Nerv Ment Dis 1981;169:213-9.
232. Moos R, Cronkite R, Billings A, Finney J. Health and Daily Living Form manual, revised version: Social Ecological Laboratory, Veterans Administration and Stanford University Medical Centers, 1985.
233. Ritsher JE, Warner V, Johnson JG, Dohrenwend BP. Inter-generational longitudinal study of social class and depression: a test of social causation and social selection models. Br J Psychiatry 2001;(Suppl):84-90.
234. Costello EJ, Compton SN, Keeler G, Angold A. Relationships between poverty and psychopathology: a natural experiment. Jama 2003;290:2023-9.
235. Baum A, Garofalo JP, Yali AM. Socioeconomic status and chronic stress. Does stress account for SES effects on health? Ann N Y Acad Sci 1999;896:131-44.
236. George LK, Blazer DG, Hughes DC, Fowler N. Social support and the outcome of major depression. Br J Psychiatry 1989;154:478-85.

237. McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. Ann N Y Acad Sci 1999;896:30-47.
238. Wilkinson RG. Health, hierarchy, and social anxiety. Ann N Y Acad Sci 1999;896:48-63.
239. Wilkinson RG. Socioeconomic determinants of health. Health inequalities: relative or absolute material standards? Bmj 1997;314:591-5.
240. Nesse RM. Is depression an adaptation? Arch Gen Psychiatry 2000;57:14-20.
241. van Os J, Park SB, Jones PB. Neuroticism, life events and mental health: evidence for person-environment correlation. Br J Psychiatry 2001;(Suppl):72-7.
242. Vollset SE, Lande B. Knowledge and attitudes of folate, and use of dietary supplements among women of reproductive age in Norway 1998. Acta Obstet Gynecol Scand 2000;79:513-9.
243. Refsum H, Ueland PM, Nygard O, Vollset SE. Homocysteine and cardiovascular disease. Annu Rev Med 1998;49:31-62.
244. Collaboration HS. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. Jama 2002;288:2015-22.
245. Kim YI. Folate and cancer prevention: a new medical application of folate beyond hyperhomocysteinemia and neural tube defects. Nutr Rev 1999;57:314-21.
246. Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol 1998;55:1449-55.
247. Selhub J, Bagley LC, Miller J, Rosenberg IH. B vitamins, homocysteine, and neurocognitive function in the elderly. Am J Clin Nutr 2000;71:614-20.
248. Scholl TO, Johnson WG. Folic acid: influence on the outcome of pregnancy. Am J Clin Nutr 2000;71:1295-303.
249. Nelen WL. Hyperhomocysteinaemia and human reproduction. Clin Chem Lab Med 2001;39:758-63.
250. Den Norske Mor & Barn undersøkelsen. Nasjonalt Folkehelseinstitutt 2004. http://www.fhi.no/
251. Barn i Bergen 2004. http://www.uib.no/bib/
252. Bjelland I. Associations between neurodevelopmental and emotional problems. European Child & Adolescent Psychiatry 2003;12 (Suppl 2):204.
253. Skrondal A, Rabe-Hesketh. Some applications of generalized linear latent and mixed models in epidemiology: Repeated measures, measurement error and multilevel modeling. Norsk Epidemiologi 2003;13:265-78.
254. Hoyle RH, Smith GT. Formulating clinical research hypotheses as structural equation models: a conceptual overview. J Consult Clin Psychol 1994;62:429-40.

APPENDIX I:

HUNT 1

QUESTIONNAIRE 1

MELDING OM SKJERMBILDEFOTOGRAFERING OG UNDERSØKELSE AV BLODTRYKK OG BLODSUKKER

Skjermbildefotograferingen kommer nå til ditt distrikt. Denne gangen inngår fotograferingen i en større helseundersøkelse, og vi viser til orienteringen som er gitt i den vedlagte brosjyre.

Tid og sted for frammøte vil du finne nedenfor.

Vennligst fyll ut spørreskjemaet på baksiden og ta det med til undersøkelsen. Ta også med skjermbildebevis, tuberkulinkort eller helsebok om du har.

Det er viktig at du møter fram selv om du nylig har fått kontrollert blodtrykk eller blodsukker, og selv om du er under behandling for høyt blodtrykk eller for sukkersyke.

Med vennlig hilsen

Statens skjermbildefotografering

Postboks 8155 Dep, Oslo 1

Fylkeslegen • Helserådet • Statens Institutt For Folkehelse

Født dato | Personnr. | Kommune | Kretsnr.

Møtested | Kjønn | Første bokstav etternavn | Dag og dato | Klokkeslett

H. 14 | V. 18 | SBT_1 21 | DBT_1 24 | PULS 27 | SBT_2 30 | DBT_2 33 | SYKEPL 35

TID 36 | GLUC 39 | $GLUC_2$ 42 | $GLUC_2$ 45 | HG 46 | BT 47 | P 48 | Ø.M. 49

A. Hvordan er helsa di for tida?
(Sett kryss i bare *en* rute.)

Dårlig	50	1
Ikke helt god		2
God		3
Svært god		4

B. Har du i løpet av de siste 12 måneder vært hos?

	JA	NEI
Almenpraktiserende lege (distriktslege, privatpraktiserende lege,turnuskandidat)	51	
Bedriftslege	52	
Militærlege	53	
Lege ved sykehus (uten at du var innlagt)	54	
Annen lege	55	

C. Har du vært innlagt i sykehus de siste 5 åra? 56

D. Bruker du, eller har du brukt, medisin for høyt blodtrykk? 57

E. Har du eller har du hatt noen av disse sykdommene?

	JA	NEI
Sukkersyke	58	
Hjerteinfarkt	59	
Angina pectoris (hjertekrampe)	60	
Hjerneslag eller hjerneblødning	61	

F. Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? (Med langvarig menes at det har vart, eller vil vare i minst ett år.) 62

Hvis «JA», vil du si at dine funksjoner er litt, middels eller mye nedsatt?

	LITT	MIDDELS	MYE
Er bevegelseshemmet	63		
Har nedsatt syn	64		
Har nedsatt hørsel	65		
Hemmet pga. kroppslig sykdom	66		
Hemmet pga. psykiske plager	67		

G. Har du noen søsken? (Nålevende eller døde) 68

Hvis «JA», har en eller flere av dem hatt noen av disse sykdommene?

	JA	NEI	VET IKKE
Sukkersyke	69		
Hjerteinfarkt/hjertekrampe	70		
Forhøyet blodtrykk	71		

H. Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen, eller er du stort sett misfornøyd?
(Sett kryss i bare *en* rute.)

Svært fornøyd	72	1
Meget fornøyd		2
Ganske fornøyd		3
Både/og		4
Nokså misfornøyd		5
Meget misfornøyd		6
Svært misfornøyd		7

SE BILDET AV BLODTRYKKSMÅLINGEN I DEN VEDLAGTE BROSJYREN

	JA	NEI	VET IKKE
I. Er blodtrykket ditt målt noen gang før? Hvis «NEI», gå videre til spørsmål M	73		

J. Hvilket år ble blodtrykket målt siste gang?

19 ☐☐ vet ikke 74

Skriv årstallet her (ca.)

K. Hvor ble blodtrykket målt siste gang?
(Sett kryss i bare *en* rute.)

Hos almenpraktiserende lege (distriktslege, privatpraktiserende lege, turnuskandidat	76	1
Hos bedriftslege		2
Hos militærlege		3
På sykehus		4
Hos annen lege		5
Vet ikke		6

L. Hva ble resultatet av målingen?
(Sett kryss i bare *en* rute.)

Jeg skulle begynne med eller fortsette med medisin for høyt blodtrykk	77	1
Jeg skulle komme til kontroll, men skulle *ikke* ta medisin		2
Jeg skulle *ikke* ta medisin og *ikke* komme til kontroll		3

M. Dersom denne helseundersøkelsen viser at du bør undersøkes nærmere: Hvilken almenpraktiserende lege ønsker du da å bli henvist til?

Skriv navnet på legen her

_____

Ingen spesiell lege.. 78

IKKE SKRIV HER

OM ARBEIDET DITT

N. Er du i arbeid for tida?
(Sett kryss i bare *en* rute.)

Ja, heltidsarbeid (utenom husarbeid)	81	1
Ja, deltidsarbeid (utenom husarbeid)		2
Ja, heltids husarbeid		3
Nei, ikke i arbeid		4

O. Hvis du ikke er i heltids arbeid, er det på grunn av:
(Sett kryss i bare *en* rute.)

Arbeidsløshet, permittering	82	1
Pensjon eller trygd		2
Utdanning eller militærtjeneste		3
Annet		4

HVIS DU ER I ARBEID, VENNLIGST SVAR PÅ DE NESTE TO SPØRSMÅLENE

P. Er det mye stress og mas på arbeidet ditt?
(Sett kryss i bare *en* rute.)

Nei, ikke i det hele tatt	83	1
Sjelden		2
Ja, en god del		3
Ja, nesten hele tida		4

Q. Kan du sjøl bestemme hvordan arbeidet ditt skal legges opp? (Sett kryss i bare *en* rute)

Nei, ikke i det hele tatt	84	1
I liten grad		2
Ja, stort sett		3
Ja, det bestemmer jeg sjøl		4

APPENDIX II:

HUNT 1

QUESTIONNAIRE 2

Vi takker for frammøtet til undersøkelsen.

Vi vil også be deg være vennlig å fylle ut dette spørreskjemaet. Opplysninger vil bli brukt i et større forskningsarbeid om forhold som har betydning for helsen.

Svar etter beste skjønn. Kryss av for bare en av svar-mulighetene (dersom det ikke står nevnt noe annet). Det utfylte skjema returneres i vedlagte svarkonvolutt. Porto er betalt.

Alle opplysningene er underlagt streng taushetsplikt.

Med hilsen

Statens skjermbildefotografering
Fylkeslegen ● Helserådet ● Statens Institutt For Folkehelse
Institutt for anvendt sosialvitenskapelig forskning/
Institutt for samfunnsforskning

Til etikett

Navn: _____

Adr. : _____

_____

_____

Postnr. Postkontor

F.nr. : _____

MOSJON

Med mosjon mener vi at du f.eks. går tur, går på ski, svømmer eller driver trening/idrett.

Hvor ofte driver du mosjon?
(Ta et gjennomsnitt)

Aldri	12	1
Sjeldnere enn en gang i uka		2
En gang i uka		3
2–3 ganger i uka		4
Omtrent hver dag		5

Dersom du driver slik mosjon så ofte som en eller flere ganger i uka:
Hvor hardt mosjonerer du?
(Ta et gjennomsnitt)

Tar det rolig uten å bli andpusten eller svett	13	1
Tar det så hardt at jeg blir andpusten og svett		2
Tar meg nesten helt ut		3

Hvor lenge holder du på hver gang?
(Ta et gjennomsnitt)

Mindre enn 15 minutter	14	1
16–30 minutter		2
30 minutter–1 time		3
Mer enn 1 time		4

SALT

Hvor ofte bruker du salt kjøtt eller salt fisk/sild til middag?

Aldri, eller sjeldnere enn en gang i måneden	15	1
1–2 ganger i måneden		2
Opptil en gang i uka		3
Opptil to ganger i uka		4
Mer enn to ganger i uka		5

Hvor ofte pleier du å strø ekstra salt på middagsmaten?

Sjelden eller aldri	16	1
Av og til		2
Ofte		3
Alltid eller nesten alltid		4

RØYKEVANER

		JA	NEI
Røyker du daglig for tiden?	17		
Hvis du svarte «JA», røyker du DAGLIG for tiden:		JA	NEI
Sigaretter?	18		
Pipe?	19		
Sigarer (eller serutter/sigarillos)?	20		
Hvis du IKKE røyker SIGARETTER daglig for tiden: Har du røykt SIGARETTER daglig tidligere?	21	JA	NEI

Hvis du svarte «JA», hvor lenge er det siden du sluttet å røyke sigaretter daglig?

Mindre enn 3 måneder	22	1
3 måneder– 1 år		2
1–5 år		3
Mer enn 5 år		4

Hvis du røyker SIGARETTER daglig nå, eller har gjort det tidligere:

Hvor mange sigaretter røyker eller røykte du pr. dag? (Oppgi antall pr. dag medregnet håndrullede) 23 — Antall

Besvares av dem som røyker daglig nå eller har røykt daglig tidligere:
(Gjelder både sigarett-, pipe- og sigar-røykere)

Hvor gammel var du da du begynte å røyke daglig? 25 — år

Hvor mange år tilsammen har du røykt daglig? 27 — år

ALKOHOLBRUK

Hvor ofte har du drukket alkohol (øl, vin eller brennevin) de SISTE 14 DAGENE?

Jeg har ikke drukket alkohol, men er ikke totalavholdende	29	1
Jeg har drukket 1–4 ganger		2
Jeg har drukket 5–10 ganger		3
Jeg har drukket mer enn 10 ganger		4
Jeg er totalavholdende, drikker aldri alkohol		5

		JA	NEI
Dersom du har drukket alkohol de siste 14 dagene, har det ført til at du noen gang har følt deg beruset?	30		

Har det vært perioder i livet ditt da du har drukket for mye, eller i hvert fall i meste laget?

Nei	31	1
I tvil, kanskje		2
Ja		3

BOSITUASJONEN

Bor du alene eller sammen med andre?
Kryss av for de du bor sammen med. (Her kan du sette flere kryss.)

Bor alene	32	
Ektefelle eller samboer	33	
Foreldre eller svigerforeldre	34	
Andre voksne personer	35	
Barn under 5 år	36	
Barn 6–15 år	37	
Barn over 15 år	38	

Bor du fast i institusjon?
(sykehjem, aldershjem eller liknende) 39

JA	NEI

UTDANNINGEN

Hvilken utdanning har du fullført?
Oppgi bare høyest fullførte utdanning.

7-årig folkeskole eller kortere	40	1
Framhalds- eller fortsettelsesskole		2
9-årig grunnskole		3
Real- eller middelskole, grunnskolens 10. år		4
Ett- eller to-årig videregående skole		5
Artium, økonomisk gymnas eller almenfaglig retning i videregående skoler		6
Høyskole eller universitet, mindre enn 4 år		7
Høyskole eller universitet, 4 år eller mer		8

Har du fullført annen heldags utdanning, og i tilfelle i hvor mange år?

Skriv antall år her .... 41 ____ år

ARBEID

Hvis du er eller har vært i inntektsgivende arbeid, kan du angi hvilken av disse yrkesgruppene ditt yrke faller innenfor? (Hvis du ikke er i arbeid nå, svarer du ut fra det yrket du hadde sist.)

Hvis du har en ektefelle (eller samboer) som er i inntektsgivende arbeid nå, eller har vært det tidligere, angi tilsvarende hvilken yrkesgruppe han/hun tilhører. (Evt. angi om han/hun *ikke* har hatt inntektsgivende arbeid.)

		Deg selv	Ektefellen
Spesialarbeider, ufaglært arbeider	43, 44		1
Fagarbeider, håndverker, formann			2
Underordnet funksjonær (butikk, kontor, offentlige tjenester)			3
Fagfunksjonær (f.eks. sykepleier, tekniker, lærer)			4
Overordnet stilling i offentlig eller privat virksomhet			5
Gårdbruker eller skogeier			6
Fisker			7
Selvstendig i akademisk erverv (f.eks. tannlege, advokat)			8
Selvstendig næringsdrivende (Industi, transport, handel)			9
Har *ikke* hatt inntektsgivende arbeid (f.eks. pga. heltids husarbeid, studier, trygd)			0

Hvis du er i arbeid (gjelder også heltids husarbeid), **ber vi deg fylle ut de neste spørsmålene:**

Er arbeidet ditt så fysisk anstrengende at du ofte er sliten i kroppen etter en arbeidsdag?

Ja, nesten alltid	45	1
Ganske ofte		2
Ganske sjelden		3
Aldri, eller nesten aldri		4

Krever arbeidet ditt så mye konsentrasjon og oppmerksomhet at du ofte føler deg utslitt etter en arbeidsdag?

Ja, nesten alltid	46	1
Ganske ofte		2
Ganske sjelden		3
Aldri, eller nesten aldri		4

Hvordan trives du alt i alt med arbeidet ditt?

Veldig godt	47	1
Ganske godt		2
Godt		3
Ikke særlig godt		4
Dårlig		5

Hvis du er gårdbruker eller annen selvstendig næringsdrivende, har du noen ansatte som arbeider fast for deg?

Ingen fast ansatte	48	1
1–2 fast ansatte		2
3–10 fast ansatte		3
Mer enn 10 fast ansatte		4

HVORDAN HAR DU DET?

Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen, eller er du stort sett misfornøyd?

Svært fornøyd	49	1
Meget fornøyd		2
Nokså fornøyd		3
Både - og		4
Nokså misfornøyd		5
Meget misfornøyd		6
Svært misfornøyd		7

Føler du deg stort sett sterk og opplagt, eller trett og sliten?

Meget sterk og opplagt	50	1
Sterk og opplagt		2
Ganske sterk og opplagt		3
Både - og		4
Ganske trett og sliten		5
Trett og sliten		6
Svært trett og sliten		7

MEDISIN/PLAGER

Har du vanligvis:

		JA	NEI
Hoste om morgenen?	51	☐	☐
Oppspytt fra brystet om morgenen?	52	☐	☐

Hvor ofte har du brukt smertestillende medisin den siste måneden?

Daglig	53	1
Hver uke, men ikke hver dag		2
Sjeldnere enn hver uke		3
Aldri		4

Hvor ofte har du brukt avslappende/beroligende medisin eller sovemedisin den siste måneden?

Daglig	54	1
Hver uke, men ikke hver dag		2
Sjeldnere enn hver uke		3
Aldri		4

Har du i løpet av siste måned vært plaget av nervøsitet (irritabel, urolig, anspent eller rastløs)**?**

Nesten hele tida	55	1
Ofte		2
Av og til		3
Aldri		4

Har du i løpet av siste måned hatt innsoving- eller søvnproblemer?

Nesten hver natt	56	1
Ofte		2
Av og til		3
Aldri		4

Har du i det store og hele en rolig og god følelse inne i deg?

Nesten hele tida	57	1
Ofte		2
Av og til		3
Aldri		4

VENNER/HJELP

Dersom du ble syk og måtte holde senga i lengre tid, hvor sannsynlig tror du det er at du kunne få nødvendig hjelp og støtte av familie, venner eller naboer?

Svært sannsynlig	58	1
Nokså sannsynlig		2
Usikkert		3
Usannsynlig		4
Helt usannsynlig		5

Hender det ofte at du føler deg ensom?

Meget ofte	59	1
Ofte		2
Av og til		3
Meget sjelden		4
Aldri		5

HVORDAN ER DU?

Har du tendens til å ta dine oppgaver mer alvorlig enn folk flest?

Ja, nettopp slik er jeg	60	1
Ja, stort sett		2
Både - og		3
Nei, stort sett ikke		4
Nei, tvert imot		5

		JA	NEI	VET IKKE
Har du i løpet av det siste året ofte følt at du har presset deg, eller stadig drevet deg selv framover?	61	☐	☐	☐

Føler du deg alltid under tidspress, også når det gjelder daglige gjøremål?

Alltid, eller nesten alltid	62	1
Noen ganger		2
Aldri		3

Er du vanligvis glad eller nedstemt?

Svært nedstemt	63	1
Nedstemt		2
Nokså nedstemt		3
Både - og		4
Nokså glad		5
Glad		6
Svært glad		7

HVA ER VIKTIG?

Synes du det er viktig at man prøver å være fornøyd med det man har?

Dette er særlig viktig	64	1
Dette er viktig		2
Både - og		3
Dette er mindre viktig		4
Dette er overhodet ikke viktig		5

Synes du det er viktig at man kan slå av på kravene?

Dette er særlig viktig	65	1
Dette er viktig		2
Både - og		3
Dette er mindre viktig		4
Dette er overhodet ikke viktig		5

Synes du det er viktig at man alltid er i godt humør?

Dette er særlig viktig	66	1
Dette er viktig		2
Både - og		3
Dette er mindre viktig		4
Dette er overhodet ikke viktig		5

Tusen takk for den hjelp du har gitt oss ved å fylle ut dette skjema.

APPENDIX III:

HUNT 2

QUESTIONNAIRE 1

HELSEUNDERSØKELSEN
I NORD-TRØNDELAG

«JA, nå er det min tur!»

Personlig innbydelse

Spørreskjemaet er en viktig del av Helseundersøkelsen. Her finner du spørsmål om tidligere sykdom og om andre forhold som har betydning for helsa. Vennligst fyll ut skjemaet på forhånd og ta det med til Helseundersøkelsen. Dersom enkelte spørsmål er uklare, lar du dem bare stå ubesvarte til du møter fram, og drøfter dem med personalet som gjennomfører undersøkelsen. Alle svar vil bli behandlet strengt fortrolig.

Flere steder i skjemaet ber vi deg oppgi din alder da eventuell sykdom inntrådte. Hvis du ikke husker nøyaktig hvor gammel du var, skriver du et tall som er nærmest det du antar er korrekt.

Når resultatene fra undersøkelsen foreligger, vil det være enkelte som trenger ny undersøkelse hos egen lege. Dette vil du få beskjed om i det brevet som vi sender deg om dine resultater. Samtidig sender vi melding om resultatene dine til legen din. Det er derfor om å gjøre at du i rubrikken helt til slutt i skjemaet oppgir navnet på den allmennpraktiserende lege, kommunelege eller det helsesenter som du ønsker skal ta hånd om eventuell etterundersøkelse, og som vi skal sende resultatene til.

Med vennlig hilsen

Helsetjenesten i Nord-Trøndelag • Statens helseundersøkelser • Statens Institutt for Folkehelse

DET HANDLER OM HELSA DI

Hvordan er helsa di nå?

Bare ett kryss

Dårlig	12	☐ 1
Ikke helt god		☐ 2
God		☐ 3
Svært god		☐ 4

LUFTVEGSPLAGER

	JA	NEI
Hoster du daglig i perioder av året?		
Hvis JA:		
Er hosten vanligvis ledsaget av oppspytt? .. 14		
Har du hatt hoste med oppspytt i minst 3 mnd. sammenhengende i hvert av de to siste åra?		
Har du hatt noe anfall med pipende eller tung pust de siste 12 måneder? 16		

	JA	NEI	Alder første gang
Har du eller har du hatt astma? 17			år

	JA	NEI
Har du brukt eller bruker du astmamedisiner? 20		

HJERTE-KARSYKDOMMER, DIABETES

Har du, eller har du hatt:	JA	NEI	Alder første gang
Hjerteinfarkt 21			år
Angina pectoris (hjertekrampe) 24			år
Hjerneslag/hjerneblødning 27			år
Diabetes (sukkersyke) 30			år

Hva ble resultatet siste gang du målte blodtrykket ditt?

Bare ett kryss

Begynne med/fortsette med blodtrykksmedisin	33	☐ 1
Komme til kontroll, men ikke ta blodtrykksmedisin		☐ 2
Ingen kontroll og ingen medisin nødvendig		☐ 3
Har aldri fått målt blodtrykket		☐ 4

Bruker du medisin mot høyt blodtrykk?

Bare ett kryss

Nå	34	☐ 1
Før, men ikke nå		☐ 2
Aldri brukt		☐ 3

	JA	NEI	VET IKKE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)?			

STOFFSKIFTE

Har du noen gang fått påvist:	JA	NEI	Alder første gang
for høyt stoffskifte 36			år
for lavt stoffskifte 39			år
struma 42			år
annen sykdom i skjoldbruskkjertelen			år
Bruker du eller har du brukt noen av disse medisinene:			
Thyroxin 48			år
Neo-Mercazole 51			år
Er du operert i skjoldbruskkjertelen			år
Har du fått radiojodbehandling 57			år

MUSKEL/SKJELETT-PLAGER

	JA	NEI
Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende? 60		

Hvis NEI, gå videre til neste side øverst.

Hvis JA, svar på følgende:

Hvor har du hatt disse plagene?	JA	NEI
Nakke 61		
Skuldre (aksler)		
Albuer		
Håndledd, hender		
Bryst/mage 65		
Øvre del av ryggen		
Korsryggen		
Hofter		
Knær		
Ankler, føtter 70		

Hvis du har hatt plager i flere områder i minst 3 mnd. det siste året, setter du ring rundt det ja-krysset hvor plagene har vart lengst

Hvor lenge har plagene vart sammenhengende?

Svar for det området hvor plagene har vart lengst

Hvis under 1 år, oppgi antall mnd. . 71	Antall mnd.
Hvis 1 år eller mer, oppgi antall år.. 73	Antall år

Har plagene redusert din arbeidsevne det siste året?

Gjelder også hjemmearbeidende. Bare ett kryss

Nei/ubetydelig	I noen grad	I betydelig grad	Vet ikke
☐	☐	☐	☐

	JA	NEI	IKKE I ARBEID
Har du vært sykmeldt pga. disse plagene det siste året? 76			

	JA	NEI
Har plagene ført til redusert aktivitet i fritida?		

Har lege noen gang sagt at du har/har hatt noen av disse sykdommene:

	JA	NEI
Beinskjørhet (osteoporose) 78		
Fibromyalgi (fibrositt/kronisk smertesyndrom)		
Leddgikt (reumatoid artritt)		
Slitasjegikt (artrose)		
Bechterews sykdom 82		
Andre langvarige skjelett- eller muskelsykdommer		

Har du noen gang hatt:

	JA	NEI	Alder *siste* gang
Lårhalsbrudd 84			år
Brudd i håndledd/underarm 87			år
Nakkesleng (whiplash) 90			år
Skade som førte til sykehusinnleggelse			år

ANDRE PLAGER

I hvilken grad har du hatt disse plagene i de siste 12 månedene?

	Ikke plaget	Litt plaget	Mye plaget
Kvalme 96	☐	☐	☐
Brystbrann/sure oppstøt	☐	☐	☐
Diaré	☐	☐	☐
Treg mage	☐	☐	☐
Hjertebank	☐	☐	☐
Åndenød 101	☐	☐	☐

ANDRE SYKDOMMER

Har du eller har du noen gang hatt:

	JA	NEI	Alder første gang
Epilepsi 102			år
Psykiske plager hvor du har søkt hjelp			år
Kreftsykdom 108			år
Annen langvarig sykdom 111			

DAGLIGE FUNKSJONER

Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? ... 112

JA	NEI

Langvarig: minst ett år

Hvis JA:

Hvor mye vil du si at dine funksjoner er nedsatt?

	Litt nedsatt	Middels nedsatt	Mye nedsatt
Er bevegelseshemmet 113	☐	☐	☐
Har nedsatt syn	☐	☐	☐
Har nedsatt hørsel	☐	☐	☐
Hemmet pga. kroppslig sykdom.	☐	☐	☐
Hemmet pga. psykiske plager... 117	☐	☐	☐

MENN fortsetter øverst neste spalte

BESVARES BARE AV KVINNER

Hvor mange barn har du født?..... 118
Sett 0 hvis du ikke har født barn

Antall barn

Hvis du har født barn, besvar:

Hvor gammel var du da du fødte ditt første barn? 120

Alder ____ år

Hvor gammel var du da du fødte ditt siste barn? 122
Besvares ikke hvis du har født bare ett barn

____ år

Hvor gammel var du da du fikk menstruasjon? 124
Sett 0 hvis du ikke noen gang har hatt menstruasjon

____ år

Fortsett neste spalte øverst

RØYKING

Røykte noen av de voksne hjemme da du vokste opp? 126

JA	NEI

Bor du, eller har du bodd, sammen med noen dagligrøykere etter at du fylte 20 år? 127

JA	NEI

Hvor lenge er du vanligvis daglig til stede i røykfylt rom? 128
Sett 0 hvis du ikke oppholder deg i røykfylt rom

Antall timer

Røyker du selv?

	JA	NEI
Sigaretter daglig? 130		
Sigarer/sigarillos daglig?		
Pipe daglig? 132		

Aldri røykt daglig ..... *(Sett kryss)* ☐

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?..... 134

Antall år

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? 136

Antall sigaretter

Hvor gammel var du da du begynte å røyke daglig?..... 140

Alder ____ år

Hvor mange år tilsammen har du røykt daglig? 142

Antall år

KAFFE/TE/ALKOHOL

Hvor mange kopper kaffe/te drikker du daglig?
Sett 0 hvis du ikke drikker kaffe/te daglig

	Antall kopper
Kokekaffe 144	
Annen kaffe 146	
Te 148	

Alkohol:
Er du total avholdsmann/-kvinne? 150

JA	NEI

Hvor mange ganger i måneden drikker du vanligvis alkohol? 151
Regn ikke med lettøl. Sett 0 hvis mindre enn 1 gang i mnd.

Antall ganger

Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av to uker?

Regn ikke med lettøl.
Sett 0 hvis du ikke drikker alkohol 153

Øl	Vin	Brennevin
glass	glass	glass

FYSISK AKTIVITET

I FRITIDA

Hvordan har din fysiske aktivitet i fritida vært det siste året? *Tenk deg et ukentlig gjennomsnitt for året.*

Arbeidsveg regnes som fritid

	Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)* 159	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)* 160	☐ 1	☐ 2	☐ 3	☐ 4

UNDER ARBEID
Hvis du er i lønnet eller ulønnet arbeid:

Hvorledes vil du beskrive arbeidet ditt?
Bare ett kryss

For det meste stillesittende arbeid
(f.eks. skrivebordsarbeid, montering) ..... 161 ☐ 1

Arbeid som krever at du går mye
(f.eks. ekspeditørarb., lett industriarb., undervisning) ..... ☐ 2

Arbeid hvor du går og løfter mye
(f.eks. postbud, pleier, bygningsarbeid) ..... ☐ 3

Tungt kroppsarbeid
(f.eks. skogsarbeid, tungt jordbruksarb.,tungt bygningsarb.) ☐ 4

Bla om!

HVORLEDES FØLER DU DEG?

Har du de siste to ukene følt deg:

	Nei	Litt	En god del	Svært mye
Trygg og rolig? 162	☐	☐	☐	☐
Glad og optimistisk?	☐	☐	☐	☐
Har du følt deg:				
Nervøs og urolig?	☐	☐	☐	☐
Plaget av angst? 165	☐	☐	☐	☐
Irritabel?	☐	☐	☐	☐
Nedfor/deprimert?	☐	☐	☐	☐
Ensom? 168	☐ 1	☐ 2	☐ 3	☐ 4

*Her kommer noen flere spørsmål om hvorledes du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser **den siste uka.** Ikke tenk for lenge på svaret - de spontane svarene er best*

Jeg gleder meg fortsatt over ting slik jeg pleide før 169
Avgjort like mye ..... ☐ 1 Bare lite grann ..... ☐ 3
Ikke fullt så mye ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg har en urofølelse som om noe forferdelig vil skje 170
Ja, og noe svært ille .... ☐ 1 Litt, bekymrer meg lite . ☐ 3
Ja, ikke så veldig ille ... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg kan le og se det morsomme i situasjoner 171
Like mye nå som før .... ☐ 1 Avgjort ikke som før .... ☐ 3
Ikke like mye nå som før ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg har hodet fullt av bekymringer 172
Veldig ofte ..... ☐ 1 Av og til ..... ☐ 3
Ganske ofte ..... ☐ 2 En gang i blant ..... ☐ 4

Jeg er i godt humør 173
Aldri ..... ☐ 1 Ganske ofte ..... ☐ 3
Noen ganger ..... ☐ 2 For det meste ..... ☐ 4

Jeg kan sitte i fred og ro og kjenne meg avslappet 174
Ja, helt klart ..... ☐ 1 Ikke så ofte ..... ☐ 3
Vanligvis ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg føler meg som om alt går langsommere 175
Nesten hele tiden ..... ☐ 1 Fra tid til annen ..... ☐ 3
Svært ofte ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg føler meg urolig som om jeg har sommerfugler i magen 176
Ikke i det hele tatt ..... ☐ 1 Ganske ofte ..... ☐ 3
Fra tid til annen ..... ☐ 2 Svært ofte ..... ☐ 4

Jeg bryr meg ikke lenger om hvordan jeg ser ut 177
Ja, har sluttet å bry meg ☐ 1 Kan hende ikke nok .... ☐ 3
Ikke som jeg burde ..... ☐ 2 Bryr meg som før ..... ☐ 4

Jeg er rastløs som om jeg stadig må være aktiv 178
Uten tvil svært mye ..... ☐ 1 Ikke så veldig mye ..... ☐ 3
Ganske mye..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg ser med glede frem til hendelser og ting 179
Like mye som før ..... ☐ 1 Avgjort mindre enn før . ☐ 3
Heller mindre enn før ... ☐ 2 Nesten ikke i det hele tatt ☐ 4

Jeg kan plutselig få en følelse av panikk 180
Uten tvil svært ofte ..... ☐ 1 Ikke så veldig ofte ..... ☐ 3
Ganske ofte ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg kan glede meg over gode bøker, radio og TV 181
Ofte ..... ☐ 1 Ikke så ofte ..... ☐ 3
Fra tid til annen ..... ☐ 2 Svært sjelden ..... ☐ 4

UTDANNING

Hvilken utdanning er den høyeste du har fullført?

Grunnskole 7-10 år, framhaldsskole, folkehøgskole ..... 182 ☐ 1
Realskole, middelskole, yrkesskole, 1-2 årig videregående skole ..... ☐ 2
Artium, øk.gymnas, allmennfaglig retning i videregående skole ..... ☐ 3
Høgskole/universitet, mindre enn 4 år ..... ☐ 4
Høgskole/universitet, 4 år eller mer ..... ☐ 5

ARBEID

Hva slags arbeidssituasjon har du nå?
Ett eller flere kryss

Lønnet arbeid ..... 183 ☐
Selvstendig næringsdrivende..... ☐
Heltids husarbeid ..... ☐
Utdanning, militærtjeneste ..... ☐
Arbeidsledig, permittert..... ☐
Pensjonist/trygdet..... 188 ☐

Hvor mange timer lønnet arbeid har du i uka? ..... 189 Antall timer

Har du skiftarbeid, nattarbeid eller går vakt?

JA	NEI

ALT I ALT

Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd?
Bare ett kryss

Svært fornøyd ..... 192 ☐ 1
Meget fornøyd ..... ☐ 2
Ganske fornøyd..... ☐ 3
Både/og..... ☐ 4
Nokså misfornøyd ..... ☐ 5
Meget misfornøyd..... ☐ 6
Svært misfornøyd..... ☐ 7

DIN LEGE

Hvis denne helseundersøkelsen viser at du bør undersøkes nærmere, hvilken allmennpraktiserende lege/kommunelege ønsker du skal foreta undersøkelsen?

Skriv navnet på legen her: 193

Ikke skriv her

Takk for utfyllingen!

Nok en gang:

Velkommen til undersøkelsen!

IE 332 5201 - 50.000 - 09.96

APPENDIX IV:

HUNT 2

QUESTIONNAIRE 2

(The chosen questionnaire is for men aged 20-69 years, but it contains all the relevant items for the other age and gender groups as well)

hunt

Helseundersøkelsen i Nord-Trøndelag

SKJEMA FOR MENN 20–69 ÅR

Takk for frammøtet til undersøkelsen!

Vi vil også be deg fylle ut dette spørreskjemaet. Opplysningene vil bli brukt i større forskningsarbeider om forebyggende helsearbeid. Noen av spørsmålene likner på spørsmål du har svart på i det skjemaet du fylte ut heime og leverte ved frammøte til helseundersøkelsen. Det er likevel viktig at du svarer på alle spørsmålene også i dette skjemaet. Det utfylte skjemaet returneres i vedlagte svarkonvolutt. Porto er betalt.

Alle opplysningene er underlagt streng taushetsplikt.

Vennlig hilsen

Helsetjenesten i Nord-Trøndelag

Statens Institutt for Folkehelse Statens helseundersøkelser

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss her og returner skjemaet. Da slipper du purring.

Jeg ønsker ikke å besvare skjemaet ○

UTFYLLING

Dato for utfylling av skjema: / 19 19

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

*Hvis du ikke bodde i Norge, oppgi **land** i stedet for kommune.*

24

ARBEID

Nåværende eller tidligere arbeid:

Hva slags inntektsgivende arbeid har du og event. din ektefelle/samboer? *Hvis du/dere ikke har inntektsgivende arbeid nå: Oppgi det siste yrket.*

		Deg selv		Ektefelle/ samboer	
Spesialarbeider eller ufaglært arbeider	25	☐		☐	36
Fagarbeider, handverker, formann		☐		☐	
Underordnet funksjonær (f.eks. butikk, kontor, off. tjenester)		☐		☐	
Fagfunksjonær (f.eks. sykepleier, tekniker, lærer)		☐		☐	
Overordnet stilling i off. eller privat virksomhet		☐		☐	
Sjåfør	30	☐		☐	41
Gårdbruker eller skogeier		☐		☐	
Fisker		☐		☐	
Selvstendig i akademisk erverv (f.eks. tannlege, advokat)		☐		☐	
Annen selvstendig næringsvirksomhet		☐		☐	
Har ikke vært i inntektsgivende arbeid	35	☐		☐	46

Hvis du NÅ ikke har inntektsgivende arbeid eller du ikke har heltids husarbeid: Gå til BOLIG.

Har du i løpet av de siste 12 månedene hatt sykefravær:

		Ja	Nei
med egenmelding	47	☐	☐
med sykmelding fra lege	48	☐	☐

Hvis «Ja»: **Hvor lenge *tilsammen*?** *Bare ett kryss*

2 uker eller mindre	49	☐ 1
2-8 uker		☐ 2
Mer enn 8 uker		☐ 3

Har du i løpet av de siste 12 månedene vurdert å skifte yrke eller arbeidsplass? 50 Ja ☐ Nei ☐

Er arbeidet ditt så fysisk anstrengende at du ofte er sliten i kroppen etter en arbeidsdag? *Bare ett kryss* 51

Ja, nesten alltid ☐ 1 Ganske sjelden ☐ 3
Ganske ofte ☐ 2 Aldri, eller nesten aldri ☐ 4

Krever arbeidet ditt så mye konsentrasjon og oppmerksomhet at du ofte føler deg utslitt etter en arbeidsdag? 52

Ja, nesten alltid ☐ 1 Ganske sjelden ☐ 3
Ganske ofte ☐ 2 Aldri, eller nesten aldri ☐ 4

Hvordan trives du alt i alt med arbeidet ditt? 53

Veldig godt ☐ 1 Ikke særlig godt ☐ 3
Godt ☐ 2 Dårlig ☐ 4

BOLIG

Hvem bor du sammen med?

Ett kryss for hver linje og angi antall

		Ja	Nei	Antall
Ektefelle/samboer	54	☐	☐	
Andre personer over 18 år	55	☐	☐	
Personer under 18 år	58	☐	☐	

Hvor mange av barna har plass i barnehage? 61 Antall

Hvilken type bolig bor du i? *Bare ett kryss*

Enebolig/villa	63	☐ 1
Gårdsbruk		☐ 2
Blokk/terrasseleilighet		☐ 3
Rekkehus/2-4 mannsbolig		☐ 4
Annen bolig		☐ 5

Hvor stor er din boenhet? 64 kvm

		Ja	Nei
Er det heldekkende tepper i stua?	67	☐	☐
Er det heldekkende tepper på ditt soverom?		☐	☐
Er det katt i boligen?	69	☐	☐
Er det hund i boligen?		☐	☐
Er det andre pelskledde dyr eller fugler i boligen?		☐	☐

ØKONOMI

Mottar du noen av følgende *offentlige* ytelser?

		Ja	Nei
Sykepenger/sykelønn/rehabiliteringspenger	72	☐	☐
Ytelser under yrkesrettet attføring		☐	☐
Uførepensjon	74	☐	☐
Alderspensjon		☐	☐
Sosialstøtte		☐	☐
Arbeidsløshetstrygd		☐	☐
Overgangsstønad		☐	☐
Etterlattepensjon	79	☐	☐
Andre ytelser		☐	☐

Har det i løpet av det siste året hendt at husholdningen har hatt vansker med å klare de løpende utgifter til mat, transport, bolig og liknende? *Bare ett kryss* 81

Ja, ofte ☐ 1 Ja, en sjelden gang ☐ 3
Ja, av og til ☐ 2 Nei, aldri ☐ 4

VENNER

Hvor mange gode venner har du? Antall

Regn med de du kan snakke fortrolig med og som kan gi deg god hjelp når du trenger det 82

Tell ikke med de du bor sammen med, men regn med andre slektninger

Føler du at du har mange nok gode venner? 84 Ja ☐ Nei ☐

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger? 85

Aldri, eller noen få ganger i året ☐ 1 Omtrent en gang i uka ☐ 1
1-2 ganger i måneden ☐ 2 Mer enn en gang i uka ☐ 2

DER DU BOR

Svar ut fra nærmiljøet, dvs. nabolaget/grenda.
Ett kryss for hvert spørsmål

Jeg føler et sterkt fellesskap med de som bor her 86
Helt enig ☐ 1 Delvis enig ☐ 2 Usikker ☐ 3 Delvis uenig ☐ 4 Helt uenig ☐ 5

Selv om noen tar initiativ, er det ingen som blir med på det som settes i gang her 87
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Hvis jeg flytter herfra, vil jeg lengte tilbake 88
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Man kan ikke stole på hverandre her 89
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Når noe skal gjøres her, er det lett å få folk med 90
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er vanskelig å få kontakt med folk her 91
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er godt samhold her 92
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Ingen orker å ta initiativ til noe lenger her 93
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk trives godt her 94
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk her kan ha store problemer uten at naboen vet noe 95
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er alltid noen som tar initiativ til å løse nødvendige oppgaver her 96
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk snakker lite med hverandre her 97
Helt enig ☐ 1 Delvis enig ☐ 2 Usikker ☐ 3 Delvis uenig ☐ 4 Helt uenig ☐ 5

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene. Kryss av for «ingen» hvis ingen av slektningene har hatt denne sykdommen. *Evt. flere kryss på hver linje*

		Mor	*Far*	*Bror*	*Søster*	*Barn*	*Ingen*
Hjerneslag eller hjerneblødning	98	☐	☐	☐	☐	☐	☐
Hjerteinfarkt før 60 års alder	104	☐	☐	☐	☐	☐	☐
Astma	110	☐	☐	☐	☐	☐	☐
Allergi	116	☐	☐	☐	☐	☐	☐
Kreftsykdom	122	☐	☐	☐	☐	☐	☐
Høyt blodtrykk	128	☐	☐	☐	☐	☐	☐
Psykiske plager	134	☐	☐	☐	☐	☐	☐
Osteoporose (benskjørhet)	140	☐	☐	☐	☐	☐	☐
Diabetes (sukkersyke)	146	☐	☐	☐	☐	☐	☐
Alder da de fikk diabetes	152	år	år	år	år	år	

Har du *selv* høysnue eller neseallergi? 162 *Ja* ☐ *Nei* ☐

BRUK AV HELSETJENESTER

Har du i løpet av de siste 12 månedene vært hos :

Ett kryss på hver linje		*Ja*	*Nei*
allmennpraktiserende lege (kommunelege, privatpraktiserende lege, turnuskandidat)	163	☐	☐
bedriftslege		☐	☐
lege ved sykehus (uten at du var innlagt)		☐	☐
annen lege		☐	☐
fysioterapeut		☐	☐
kiropraktor		☐	☐
homøopat	169	☐	☐
annen behandler (naturmedisiner, fotsoneterapeut, håndspålegger, "healer", "synsk", e.l.)		☐	☐

		Ja	*Nei*
Har du vært innlagt i sykehus de siste 5 åra?	171	☐	☐

ALKOHOL

Hvis du er totalavholdsmann: Gå til KOSTHOLD.

Ett kryss for hver spørsmål

		Ja	*Nei*
Har du noen gang følt at du burde redusere alkoholforbruket ditt?	172	☐	☐
Har andre noen gang kritisert alkoholbruken din?	173	☐	☐
Har du noen gang følt ubehag eller skyldfølelse pga. alkoholbruken din?	174	☐	☐
Har det å ta en drink noen gang vært det første du har gjort om morgenen for å roe nervene, kurere bakrus eller som en oppkvikker?	175	☐	☐

KOSTHOLD

		Antall
Hvor mange måltider spiser du vanligvis daglig (middag og brødmåltid)?	176	
Hvor mange dager i uka spiser du varm middag?		

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis? *Inntil to kryss.*

Brødtypen ligner mest på		*Loff*	*Fint brød*	*Kneipp-brød*	*Grov-brød*	*Knekke-brød*
	178	☐	☐	☐	☐	☐

Hva slags *fett* blir vanligvis brukt i din husholdning?

Ett kryss for matlaging og ett kryss for brød	*Til matlaging*	*På brød*
Bruker *ikke* smør eller margarin	183 ☐ 1	184 ☐ 1
Meierismør	☐ 2	☐ 2
Hard margarin	☐ 3	☐ 3
Bløt (soft) margarin	☐ 4	☐ 4
Smør/margarin blanding	☐ 5	☐ 5
Lettmargarin	☐ 6	☐ 6
Oljer	☐ 7	

MEDISINBRUK

		Ja	*Nei*
Har du i deler av de siste 12 måneder brukt noen medisiner daglig eller nesten daglig?	185	☐	☐

Hvis «Ja»:
Angi hvor mange måneder du brukte følgende medisiner: *Sett 0 hvis du ikke har brukt medisinene*

		Antall mndr.		Antall mndr.
smertestillende	186		hjertemedisin (ikke blodtrykksmedisin)	
sovemedisin	188			
beroligende medisin			annen medisin	
medisin mot depresjon			*Kosttilskudd:*	
allergimedisin	194		jerntabletter	202
astmamedisin	196		vitamintilskudd	
			tran/fiskeoljer	206

Hvor ofte har du brukt avslappende/beroligende medisin eller sovemedisin den siste måneden? 208
Daglig ☐ 1 Sjeldnere enn hver uke ☐ 3
Hver uke, men ikke hver dag ☐ 2 Aldri ☐ 4

HODEPINE

Har du vært plaget av hodepine i løpet av de siste 12 måneder? 209

Ja, anfallsvis (migrene) ☐ 1
Ja, annen slags hodepine ☐ 2
Nei ☐ 3

Antall anfall siste 12 mndr. 210 ☐

Hvis «Nei»: Gå til MUSKEL-/SKJELETTPLAGER

Omtrent hvor mange dager i pr. måned har du hodepine?
Mindre enn 7 dager ☐ 1 7 til 14 dager ☐ 2 Mer enn 14 d. ☐ 3

Hvor lenge varer hodepinen vanligvis hver gang? 213
Mindre enn 4 timer ☐ 1 4 timer–3 døgn ☐ 2 Mer enn 3 døgn ☐ 3

Hvor ofte er hodepinen preget av eller ledsaget av:

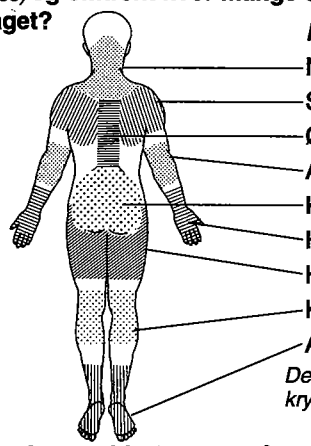
Ett kryss på hver linje	*Sjelden eller aldri*	*Av og til*	*Ofte*
bankende/dunkende smerte 214	☐	☐	☐
pressende smerte	☐	☐	☐
halvsidighet, alltid samme side	☐	☐	☐
halvsidighet, vekselvis h. og v. side	☐	☐	☐
smerter i «hele hodet»	☐	☐	☐
kvalme 219	☐	☐	☐
lys- og/eller lydskyhet	☐	☐	☐
forverring ved fysisk aktivitet	☐	☐	☐
synsforstyrrelser *før* hodepine 222	☐	☐	☐

Hvor mange tabletter/stikkpiller har du eventuelt brukt av disse medisinene *alt i alt i løpet av den siste måneden*?
Skriv 0 hvis du ikke har brukt medisinen.
Cafergot 223 ☐ Anervan 225 ☐ Imigran 227 ☐

MUSKEL-/SKJELETTPLAGER

Har du hatt plager (smerter, verk, ubehag) i muskler og/eller ledd i *den siste måneden*? 229 Ja ☐ Nei ☐

Hvis «Ja»: **Hvor har du hatt disse plagene** *(ett eller flere kryss)* **og omtrent hvor mange dager tilsammen var du plaget?**



Plager (Sett kryss)	Antall dager
Nakke 230	☐
Skuldre/aksler 233	☐
Øvre del av ryggen	☐
Albuer 239	☐
Korsryggen 242	☐
Handledd/hender 245	☐
Hofter 248	☐
Knær 251	☐
Ankler/føtter 254	☐

*Dersom flere kryss: Sett **ring** rundt krysset **der plagen var verst***

Har plagene hindret deg i å utføre daglige aktiviteter den siste måneden?

	Ja	*Nei*
I arbeidet 257	☐	☐
I fritida 258	☐	☐

SMERTER I BEINA

	Ja	*Nei*
Har du sår på tå, fot eller ankel som ikke vil gro? 259	☐	☐
Har du smerter i det ene eller i begge beina når du går? 260	☐	☐
Har du oppsøkt lege p.g.a. smerter i beina? 261	☐	☐

Hvis «NEI» på disse spørsmålene: Gå til URINVEGS...

	Ja	*Nei*
Kan du gå lenger enn 50 meter? 262	☐	☐
Forsvinner smerten når du står stille en stund? 263	☐	☐
Må du sette deg for at smerten skal gå over? 264	☐	☐

Hvor gjør det mest vondt? *Ett kryss* 265

Fot ☐ Legg ☐ Lår ☐ Hofte ☐

	Ja	*Nei*
Har du smerter i beina når du er i ro? 266	☐	☐
Er smertene verst når du ligger i senga? 267	☐	☐
Blir søvnen forstyrret av smertene? 268	☐	☐
Får du mindre vondt når beinet ligger høyt? 269	☐	☐
Får du mindre vondt når beinet ligger lavt, f.eks. om beinet henger utfor sengekanten? 270	☐	☐
Bedres smertene når du står opp og går litt? 271	☐	☐

URINVEGS- OG PROSTATAPLAGER

Ett kryss på hver linje

Har du noen gang blitt fortalt av lege at du har:	*Ja*	*Nei*
forstørret prostata 272	☐	☐
prostatakreft 273	☐	☐

Har du gjennomgått noe av følgende:	*Ja*	*Nei*
sterilisering 274	☐	☐
tatt vevsprøve (biopsi) av prostata 275	☐	☐
kirurgisk fjerning av prostata (helt eller delvis) 276	☐	☐

De neste spørsmålene gjelder siste måned
Bare ett kryss for hvert hver spørsmål

Hvor ofte har du hatt følelsen av at blæren ikke er blitt fullstendig tømt etter avsluttet vannlating? 277
Aldri ☐ 1 Omtrent annenhver gang ☐ 4
Omtrent 1 av 5 ganger ☐ 2 Omtrent 2 av 3 ganger ☐ 5
Omtrent 1 av 3 ganger ☐ 3 Nesten alltid ☐ 6

Hvor ofte har du måttet late vannet på nytt mindre enn 2 timer etter forrige vannlating? 278
Aldri ☐ 1 Omtrent annenhver gang ☐ 4
Omtrent 1 av 5 ganger ☐ 2 Omtrent 2 av 3 ganger ☐ 5
Omtrent 1 av 3 ganger ☐ 3 Nesten alltid ☐ 6

Hvor ofte har du måttet stoppe og starte flere ganger under vannlatingingen? 279
Aldri ☐ 1 Omtrent annenhver gang ☐ 4
Omtrent 1 av 5 ganger ☐ 2 Omtrent 2 av 3 ganger ☐ 5
Omtrent 1 av 3 ganger ☐ 3 Nesten alltid ☐ 6

Hvor ofte syns du det har vært vanskelig å holde igjen når du har følt trang til å late vannet? 280
Aldri ☐ 1 Omtrent annenhver gang ☐ 4
Omtrent 1 av 5 ganger ☐ 2 Omtrent 2 av 3 ganger ☐ 5
Omtrent 1 av 3 ganger ☐ 3 Nesten alltid ☐ 6

Hvor ofte har du hatt svak urinstråle? 281
Aldri ☐ 1 Omtrent annenhver gang ☐ 4
Omtrent 1 av 5 ganger ☐ 2 Omtrent 2 av 3 ganger ☐ 5
Omtrent 1 av 3 ganger ☐ 3 Nesten alltid ☐ 6

Hvor ofte har du måttet trykke eller presse for å begynne vannlatingen? 282
Aldri ☐ 1 Omtrent annenhver gang ☐ 4
Omtrent 1 av 5 ganger ☐ 2 Omtrent 2 av 3 ganger ☐ 5
Omtrent 1 av 3 ganger ☐ 3 Nesten alltid ☐ 6

Hvor mange ganger har du vanligvis måttet stå opp i løpet av natta for å late vannet? 283
Ingen ☐ 1 2 ganger ☐ 3 4 ganger ☐ 5
1 gang ☐ 2 3 ganger ☐ 4 5 ganger eller mer ☐ 6

Hvis du resten av livet måtte leve med de vannlatings-problemene du har nå, hvordan ville du føle det? 284
Være meget godt fornøyd ☐ 1 Være for det meste utilfreds ☐ 5
Være fornøyd ☐ 2 Være misfornøyd ☐ 6
Være for det meste tilfreds ☐ 3 Ha det forferdelig ☐ 7
Ha blandete følelser ☐ 4

HUMØR OG TRIVSEL

Ett kryss på hver linje

Angi hvordan du har følt deg den siste måneden:	*Aldri*	*Noen ganger*	*Ganske ofte*	*For det meste*
i godt humør 285	☐	☐	☐	☐
i dårlig humør 286	☐	☐	☐	☐

Er du rask til å oppfatte et humoristisk poeng? 287	*Svært treg*	*Ganske treg*	*Ganske rask*	*Svært rask*
	☐	☐	☐	☐

Er du enig i at det er noe ansvarsløst over folk som stadig prøver å være morsomme? 288

Nei, slett ikke ☐1 Ganske enig ☐3
I noen grad ☐2 Ja, absolutt ☐4

Er du en munter person? 289

Nei, slett ikke ☐1 Ganske munter ☐3
I noen grad ☐2 Ja, absolutt ☐4

SINNE

Sett kryss på det svaret som best beskriver deg i forhold til de to påstandene nedenfor:

Jeg gir uttrykk for mitt sinne, og andre mennesker vet at jeg er sint. 290

Nesten aldri ☐1 Ganske ofte ☐3
Noen ganger ☐2 Nesten alltid ☐4

Jeg koker av sinne, men jeg viser det ikke til andre. 291

Nesten aldri ☐1 Ganske ofte ☐3
Noen ganger ☐2 Nesten alltid ☐4

HVILE OG AVSLAPPING

Hvor mange timer tilbringer du *vanligvis* i *liggende* stilling i løpet av et døgn?
(nattesøvn, middagshvil) ....292 Antall timer ____

Hvor mange timer tilbringer du *vanligvis* i *sittende* stilling i løpet av et døgn?
(arbeid, måltider, TV, bil etc.) ....294 Antall timer ____

Hvor ofte er du plaget av søvnløshet? 296

Aldri, eller noen få ganger i året ☐1
1–2 ganger i måneden ☐2
Omtrent 1 gang i uka ☐3
Mer enn en gang i uka ☐4

Har du siste år vært plaget av søvnløshet slik at det har gått ut over arbeidsevnen? 297	*Ja*	*Nei*
	☐	☐

Har du i løpet av siste måned hatt innsovningsproblemer? *Bare ett kryss* 298

Nesten hver natt ☐1 Av og til ☐3
Ofte ☐2 Aldri ☐4

Har du i løpet av siste måned våknet for tidlig og ikke fått sove igjen? *Bare ett kryss* 299

Nesten hver natt ☐1 Av og til ☐3
Ofte ☐2 Aldri ☐4

Har du i løpet av siste måned vært plaget av nervøsitet (irritabel, urolig, anspent eller rastløs)? 300

Nesten hele tida ☐1
Ofte ☐2
Av og til ☐3
Aldri ☐4

HVORDAN DU HAR HATT DET

Har det noen gang i løpet av ditt liv vært *sammenhengende perioder på 2 uker eller mer* da du:	*Ja*	*Nei*
følte deg deprimert, trist og nedfor 301	☐	☐
hadde problemer med matlysten eller spiste alt for lite	☐	☐
var plaget av kraftløshet eller mangel på overskudd	☐	☐
virkelig bebreidet deg selv og følte deg verdiløs ...	☐	☐
hadde problemer med å konsentrere deg eller vanskelig for å ta beslutninger	☐	☐
hadde minst tre av de problemene som er nevnt ovenfor samtidig 306	☐	☐

HVORDAN DU SER PÅ DEG SELV

Folk ser på seg selv på ulike måter. Kryss av for hvert utsagn hvor enig eller uenig du er. *Ett kryss på hver linje*

	Svært enig	*Enig*	*Uenig*	*Svært uenig*
Jeg har en positiv holdning til meg selv 307	☐	☐	☐	☐
Jeg føler meg virkelig ubrukelig til tider 308	☐	☐	☐	☐
Jeg føler at jeg ikke har mye å være stolt av 309	☐	☐	☐	☐
Jeg føler at jeg er en verdifull person, i allefall på lik linje med andre 310	☐	☐	☐	☐

	Ja	*Nei*
Synes du at du har funnet et virkelig betydningsfullt innhold i livet ditt? 311	☐	☐
Føler du at du lever fullt ut? 312	☐	☐

HVORDAN DU FØLER DEG NÅ

*Sett kryss i den ruta utenfor det svaret som best beskriver dine følelser **den siste uka.** Bare ett kryss*

Er du vanligvis glad eller nedstemt? 313

Svært nedstemt ☐1
Nedstemt ☐2
Nokså nedstemt ☐3
Både – og ☐4
Nokså glad ☐5
Glad ☐6
Svært glad ☐7

Har du i det store og hele en rolig og god følelse inne i deg? 314

Nesten hele tida ☐1
Ofte ☐2
Av og til ☐3
Aldri ☐4

Føler du deg stort sett sterk og opplagt, eller trøtt og sliten? 315

Meget sterk og opplagt ☐1
Sterk og opplagt ☐2
Ganske sterk og opplagt ☐3
Både – og ☐4
Ganske trøtt og sliten ☐5
Trøtt og sliten ☐6
Svært trøtt og sliten ☐7

Legg det utfylte spørreskjemaet i den vedlagte svarkonvolutten og postlegg den så snart som mulig!
Porto er betalt.

Hjertelig takk for hjelpa!

Steinkjer Trykkeri AS – 74 16 30 00

APPENDIX V:

HUSK

QUESTIONNAIRE 1

HELSEUNDERSØKELSEN I HORDALAND 1997-99

☐ Adresse endring

HUSK

Personlig innbydelse

Spørreskjemaet er en viktig del av helseundersøkelsen. Vennligst fyll ut skjemaet på forhånd og ta det med til helseundersøkelsen. Dersom enkelte spørsmål er uklare, lar du dem stå ubesvart til du møter fram, og drøfter dem med personalet som gjennomfører undersøkelsen. *Alle svar vil bli behandlet strengt fortrolig.*

Det utfylte skjemaet vil bli lest av en maskin. Bruk blå eller sort farge ved utfylling. Det er viktig at du går fram slik:

- i de små boksene setter du kryss for det svaret som passer best for deg
- i de store boksene skriver du tall eller blokkbokstaver – NB! innenfor rammen for boksen.

Eksempler:
Avkryssing: [X] Tall: 1 2 3 4 5 6 7 8 9 0 Bokstaver: A B C

Med vennligh hilsen

Statens helseundersøkelser ♥ Kommunehelsetjenesten ♥ Helseundersøkelsen i Hordaland

1. EGEN HELSE

Hvordan er helsen din nå? *(Sett bare ett kryss)*

Dårlig	Ikke helt god	God	Svært god
☐ 1	☐ 2	☐ 3	☐ 4

Har du, eller har du hatt:	JA	NEI	Alder første gang
Hjerteinfarkt	☐	☐	☐☐ år
Angina pectoris (hjertekrampe)	☐	☐	☐☐ år
Hjerneslag/hjerneblødning	☐	☐	☐☐ år
Astma	☐	☐	☐☐ år
Diabetes (sukkersyke)	☐	☐	☐☐ år
Multippel sklerose	☐	☐	☐☐ år

Bruker du medisin mot høyt blodtrykk?

Nå	Før, men ikke nå	Aldri brukt
☐ 1	☐ 2	☐ 3

Har du noen gang det siste året hatt eksem (rød, kløende, sår og sprukken hud):	JA	NEI
På hendene?	☐	☐
I ansiktet?	☐	☐
Andre steder på kroppen?	☐	☐

Med «hvite fingre» mener vi plager i form av at en eller flere fingre blir hvite og at man samtidig mister følelsen i dem når det er kaldt. Har du slike plager?	JA	NEI
	☐	☐

2. HVORDAN FØLER DU DEG?

Har du de siste to ukene følt deg:

	Nei	Litt	En god del	Svært mye
Nervøs og urolig?	☐	☐	☐	☐
Plaget av angst?	☐	☐	☐	☐
Trygg og rolig?	☐	☐	☐	☐
Irritabel?	☐	☐	☐	☐
Glad og optimistisk?	☐	☐	☐	☐
Nedfor/deprimert?	☐	☐	☐	☐
Ensom?	☐	☐	☐	☐
	1	2	3	4

3. SYKDOM I FAMILIEN

Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)?	JA	NEI	VET IKKE
	☐	☐	☐

Har en eller flere foreldre/søsken hatt:

Hjerteinfarkt *før* de fylte 60 år?	☐	☐	☐
Hjerneslag/hjerneblødning *før* de fylte 70 år?	☐	☐	☐

4. MUSKEL- OG SKJELETTPLAGER

Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende?	JA	NEI
	☐	☐

Hvis NEI, gå til avsnitt 5.
Hvis JA, svar på følgende:

Hvor har du hatt disse plagene?	JA	NEI
Nakke	☐	☐
Skuldre (aksler)	☐	☐
Albuer	☐	☐
Håndledd/hender	☐	☐
Bryst, mage	☐	☐
Øvre del av ryggen	☐	☐
Korsryggen	☐	☐
Hofter	☐	☐
Knær	☐	☐
Ankler, føtter	☐	☐

Hvor lenge har plagene vart sammenhengende?
Svar for det området hvor plagene har vart lengst.

Hvis under 1 år, oppgi antall måneder. ☐☐ *Antall mnd.*

Hvis 1 år eller mer, oppgi antall år ☐☐ *Antall år*

Har plagene redusert din arbeidsevne det siste året?
Gjelder også hjemmearbeidende. Sett bare ett kryss.

Nei/ubetydelig	I noen grad	I betydelig grad	Vet ikke
☐ 1	☐ 2	☐ 3	☐ 4

Har du vært sykmeldt p.g.a. disse plagene det siste året?	JA	NEI	Ikke i arbeid
	☐	☐	☐

Har plagene ført til redusert aktivitet i fritiden?	JA	NEI
	☐	☐

5. MOSJON

Hvordan har din fysiske aktivitet i fritiden vært det siste året?
Tenk deg et ukentlig gjennomsnitt for året.
Arbeidsvei regnes som fritid. Besvar begge spørsmålene.

	Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)*	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)*	☐	☐	☐	☐
	1	2	3	4

6. KAFFE / TE / ALKOHOL

Hvor mange kopper kaffe/te drikker du daglig?
Sett 0 hvis du ikke drikker kaffe/te daglig.

Antall kopper daglig

Kokekaffe	Annen kaffe	Te

Er du total avholdsmann/-kvinne? ..... JA ☐ NEI ☐

Hvor mange ganger i måneden drikker du vanligvis alkohol? *Regn ikke med lettøl.*
Sett 0 hvis mindre enn 1 gang i mnd. ..... *Antall ganger* ☐☐

Hvor mange glass øl, vin eller brennevin drikker du VANLIGVIS i løpet av to uker?
Regn ikke med lettøl. Sett 0 hvis du ikke drikker alkohol.

Glass øl	Glass vin	Glass brennevin
☐☐	☐☐	☐☐

7. RØYKING

Hvor lenge er du vanligvis daglig tilstede i røykfylt rom? ..... *Antall hele timer* ☐☐
Sett 0 hvis du ikke oppholder deg i røykfylt rom.

Røyker du selv:

	JA	NEI
Sigaretter daglig?	☐	☐
Sigarer/sigarillos daglig?	☐	☐
Pipe daglig?	☐	☐

Aldri røykt daglig ..... (Sett kryss) ☐

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? ..... *Antall år* ☐☐

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? ..... *Antall sigaretter* ☐☐

Hvor gammel var du da du begynte å røyke daglig? ..... *Alder i år* ☐☐

Hvor mange år til sammen har du røykt daglig? ..... *Antall år* ☐☐

8. ENDRING AV HELSEVANER

Dette gjelder din interesse for å endre helsevaner. Røykespørsmålet besvares bare av dem som røyker.

	Spise sunnere		Trimme mer		Slutte å røyke	
Har du de siste 12 mnd. forsøkt å:	JA ☐	NEI ☐	JA ☐	NEI ☐	JA ☐	NEI ☐
Om 5 år, tror du at du har endret vaner på noen av disse områdene?	JA ☐	NEI ☐	JA ☐	NEI ☐	JA ☐	NEI ☐

Anslå din høyeste og laveste vekt i løpet av de siste 5 år. *(Hele kg)* *(Se bort fra vekt under svangerskap)*	Høyeste vekt	Laveste vekt
	☐☐☐	☐☐☐

9. UTDANNING

Hvilken utdanning er den høyeste du har fullført?
Sett bare ett kryss.

Mindre enn 7 år grunnskole	☐
Grunnskole 7-10 år, framhaldsskole, folkehøgskole	☐ 1
Realskole, middelskole, yrkesskole, 1-2 årig videregående skole	☐ 2
Artium, øk.gymnas, allmennfaglig retning i videregående skole	☐ 3
Høgskole/universitet, mindre enn 4 år	☐ 4
Høgskole/universitet, 4 år eller mer	☐ 5

10. HELSE OG TRIVSEL

De neste spørsmålene handler om hvordan du ser på din egen helse. Hvis du er usikker på hva du skal svare, vennligst svar så godt du kan.

Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene NÅ?

Moderate aktiviteter som å flytte bord, støvsuge, gå en tur eller drive med hagearbeid:

Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
☐	☐	☐

Gå opp trappen flere etasjer:

Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
☐	☐	☐

I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

	JA	NEI
Du har utrettet mindre enn du hadde ønsket	☐	☐
Du har vært hindret i å utføre visse typer arbeid eller gjøremål	☐	☐

I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål p.g.a. følelsesmessige problemer?
(Som f.eks. å være deprimert eller engstelig)

	JA	NEI
Du har utrettet mindre enn du hadde ønsket	☐	☐
Du har utført arbeidet eller andre gjøremål mindre grundig enn vanlig	☐	☐

I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid?
(Gjelder både i og utenfor hjemmet) Sett bare ett kryss.

	JA
Ikke i det hele tatt	☐ 1
Litt	☐ 2
En del	☐ 3
Mye	☐ 4
Svært mye	☐ 5

Hvor ofte i løpet av de siste 4 ukene har du følt deg rolig og harmonisk? Sett bare ett kryss.

	JA
Hele tiden	☐ 1
Nesten hele tiden	☐ 2
Mye av tiden	☐ 3
En del av tiden	☐ 4
Litt av tiden	☐ 5
Ikke i det hele tatt	☐ 6

Hvor ofte i løpet av de siste 4 ukene har du hatt mye overskudd? Sett bare ett kryss.

	JA
Hele tiden	1
Nesten hele tiden	2
Mye av tiden	3
En del av tiden	4
Litt av tiden	5
Ikke i det hele tatt	6

Hvor ofte i løpet av de siste 4 ukene har du følt deg nedfor og trist? Sett bare ett kryss.

	JA
Hele tiden	1
Nesten hele tiden	2
Mye av tiden	3
En del av tiden	4
Litt av tiden	5
Ikke i det hele tatt	6

I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang(som det å besøke venner, slekt)? Sett bare ett kryss.

	JA
Hele tiden	1
Nesten hele tiden	2
Mye av tiden	3
En del av tiden	4
Litt av tiden	5
Ikke i det hele tatt	6

Stort sett, vil du si at din helse er:

Utmerket	Meget god	God	Nokså god	Dårlig
1	2	3	4	5

11. BRUK AV MEDISINER

Med medisiner mener vi her alle slags medisiner, både:

- *med og uten resept, naturmedisin, vitaminer og mineraler*
- *medisin som svelges, inhaleres eller injiseres, stikkpiller, salver, kremer eller dråper.*

Tok du noen slags medisiner I GÅR? JA NEI

Hvis NEI, kan du gå til avsnitt 12.

Hvis JA, besvar følgende:

Hvilke medisiner tok du I GÅR, og hva var grunnen til at du tok medisinen (diagnose, sykdom, symtom, helseeffekt)?

Sett svarene inn i skjemaet nedenfor, en linje for hver medisin. Kryss av for ja om du bruker medisinen daglig eller nesten daglig.

Navn på medisinen *(ett navn pr. linje):*	Grunn til bruk av medisinen I GÅR var:	Daglig JA	Daglig NEI

Dersom det ikke er nok plass her, kan du fortsette på eget ark som legges ved.

12. ARBEID

Besvares av dem som har hatt inntektsgivende arbeid i minst 100 timer det siste året:

Beskriv virksomheten på det arbeidsstedet der du utførte inntektsgivende arbeid i lengst tid de siste 12 mnd. *(Skriv f.eks. jordbruk, barneavd. på sykehus, snekkeravd. på skipsverft e.l.).*

Virksomhet:

Hvilket yrke/tittel har eller hadde du på dette arbeidsstedet? *(Skriv f.eks. kornbonde, anestesisykepleier, snekker e.l.)*

Yrke:

Hvor lenge har du praktisert i dette yrket i ditt liv? ..... *Antall år i yrket*

Har du noen av de følgende yrker (*heltid eller deltid*)?
Sett kryss for hvert spørsmål.

	JA	NEI
Sjåfør		
Bonde/gårdbruker		
Fisker		

Har du tidligere i ditt liv (*ikke i dag*) hatt inntektsgivende arbeid som:

	JA	NEI
Bilmekaniker/biloppretter		
Frisør		

13. SAMLIV

Oppgi antall egne barn (eventuelt 0) av hvert kjønn:

Antall gutter *Antall jenter*

Har du noen gang hatt regelmessig samliv uten prevensjon i ett år eller mer uten at det har ført til graviditet?... JA NEI

Med prevensjon menes også mer usikre metoder som avbrutt samleie, «sikre perioder» etc.

De følgende spørsmål besvares bare av kvinner

Har du noen gang spontanabortert (ufrivillig mistet fosteret) etter at graviditet var sikkert påvist?

NEI USIKKER JA

Hvis JA: *Antall ganger*

Følgende spørsmål besvares bare hvis du har vært gravid:

Oppgi antall måneder det tok med regelmessig samliv uten prevensjon (eller evt. amming), til du ble gravid:

Siste svangerskap ..... *mnd. uten prevensjon*

Nest siste svangerskap..... *mnd. uten prevensjon*

Tredje siste svangerskap ..... *mnd. uten prevensjon*

14. ETTERUNDERSØKELSE

Hvis denne helseundersøkelsen viser at du bør undersøkes nærmere, hvilken allmennpraktiserende lege/kommunelege ønsker

Ikke skriv i disse rutene

Takk for utfyllingen!

Nok en gang: *Velkommen til undersøkelsen*

IE 3215801 (ID.NR. 1.97)- 30.000- Beyer-Hecos 9.97

APPENDIX VI:

HUSK

QUESTIONNAIRE 2
FOR THE
HOMOCYSTEINE
COHORT

HELSEUNDERSØKELSEN I HORDALAND 1997-99

Dato for utfylling av skjema DAG MÅNED ÅR

HUSK

Takk for at du har tatt deg tid til å komme til en ny helseundersøkelse i Hordaland. Dere som inviteres nå, deltok også i 1992-93. Den gang fikk vi verdifulle resultater som har gitt viktig ny kunnskap. For å øke vår forståelse av forhold som påvirker risikoen for hjerte- og karsykdom er det viktig å kartlegge både fysiske (f.eks. blodkolesterol) og psykososiale (f.eks. sosial støtte) faktorer. Vi ser frem til din deltakelse også i denne helseundersøkelsen. Mer informasjon om årets undersøkelse finner du i HUSK brosjyren og i eget informasjonsskriv.

Alle svar vil bli behandlet strengt fortrolig.

Det utfylte skjemaet vil bli lest av en maskin. Bruk blå eller sort farge ved utfylling.
Det er viktig at du går frem slik:

- i de små boksene setter du kryss for det svaret som passer best for deg
- i de store boksene skriver du tall eller blokkbokstaver – NB! innenfor rammen for boksene.

Eksempler:
Avkryssing: [X] Tall: 1 2 3 4 5 6 7 8 9 0 Bokstaver: A B C

Vennlig hilsen
Helseundersøkelsen i Hordaland 1997–99. Statens helseundersøkelser - Universitetet i Bergen - Kommunehelsetjenesten

SYMPTOMER PÅ HJERTE- OG KARSYKDOM

Har du noen gang siden 1992 hatt store smerter i brystet som varte i mer enn 30 minutter?

NEI ☐

Dersom JA, angi år

92 ☐ 93 ☐ 94 ☐ 95 ☐ 96 ☐ 97 ☐ 98 ☐ 99 ☐

Bruker du nitroglyserin?

JA ☐ NEI ☐

Hvis JA, hvor ofte?

Daglig, eller nesten daglig ☐
1–3 ganger pr. uke ☐
1–3 ganger pr. måned ☐
Sjeldnere enn 1 gang pr. måned ☐

Får du smerter eller ubehag i brystet når du:

	JA	NEI
går i bakker, trapper eller fort på flat mark?	☐	☐
går i vanlig takt på flat mark?	☐	☐

Dersom du får smerter eller vondt i brystet ved gange, pleier du da å:

stoppe? ☐
saktne farten? ☐
fortsette i samme fart? ☐

Dersom du stopper, eller saktner farten, forsvinner brystsmertene da? JA ☐ NEI ☐

Hvis JA, hvor lang tid tar det før de forsvinner?

10 minutter eller mindre ☐
Mer enn 10 minutter ☐

Har du vanligvis:

	JA	NEI
hoste om morgenen?	☐	☐
oppspytt fra brystet om morgenen?	☐	☐

Får du smerter i ett eller begge ben når du går?

JA ☐ NEI ☐

Hender det at denne smerten begynner mens du står stille eller sitter?

JA ☐ NEI ☐

I hvilken del av benet kjenner du smerter?

bare legger ☐
bare lår ☐
både legger og lår ☐

Får du slike smerter i bena når du går fort eller i oppoverbakke?

JA ☐ NEI ☐

Går aldri fort eller i oppoverbakke ☐

Får du slike smerter i bena når du går i vanlig fart på flat mark?

JA ☐ NEI ☐

Hender det at smertene forsvinner mens du går?

JA ☐ NEI ☐

Hva gjør du hvis smertene i bena kommer mens du går?

Stopper eller saktner farten ☐
Fortsetter som før ☐

Hva skjer dersom du stopper opp?

Smertene vedvarer ☐
Smertene opphører ☐

Hvor lang tid tar det før smertene i bena eventuelt opphører?

10 minutter eller mindre ☐
Mer enn 10 minutter ☐

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Blir du kortpustet når du skynder deg (går fort) på flat mark, eller går opp en liten bakke?

JA ☐ NEI ☐

Hvis NEI, gå til neste avsnitt. Hvis JA, fortsett med de neste spørsmålene.

	JA	NEI
Blir du kortpustet når du spaserer på flat mark sammen med mennesker på din egen alder?	☐	☐
Hender det at du må stoppe for å få igjen pusten mens du spaserer i ditt eget tempo på flat mark?	☐	☐
Får du pustevansker i forbindelse med stell og påkledning?	☐	☐
Har du pustevansker når du ligger stille, f.eks. i sengen?	☐	☐
Bruker du ekstra puter om natten p.g.a. pustevansker?	☐	☐

HJERTE- OG KARSYKDOM SIDEN 1992

Har du hatt hjerneslag, blodpropp, hjerteinfarkt, hjerte-/eller karoperasjoner i 1992 eller senere?

JA ☐ NEI ☐

Hvis NEI, ber vi deg gå til neste avsnitt. Hvis JA, ber vi deg besvare disse spørsmålene.

	92	93	94	95	96	97	98	99
Hjerneslag/Hjernedrypp	☐	☐	☐	☐	☐	☐	☐	☐
Hjerteinfarkt	☐	☐	☐	☐	☐	☐	☐	☐
Blodpropp i lunge	☐	☐	☐	☐	☐	☐	☐	☐
Blodpropp i legg/lår	☐	☐	☐	☐	☐	☐	☐	☐
Operasjon på halsåren	☐	☐	☐	☐	☐	☐	☐	☐
Hjerteoperasjon	☐	☐	☐	☐	☐	☐	☐	☐
Operasjon på hovedpulsåren	☐	☐	☐	☐	☐	☐	☐	☐
Operasjon på blodårer i legg/lår (ikke åreknuter)	☐	☐	☐	☐	☐	☐	☐	☐

For hvilke av sykdomsepisodene var du innlagt på sykehus?

	92	93	94	95	96	97	98	99
Hjerneslag/Hjernedrypp	☐	☐	☐	☐	☐	☐	☐	☐
Hjerteinfarkt	☐	☐	☐	☐	☐	☐	☐	☐
Blodpropp i legg/lår	☐	☐	☐	☐	☐	☐	☐	☐

Dersom du har hatt hjerneslag eller hjernedrypp:

Hadde du store lammelser og/eller talevansker?

Lammelser arm ☐
ben ☐
ansikt ☐

Talevansker ☐

Hvor lenge varte disse plagene?

Mindre enn 1 døgn ☐
1 døgn til 1 måned ☐
Mer enn 1 måned ☐

SKAL BARE BESVARES AV KVINNER

Bruker du eller har du brukt:

	Nå	Før	Aldri
P-pille (også minipille)	☐	☐	☐
Hormonspiral	☐	☐	☐
Østrogen (tabletter eller plaster)	☐	☐	☐
Østrogen (krem eller stikkpiller)	☐	☐	☐

ANNEN SYKDOM

Har du noen gang hatt følgende sykdommer?
*Sett kryss for hvert spørsmål. Oppgi også alderen for hendelsen. Hvis det har skjedd flere ganger, hvor gammel var du **siste** gang?*

	JA	NEI	Alder siste gang
Lårhalsbrudd	☐	☐	
Brudd ved håndledd/underarm	☐	☐	
Nakkesleng (whiplash)	☐	☐	
Skade som førte til sykehusinnleggelse	☐	☐	

Har du eller har du hatt: *Kryss JA eller NEI for hvert spørsmål.*

	JA	NEI
Høysnue?	☐	☐
Kronisk bronkitt?	☐	☐
Benskjørhet (osteoporose)?	☐	☐
Fibromyalgi/fibrositt/kronisk smertesykdom?	☐	☐

	JA	NEI
Plagsomt tørre øyne - har du hatt denne følelsen daglig i mer enn 3 måneder?	☐	☐
Har du ofte følelsen av sand på øynene?	☐	☐
Tørrhet i munnen - har du hatt denne følelsen daglig i mer enn 3 måneder?	☐	☐
Må du ofte drikke for å kunne svelge tørr mat?	☐	☐
Har du vært behandlet/operert for snorking/pustepauser?	☐	☐
Har du vært innlagt på sykehus siden 1992 av andre grunner enn hjerte-karsykdom?	☐	☐

Dersom JA, hvilke(t) år

	92	93	94	95	96	97	98	99
Kreft	☐	☐	☐	☐	☐	☐	☐	☐
Ulykke/skade	☐	☐	☐	☐	☐	☐	☐	☐
Annet	☐	☐	☐	☐	☐	☐	☐	☐

angi grunn.....

KONTAKT MED ANDRE MENNESKER

Tenk på alle (barn, foreldre, søsken, ektefelle, samboer eller kjæreste, naboer, venner, kolleger eller andre du kjenner) når du besvarer følgende spørsmål:

Jeg har noen jeg bryr meg om, som jeg kan snakke med om mine personlige problemer

- ☐ Stemmer helt
- ☐ Stemmer ganske bra
- ☐ Stemmer ikke særlig
- ☐ Stemmer slett ikke

Det er mennesker i livet mitt som jeg bryr meg om, men som misliker hverandre

- ☐ Stemmer helt
- ☐ Stemmer ganske bra
- ☐ Stemmer ikke særlig
- ☐ Stemmer slett ikke

Det finnes en person i livet mitt som trenger min hjelp, men jeg vet ikke hvordan jeg kan hjelpe

- ☐ Stemmer helt
- ☐ Stemmer ganske bra
- ☐ Stemmer ikke særlig
- ☐ Stemmer slett ikke

Det finnes en viktig person i livet mitt som ønsker å støtte meg, men som ofte sårer meg i stedet

- ☐ Stemmer helt
- ☐ Stemmer ganske bra
- ☐ Stemmer ikke særlig
- ☐ Stemmer slett ikke

Det finnes mennesker som jeg må være sammen med nesten daglig som ofte hakker på meg

- ☐ Stemmer helt
- ☐ Stemmer ganske bra
- ☐ Stemmer ikke særlig
- ☐ Stemmer slett ikke

Det finnes personer som gjør livet mitt vanskelig fordi de ønsker for mye omsorg fra meg

- ☐ Stemmer helt
- ☐ Stemmer ganske bra
- ☐ Stemmer ikke særlig
- ☐ Stemmer slett ikke

Jeg har noen jeg bryr meg om, som forventer mer av meg enn jeg kan klare

- ☐ Stemmer helt
- ☐ Stemmer ganske bra
- ☐ Stemmer ikke særlig
- ☐ Stemmer slett ikke

Det finnes minst én person som ville kunne låne meg penger for en kortere tid

- ☐ Stemmer helt
- ☐ Stemmer ganske bra
- ☐ Stemmer ikke særlig
- ☐ Stemmer slett ikke

Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg

- ☐ I svært stor grad
- ☐ I liten grad
- ☐ I ganske stor grad
- ☐ Ikke i det hele tatt
- ☐ I noen grad

Jeg føler meg ofte ensom

- ☐ I svært stor grad
- ☐ I liten grad
- ☐ I ganske stor grad
- ☐ Ikke i det hele tatt
- ☐ I noen grad

Jeg synes det er vanskelig å snakke med mennesker jeg ikke har møtt før

- ☐ I svært stor grad
- ☐ I liten grad
- ☐ I ganske stor grad
- ☐ Ikke i det hele tatt
- ☐ I noen grad

Jeg føler meg ensom selv når jeg er sammen med andre

- ☐ I svært stor grad
- ☐ I liten grad
- ☐ I ganske stor grad
- ☐ Ikke i det hele tatt
- ☐ I noen grad

Jeg føler ofte at andre ikke forstår meg og min situasjon

- ☐ I svært stor grad
- ☐ I liten grad
- ☐ I ganske stor grad
- ☐ Ikke i det hele tatt
- ☐ I noen grad

Jeg føler at andre bryr seg om meg

- ☐ I svært stor grad
- ☐ I liten grad
- ☐ I ganske stor grad
- ☐ Ikke i det hele tatt
- ☐ I noen grad

Hvor mange gode venner har du? Regn med de du kan snakke fortrolig med og som kan gi deg hjelp når du trenger det?
Tell ikke med de du bor sammen med, men ta med andre slektninger.

Gode venner ☐☐

Føler du at du har nok gode venner?

JA ☐ NEI ☐

Hvor ofte tar du del i foreningsvirksomhet som f.eks. idrettslag, politiske lag, religiøse eller andre foreninger?

- Aldri, eller noen få ganger i året ☐
- 1-3 ganger i måneden ☐
- Omtrent en gang i uken ☐
- Mer enn en gang i uken ☐

SØVN

Har du merket følgende besvær siste 3 måneder?

	Aldri	**Sjelden** *Noen ganger pr. år*	**Iblant** *Noen ganger pr. mnd.*	**For det meste** *Flere ganger pr. uke*	**Alltid**
Snorking (ifølge andre)	☐	☐	☐	☐	☐
Pustepauser under søvn (ifølge andre)	☐	☐	☐	☐	☐
Trett/søvning på arbeid eller i fritiden	☐	☐	☐	☐	☐
Behov for å kjempe mot søvnen for å holde deg våken	☐	☐	☐	☐	☐

Hvordan synes du at du sover totalt sett?

- Veldig bra ☐
- Ganske bra ☐
- Verken bra eller dårlig ☐
- Ganske dårlig ☐
- Veldig dårlig ☐

TRIVSEL OG HELSE

Her kommer noen spørsmål om hvordan du føler deg.
For hvert spørsmål setter du kryss for ett av de fire svarene som beskriver dine følelser ***den siste uken.*** *Ikke tenk for lenge på svaret - de spontane svarene er best.*

Jeg føler meg nervøs og urolig
- ☐ Mesteparten av tiden
- ☐ Mye av tiden
- ☐ Fra tid til annen
- ☐ Ikke i det hele tatt

Jeg gleder meg fortsatt over ting, slik jeg pleide før
- ☐ Avgjort like mye
- ☐ Bare lite grann
- ☐ Ikke fullt så mye
- ☐ Ikke i det hele tatt

Jeg har en urofølelse, som om noe forferdelig vil skje
- ☐ Ja, og noe svært ille
- ☐ Litt, bekymrer meg lite
- ☐ Ja, ikke så veldig ille
- ☐ Ikke i det hele tatt

Jeg kan le og se det morsomme i situasjoner
- ☐ Like mye som før
- ☐ Avgjort ikke som før
- ☐ Ikke like mye som før
- ☐ Ikke i det hele tatt

Jeg har hodet fullt av bekymringer
- ☐ Veldig ofte
- ☐ Av og til
- ☐ Ganske ofte
- ☐ En gang i blant

Jeg er i godt humør
- ☐ Aldri
- ☐ Ganske ofte
- ☐ Noen ganger
- ☐ For det meste

Jeg kan sitte i fred og ro og kjenne meg avslappet
- ☐ Ja, helt klart
- ☐ Ikke så ofte
- ☐ Vanligvis
- ☐ Ikke i det hele tatt

Jeg føler meg som om alt går langsommere
- ☐ Nesten hele tiden
- ☐ Fra tid til annen
- ☐ Svært ofte
- ☐ Ikke i det hele tatt

Jeg føler meg urolig, som om jeg har sommerfulgler i magen
- ☐ Ikke i det hele tatt
- ☐ Ganske ofte
- ☐ Fra tid til annen
- ☐ Svært ofte

Jeg bryr meg ikke lenger om hvordan jeg ser ut
- ☐ Ja, jeg har sluttet å bry meg
- ☐ Kan hende ikke nok
- ☐ Ikke som jeg burde
- ☐ Bryr meg som før

Jeg er rastløs, som om jeg stadig må være aktiv
- ☐ Uten tvil svært mye
- ☐ Ikke så veldig mye
- ☐ Ganske mye
- ☐ Ikke i det hele tatt

Jeg ser med glede frem til hendelser og ting
- ☐ Like mye som før
- ☐ Avgjort mindre enn før
- ☐ Heller mindre enn før
- ☐ Nesten ikke i det hele tatt

Jeg kan plutselig få en følelse av panikk
- ☐ Uten tvil svært ofte
- ☐ Ikke så veldig ofte
- ☐ Ganske ofte
- ☐ Ikke i det hele tatt

Jeg kan glede meg over gode bøker, radio og TV
- ☐ Ofte
- ☐ Ikke så ofte
- ☐ Fra tid til annen
- ☐ Svært sjelden

INNTEKT

Hva er for tiden husholdningens årsinntekt (lønn og pensjon) før skatt?

- Ingen inntekt ☐
- Kr. 100 – 49.900 ☐
- Kr. 50.000 – 99.900 ☐
- Kr. 100.000 – 149.900 ☐
- Kr. 150.000 – 199.900 ☐
- Kr. 200.000 – 299.900 ☐
- Kr. 300.000 – 399.900 ☐
- Kr. 400.000 – 499.900 ☐
- Kr. 500.000 – eller mer ☐

SINNSSTEMNING

Her kommer noen ord for ulike følelser. Les hvert ord og merk av det svaret som passer best for hvordan du vanligvis kjenner deg, altså hvordan du i gjennomsnitt føler deg.
Sett ett kryss for hver sinnsstemning.

Jeg er vanligvis:

	Svært lite	Litt	Middels	En del	Mye
interessert	☐	☐	☐	☐	☐
irritabel	☐	☐	☐	☐	☐
uvennlig	☐	☐	☐	☐	☐
nedtrykt	☐	☐	☐	☐	☐
årvåken	☐	☐	☐	☐	☐
entusiastisk	☐	☐	☐	☐	☐
opprømt	☐	☐	☐	☐	☐
skamfull	☐	☐	☐	☐	☐
stolt	☐	☐	☐	☐	☐
opprørt	☐	☐	☐	☐	☐
inspirert	☐	☐	☐	☐	☐
skjelven	☐	☐	☐	☐	☐
sterk	☐	☐	☐	☐	☐
nervøs	☐	☐	☐	☐	☐
aktiv	☐	☐	☐	☐	☐
full av skyldfølelse	☐	☐	☐	☐	☐
bestemt	☐	☐	☐	☐	☐
redd	☐	☐	☐	☐	☐
skremt	☐	☐	☐	☐	☐
oppmerksom/konsentrert	☐	☐	☐	☐	☐

Takk enda en gang for at du har tatt deg tid til å fylle ut dette skjemaet!
Ditt bidrag vil være viktig for forståelsen av hvordan ulike forhold kan virke inn på helse og sykdom.

Vennlig hilsen

Helseundersøkelsen i Hordaland 97-99
Statens Helseundersøkelser

HUSK

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PAPER I

ELSEVIER

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Review

The validity of the Hospital Anxiety and Depression Scale An updated literature review

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Abstract

Objective: To review the literature of the validity of the Hospital Anxiety and Depression Scale (HADS). **Method:** A review of the 747 identified papers that used HADS was performed to address the following questions: (I) How are the factor structure, discriminant validity and the internal consistency of HADS? (II) How does HADS perform as a case finder for anxiety disorders and depression? (III) How does HADS agree with other self-rating instruments used to rate anxiety and depression? **Results:** Most factor analyses demonstrated a two-factor solution in good accordance with the HADS subscales for Anxiety (HADS-A) and Depression (HADS-D), respectively. The correlations between the two subscales varied from .40 to .74 (mean .56). Cronbach's alpha for HADS-A varied from .68 to .93 (mean .83) and for HADS-D from .67 to .90 (mean .82). In most studies an optimal balance between sensitivity and specificity was achieved when caseness was defined by a score of 8 or above on both HADS-A and HADS-D. The sensitivity and specificity for both HADS-A and HADS-D of approximately 0.80 were very similar to the sensitivity and specificity achieved by the General Health Questionnaire (GHQ). Correlations between HADS and other commonly used questionnaires were in the range .49 to .83. **Conclusions:** HADS was found to perform well in assessing the symptom severity and caseness of anxiety disorders and depression in both somatic, psychiatric and primary care patients and in the general population.

Keywords: Anxiety; Depression; Psychiatric Status Rating Scales; Psychometrics; Reproducibility of results; Sensitivity and specificity

Introduction

To make cost-effective screening of mental disorders feasible, several brief questionnaires assessing a limited set of symptoms have been developed. The Hospital Anxiety and Depression Scale (HADS) [1] was developed by Zigmond and Snaith in 1983 to identify caseness (possible and probable) of anxiety disorders and depression among patients in nonpsychiatric hospital clinics. It was divided into an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D) both containing seven intermingled items. To prevent 'noise' from somatic disorders on the scores, all symptoms of anxiety or depression relating also to physical disorder, such as dizziness, headaches, insomnia, anergia and fatigue, were excluded. Symptoms relating to serious mental disorders were also excluded, since such symptoms were less common in patients attending a non-psychiatric hospital clinic. The authors [1] also intended to "define carefully and distinguish between the concepts of anxiety and depression."

HADS has been used extensively, and we identified 747 papers that referred to HADS in Medline, ISI and PsycINFO indexed journals by May 2000.

The evaluation of psychometric properties and diagnostic efficacy of questionnaires is often inadequate [2]. To our knowledge, there has been only one review of the literature addressing these issues in HADS [3]. Based on approximately 200 papers on HADS in approximately 35,000 individuals in various patient populations, Herrmann concluded in 1996 that "HADS is a reliable and

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valid instrument for assessing anxiety and depression in medical patients.''

Since Herrmann's review the number of 'HADS-papers' that have been published has increased almost fourfold. These papers also include samples from the general population, which Herrmann's review did not. Another reason for conducting an updated review of HADS-related papers was to achieve more information about the following issues: (I) How is the factor structure, discriminant validity and the internal consistency of HADS? (II) How does HADS perform as a case finder for anxiety disorders and depression? (III) To what extent does HADS agree with other self-rating instruments (concurrent validity)?

Method

A search in the Medline, ISI and PsycINFO databases was performed in May 2000. All papers containing the terms 'Hospital' and 'Anxiety' and 'Depression' or 'HAD' or 'HADS' in the title or abstract were identified. The abstracts of these studies ($n = 1403$) were then inspected to ascertain whether they contained information about the HADS. The authors then reviewed 747 studies using the HADS for information regarding issues (I), (II) and (III), and 71 relevant papers were identified.

Factor structure, discriminant validity and internal consistency

The following information was gathered: the number of factors in HADS identified by factor analyses, the correlation between the subscales of HADS, and the internal consistency of the subscales (Cronbach's alpha).

HADS as a case finder for anxiety disorders and depression

Sensitivity and specificity of HADS in the different studies were chosen according to the cut-off value determined by a receiver operating characteristic (ROC) curve giving a maximal diagnostic contribution [4,5]. In studies without ROC curves, but with at least four cut-off values with given sensitivities and specificities, we plotted the ROC curves ourselves. The area under the ROC curve (AUC) is a measure of the information value inherent in a test to determine caseness over the whole range of possible threshold values [6]. An AUC value of 0.50 reflects a test that is unable to discriminate between cases and noncases, while a value of 1.00 means perfect sensitivity and specificity at all cut-off values. In the studies where the ROC curves were plotted by us, approximations of AUC were calculated using the trapezium rule [7]. (AUC between two cut-off points on the curve is a trapezium. All the trapeziums are summarized.)

Reported positive and negative predictive values were not regarded as appropriate measures for review because of their sensitivity to varying prevalence of 'true cases.'

Only studies where the diagnoses were made by a structured or semistructured diagnostic interview were considered for sensitivity and specificity measures.

Concurrent validity

The performance of HADS relative to other commonly used questionnaires and rating scales of anxiety and depression was based on correlation coefficients for instruments with a continuous scale, and sensitivity and specificity for instruments categorising individuals as having a disorder or not.

Results

Most studies using HADS have been done on selected samples of patients with cancer or other somatic illnesses. The psychometric properties of HADS were seldom the main issue in these studies, the sample sizes were mostly relatively small ($n < 250$), and the results were frequently given without further discussion. From general population samples, psychometric properties of HADS were only reported in three papers. Spinhoven et al. [8] reported from three different Dutch samples (total $N = 5393$), Lisspers et al. [9] from a sample of 624 Swedish subjects and Jimenez et al. [10] from a sample of 207 elderly Spanish subjects.

Factor structure, discriminant validity and internal consistency

Among the 19 studies reporting factor analysis of HADS (Table 1), 11 studies (total $N = 14{,}588$) achieved a two-factor structure, 5 studies (total $N = 3459$) a three-factor structure and 2 studies (total $N = 235$) a four-factor structure. Most studies used principal component analysis. The studies of Spinhoven et al. [8] and Lisspers et al. [9] based on data from the general population both reported a two-factor structure (total $N = 6017$). Spinhoven et al. found that the two-factor solution was stable across different age groups from the general population and in different clinical samples (general practice, medical outpatients with unexplained somatic symptoms and psychiatric outpatients). Lisspers et al. found the same two-factor structure for both males and females. Dunbar et al. [11] tested different factor models using a confirmatory factor analysis on samples of three different age groups (aged approximately 18, 39 and 58 years) from the general population ($n = 2547$). A three-factor model derived from the tripartite theory of anxiety and depression [12] produced the closest fit to the data across all the age groups, though testing the two-factor model achieved by Moorey et al. [13] showed measures of goodness of fit relatively close to the three-factor model (comparative fit index 0.93 vs. 0.97 and root mean square error of approximation 0.06 vs. 0.04).

Table 1
Factor analysis and internal consistency of the HADS

Reference	Version of HADS	*n*	Method of factor analysis	Number of factors	Cronbach's α	
					HADS-A	HADS-D
Anderson [75]	Swedish	163	PCA	4		
Bedford et al. [16]	English	132	PCA	2	.83	.86
Brandberg et al. [39]	Swedish	273	PCA	3	.85	.81
Costantini et al. [38]	Italian	197	PCA	2	.85	.89
Dagnan et al. [15]	English	341	PCA	2	.84	.83
Dunbar et al. [11]	English	2547	CFA	3		
Hammerlid et al. [36]	Norwegian Swedish	351	PCA	2	.89	.82
Herrmann et al. [3]	German	5338	PCA?[a]	2	.80	.81
Leung et al. [21]	English	100	PCA	3		
	Chinese	100	PCA	3	.81	.74
Lewis [29]	English	117	PCA	3		
Lisspers et al. [9]	Swedish	624	PCA	2	.84	.82
Martin and Thompson [40]	English	72	MLA	4	.82	.78
Martin and Thompson [30]	English	194	MLA	3	.76	.72
Moorey et al. [13]	English	568	PCA	2	.93	.90
Razavi et al. [31]	French	228	PCA	3		
Savard et al. [14]	French Canadian	162	PCA	2	.89	.89
Sigurdardottir et al. [72]	Swedish	89	PCA	2		
Soriano and Salavert [17]	Spanish	621	PCA	2		
Spinhoven et al. [8]	Dutch	6165	PCA	2		
Botega et al. [34]	Portuguese	78			.68	.67
el Rufaie et al. [35]	Arabic	217			.78	.88
Wettergren et al. [37]	Swedish	20			.88	.86

CFA: confirmatory factor analysis; HADS: Hospital Anxiety and Depression Scale; HADS-A: Anxiety subscale of HADS; HADS-D: Depression subscale of HADS; MLA: maximum likelihood factor analysis; PCA: principal component analysis.
[a] Not reported.

Based on these studies HADS performed as a bidimensional test, although the factors were not absolutely consistent with the subscales of Anxiety and Depression. The most consistent finding was that the HADS-A 4 item ("I can sit at ease and feel relaxed") showed relatively low loadings (< 0.60) on the anxiety factor and some loadings on the depression factor (> 0.45) [3,9,13–17].

Twenty-one studies reported the Pearson correlation coefficient between HADS-A and HADS-D (mean .56). In seven studies of nonpatient samples [10,17–22] the correlations varied between .49 and .74 (mean .59). In 12 studies of somatic patient samples [14,20,23–32] the correlations varied between .40 and .64 (mean .55). The last two studies of psychiatric patients both achieved a correlation of .56 [8,33].

Cronbach's alpha coefficient of internal consistency was reported in 15 studies (Table 1) and varied for HADS-A from .68 to .93 (mean .83), and for HADS-D from .67 to .90 (mean .82) [3,9,13–16,21,30,34–40].

HADS as a case finder for anxiety disorders and depression

Optimal balance between sensitivity and specificity for HADS as a screening instrument was achieved most frequently at a cut-off score of 8+ for both HADS-A and HADS-D giving sensitivities and specificities for both subscales of approximately 0.80.

The findings from the 24 papers reporting sensitivity and specificity are summarised according to the populations studied. More details are given in Table 2. Only one *community* survey ($n = 330$) was found [41] and ROC curves identified 8+ to be an optimal cut-off score for caseness for both anxiety disorders and depression based on ICD-9. Sensitivity and specificity for both anxiety and depression were approximately 0.90. The author reported similar results in samples from medical inpatient populations.

HADS was tested in three studies of *primary care* populations. Wilkinson and Barczak [42] ($n = 100$) found an excellent ability of HADS to detect DSM-III-defined psychiatric morbidity, and the ROC curves showed that a score of 8+ was the optimal threshold. The AUC was found to be 0.96. el Rufaie and Absood [35] studied patients ($n = 217$) attending a primary health care centre. The ROC curves (calculated by us) showed that the optimal cut-off scores for caseness were 9+ for HADS-A (sensitivity 0.66, specificity 0.93) and 7+ for HADS-D (sensitivity 0.66, specificity 0.97), when using DSM-III diagnoses obtained by the Clinical Interview Schedule as gold standard. AUC (calculated by us) was 0.86 for both anxiety and depression. Lam et al. [43], however, identified (by ROC curves) a lower optimal cut-off in their sample from a general practice ($n = 100$), 3+ for HADS-A and 6+ for HADS-D giving the sensitivities 0.67 and 0.78 and specificities 0.83 and 0.91, respectively. Their gold standard was not reported, but the Clinical Interview Schedule was used, presumably giving DSM-III diagnoses.

Table 2
Estimated sensitivity specificity of the HADS at optimal cut-off values[a]

Reference	Diagnostic system	Diagnostic instrument	Diagnosis	Patient population	*n*	Optimal cut-off values			Sensitivity			Specificity		
						A	D	T	A	D	T	A	D	T
el-Rufaie et al. [35]	DSM-III	CIS	Anxiety, depression	Primary care	217	9+	7+		0.66	0.66		0.93	0.97	
Lam et al. [43]	DSM-III?	CIS	Anxiety, depression	Primary care	100	3+	6+		0.67	0.78		0.83	0.91	
Wilkinson and Barczak [42]	DSM-III	SCID	Anxiety, depression	Primary care	100			8+			0.90			0.86
Botega et al. [34]	DSM-III	CIS	Anxiety, depression	General medical	78	9+	9+		0.94	0.85		0.73	0.90	
Costantini et al. [38]	DSM-III	DIS	Anxiety, depression	Breast Cancer	197			10+			0.84			0.79
Hall et al. [76]	DSM-III	PSE	Anxiety, depression	Breast cancer	266	7+	7+	12+	0.72	0.37	0.57	0.80	0.93	0.93
Hopwood et al. [77]	DSM-III	CIS	Anxiety, depression	Breast cancer	81	11+	11+	18+	0.75	0.75	0.81	0.90	0.75	0.89
Ibbotson et al. [78]	DSM-III	PAS	GAD, MDD	Cancer	513			14+			0.80			0.76
Lepine et al. [86]	DSM-III	CIDI	MDD	Internal medicine	150		8+			0.74			0.77	
Razavi et al. [79]	DSM-III	DIS	Adjustment disorders + MDD	Cancer	210	8+	7+	13+	0.64	0.59	0.75	0.72	0.78	0.75
			MDD only	Cancer	210	11+	7+	19+	0.54	0.71	0.70	0.75	0.76	0.75
Hamer et al. [46]	DSM-III	SCID	Anxiety, depression	Self-harm	100		8+			0.88			0.78	
Barczak et al. [74]	DSM-III	SCID	Specific phobias, GAD, dysthymia, MDD	Medical (genitourinary)	100	8+	8+		0.82	0.70		0.94	0.68	
Johnson et al. [44]	DSM-III	PAS	Anxiety, depression	Poststroke	93	4+	4+		0.95	0.83		0.38	0.44	
Clarke et al. [62]	DSM-III-R	SCID-R	MDD	General hospital	179		10+	21+		0.71	0.76		0.92	0.93
Kugaya et al. [80]	DSM III-R	SCID	Adjustment disorders+MDD	Cancer	128	8+	5+	11+	0.75	0.92	0.92	0.80	0.58	0.65
			MDD only	Cancer	128	8+	11+	20+	0.94	0.82	0.82	0.88	0.95	0.96
Razavi et al. [73]	DSM-III-R	DIS SCID	Adjustment disorders, depression, anxiety	Cancer	117			10+			0.84			0.66
Hosaka et al. [85]	DSM-IV	'Structured interview'	Adjustment disorders + MDD	Nonmalignant otolaryngeal	50			12+			0.93			0.86
				Malign. otolaryngeal	50			12+			0.91			0.96
Silverstone [81]	DSM-III-R ICD-10	SCAN	Modified MDD	General medical	153		8+	17+		1.00	1.00		0.73	0.75
				Psychiatric	147		10+	17+		0.68	0.95		0.46	0.21
Silverstone [82]	DSM-IV	SCAN	MDD	General medical	153		8+			0.91			0.71	
Berard et al. [83]	DSM-IV	SCID	Adjustment disorders	Cancer	100		8+			0.71			0.95	
			Depression	Cancer	100		11+			0.43			0.96	
Ramirez et al. [84]	Bedford Criteria	PSE	Anxiety, depression	Breast cancer	91			11+			0.84			0.83
Spinhoven et al. [8]	ICD-8	PSE	Depression	General medical out-patient	169		10+			0.56			0.92	
Abiodun [41]	ICD-9	PSE	Anxiety, depression	Medical and surgical	275	8+	8+		0.85	0.91		0.87	0.87	
				Gynecological	233	8+	8+		0.91	0.92		0.87	0.89	
				Antenatal	240	8+	8+		0.93	0.90		0.90	0.91	
				Community	330	8+	8+		0.88	0.90		0.91	0.91	

A: Anxiety subscale of the HADS; CIS: Clinical Interview Schedule; D: Depression subscale of the HADS; DIS: Diagnostic Interview Schedule; GAD: generalised anxiety disorder; HAMA: Hamilton Anxiety Scale; MADRS: Montgomery Asberg Depression Rating Scale; MDD: major depressive disorder; PAS: Psychiatric Assessment Schedule; PSE: Present State Examination; SCAN: Structured Clinical Assessment for Neuropsychiatric Disorders; SCID: Structured Clinical Interview for DSM-III/DSM-III-R/DSM-IV; T: total score of the HADS.

[a] For example, 8+ means equal to or above 8.

Table 3
Correlation coefficients between the HADS and other questionnaires and interview-based measures

Reference	Compared questionnaire	Correlation coefficients between HADS and the other questionnaire		
		HADS-A	HADS-D	HADS-T
Beck et al. [47]	BDI-PC		.62	
Lisspers et al. [9]	BDI	.64	.71	.73
Suàrez-Mendosa et al. [48]	BDI	.83		
Savard et al. [14]	BDI	.68	.70	
Tedman et al. [49]	BDI	.61	.73	
Watson et al. [50]	BDI	.69		
Lewis and Wessely [60]	GHQ-12			.75
Caplan [18]	GHQ-28	.68	.66	
Chandarana et al. [24]	GHQ-28	.50	.50	
Elliot [54]	STAI	.64	.52	
Herrmann et al. [20]	STAI	.66	.59	
Lisspers et al. [9]	STAI-S	.64		.68
	STAI-T	.66	.64	.71
Millar et al. [55]	STAI-S	.81		
Savard et al. [14]	STAI-S	.78	.65	
Lepine et al. [59]	MADRS		.62	
Snaith and Taylor [52]	MADRS	.37	.81	
Upadhyaya and Stanley [53]	MADRS		.80	
Aylard et al. [58]	MADRS (item 3)			.77
	CAS			.67
Snaith and Taylor [52]	CAS	.69	.44	
Upadhyaya and Stanley [53]	CAS	.75		
Spinhoven and van der Does [56]	SCL-90, Anxiety, Depression	.49	.69	
Watson et al. [50]	SCL-90, Anxiety, Depression	.73	.67	
Lepine et al. [59]	HAMA-S, HAMA-P, HAMA-T	.34 .40. 44		
Millar et al. [55]	VAS	.74		

BDI: Beck Depression Inventory; BDI-PC: Beck Depression Inventory for Primary Care; CAS: Clinical Anxiety Scale; HADS-A: Anxiety subscale of HADS; HADS-D: Depression subscale of HADS; HADS-T: Total score of HADS; HAMA-S: Hamilton Anxiety Scale — Somatic Items; HAMA-P: Hamilton Anxiety Scale — Psychic Items; HAMA-T: Hamilton Anxiety Scale — Total Scale; MADRS: Montgomery–Asberg Depression Rating Scale; SCL-90: Symptom Checklist 90 Scale; STAI-S: Spielberger State-Trait Anxiety Inventory — State Form; STAI-T: Spielberger State-Trait Anxiety Inventory — Trait Form; VAS: Visual Analogue Scale.

We identified 12 studies that addressed optimal cut-off scores for caseness in *noncancer medical patients* (total $N = 2109$). For HADS-A the mean optimal cut-off score was approximately 8+ (7.5), with resulting mean sensitivity 0.90, and mean specificity 0.78. Similarly, for HADS-D the mean optimal cut-off score also was approximately 8+ (8.1), with mean sensitivity 0.83, and mean specificity 0.79. Johnson et al. [44] studied poststroke patients ($n = 93$) and we estimated their optimal cut-off scores to be 5+ for HADS-A and 4+ for HADS-D, giving significantly lower specificity for both anxiety and depression (0.46 and 0.44, respectively) than in studies of other medical samples. Using the highest score of either HADS-A or HADS-D as an indicator of psychiatric morbidity, Morriss and Wearden [45] found that a cut-off score for caseness of 10+ resulted in sensitivity 0.92 and specificity 0.71 in a sample of chronic fatigue syndrome patients ($n = 136$). Hamer et al. [46] presented findings from a sample of 100 self-harming patients with an ROC curve, which showed 8+ to be the optimal cut-off score of caseness of HADS-D giving sensitivity 0.88 and specificity 0.78.

In the 10 studies of *cancer patients* (total $N = 1803$), the mean optimal cut-off score for caseness on HADS-A was approximately 9+ (8.8), with mean sensitivity 0.72, and mean specificity 0.81. For HADS-D the mean optimal cut-off score of caseness was approximately 8+ (8.3), with mean sensitivity 0.66, and mean specificity 0.83.

Concurrent validity

Six studies reported the correlations between Beck's Depression Inventory (BDI) and HADS. The correlations between BDI and HADS-D were .62 to .73, BDI and HADS-A .61 to .83 and BDI and HADS-total score (HADS-T) .73 [9,14,47–50] (Table 3). Two studies demonstrated that the correlations between the General Health Questionnaire (GHQ-28) and HADS-D were .50 and .66, and between GHQ-28 and HADS-A .50 and .68 [18,24]. The correlations between the Clinical Anxiety Scale [51] and HADS-A were .69 and .75 in two studies [52,53]. The correlations between Spielberger's State-Trait Anxiety Inventory (STAI) and HADS were examined in five studies [9,14,20,54,55]. Between STAI and HADS-A the correlations were in the range of .64 to .81, between STAI and HADS-D .52 to .65 and between STAI and HADS-T .68 to .71. Two studies examined the relationship between the

SCL-90 subscales of Anxiety and Depression and HADS [50,56]. The correlations between SCL-90 Anxiety and HADS-A were .49 and .73, while the correlations between SCL-90 Depression and HADS-D were .69 in both studies. Finally, in four studies the correlations between the interview-based Montgomery Asberg Depression Rating Scale [57] and HADS-D were in the range .62 to .81, while the correlation with HADS-T was .77 [52,53,58,59]. Low correlations (.34 to .44) were found between Hamilton Anxiety Rating Scale and HADS-A [59].

Three studies [42,60,61] compared the sensitivity and specificity of HADS to that of various editions of GHQ. HADS and GHQ had close to identical sensitivities and specificities, both at the level of 0.80 for HADS-A, HADS-D as well as for HADS-T. Clarke et al. [62] compared HADS, GHQ and BDI (against DSM-III-R diagnoses) by using Quality ROC curves. Here the GHQ performed marginally better than HADS and BDI.

Discussion

Bidimensionality

The results of our review support the two-factor structure of HADS. In most studies where empirically based exploratory factor analyses were used HADS revealed two relatively independent dimensions of anxiety and depression closely identical to the Anxiety and Depression subscales. The three-factor model supported by the theory-driven confirmatory factor analysis of Dunbar et al. [11], however, challenge the bidimensionality of HADS. Nevertheless, the fit measures of the two-factor model proposed by Moorey et al. [13] were relatively close to the three-factor model. In addition, Dunbar et al. did not test more than one two-factor model, while four three-factor models were tested, among whom one showed a much worse fit than the two-factor model.

Recognising the extensive comorbidity between anxiety and depression [63–65], the moderate to strong correlations between HADS-A and HADS-D subscales reported were to be expected. Burns and Eidelson [66] argued that the correlation between any valid and reliable measure of depression and anxiety should be at the .70 level, not because of shared symptoms between anxiety and depression, but because of a common causal factor. However, other authors have claimed that a low correlation between the two measures of anxiety and depression is a hallmark of good discriminant validity of a bidimensional test [12]. Watson et al. [50] stated that: ''Phenomenologically, anxiety and depression are clearly distinct from each other. Anxiety is centered on the emotion of fear and involves feelings of worry, apprehension, and dread; in contrast, depression is dominated by the emotion of sadness and is associated with feelings of sorrow, hopelessness, and gloom. Nevertheless, despite their seeming distinctiveness, it has proven difficult to distinguish these constructs empirically. Many studies have shown that self-report measures are highly correlated, with coefficients typically in the .45 to .75 range.'' Some authors have recommended not only the use of correlations between subscales to assess their divergent validity, but also a multitrait–multimethod approach [67]. In our search, however, no papers reported such a comprehensive assessment.

Internal consistency

It has been recommends that Cronbach's coefficient alpha should be at least .60 for a self-report instrument to be reliable [68]. This demand was fulfilled in all studies of HADS in various translations that report data on internal consistency. Similar findings of internal consistency from different translations of HADS supported the robustness of the instrument.

HADS as a case finder for anxiety disorders and depression

In this review the threshold values identified for optimal balance between sensitivity and specificity showed relatively little variability, and they were very close to 8+, defined as the cut-off for 'possible cases' suggested by Zigmond and Snaith in their original paper on HADS [1]. This threshold was found for HADS-A and HADS-D in the general population as well as in somatic patients samples. Two papers reported some deviating cut-off values; Lam et al. [43] found an optimal cut-off value of HADS-A at 3+ and of HADS-D at 6+, while Johnson et al. [44] found the optimal cut-off values of both HADS-A and HADS-D at 4+. An explanation may be that in both studies HADS was administered completely or partly as an interview, possibly biasing the responses to the items.

The sensitivity and specificity of HADS-A and HADS-D with a threshold of 8+ were most often found to be in the range of 0.70 to 0.90. The variation in both optimal cut-off values and sensitivity and specificity might be due to differences in diagnostic systems, 'gold standard' instruments, HADS translations used [21,69,70], as well as to differences in samples and procedures in administration of HADS [71] (such an explanation may also be applied to the varying results of the other psychometric properties of HADS). Among three studies of general practice patients AUCs were found to be 0.84–0.96. These results indicate excellent case finding abilities of HADS in unselected samples of patients seeking a general practitioner.

Concurrent validity

This review revealed that HADS, despite of its brevity, exhibited similar sensitivity and specificity as longer versions of GHQ. When compared to other questionnaires for anxiety and depression in common use such as BDI, STAI,

CAS, and SCL-90 Anxiety and Depression subscales, the correlation to HADS-D and HADS-A, respectively, were between .60 and .80, which should be characterised as medium to strong correlations. The same level of correlations was found when HADS-D was compared to Montgomery Asberg Depression Rating Scale. Accordingly, our conclusion is that the concurrent validity of HADS is *good* to *very good*.

Conclusions

This review confirmed the assumption that HADS is a questionnaire that performs well in screening for the separate dimensions of anxiety and depression and caseness of anxiety disorders and depression in patients from non-psychiatric hospital clinics. Even though a limited number of studies addressed other study populations, we found evidence that HADS has the same properties when applied to samples from the general population, general practice and psychiatric patients. HADS seems to have at least as good screening properties as similar, but more comprehensive, instruments used for identification of anxiety disorders and depression.

References

[1] Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361–70.

[2] Rust J, Golombok S. Modern psychometrics. London: Routledge, 1999.

[3] Herrmann C. International experiences with the Hospital Anxiety and Depression Scale—a review of validation data and clinical results. J Psychosom Res 1997;42:17–41.

[4] Murphy JM, Berwick DM, Weinstein MC, Borus JF, Budman SH, Klerman GL. Performance of screening and diagnostic tests. Application of receiver operating characteristic analysis. Arch Gen Psychiatry 1987;44:550–5.

[5] Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin Chem 1993;39:561–77.

[6] Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143: 29–36.

[7] Altman DG. Practical statistics for medical research. Boca Raton, FL: Chapman & Hall/CRC, 1991.

[8] Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27:363–70.

[9] Lisspers J, Nygren A, Soderman E. Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample. Acta Psychiatr Scand 1997;96:281–6.

[10] Jimenez CJ, Perez TA, Prieto FS, Navia-Osorio PM. Behavioural habits and affective disorders in old people. J Adv Nurs 1989;14: 356–64.

[11] Dunbar M, Ford G, Hunt K, Der G. A confirmatory factor analysis of the Hospital Anxiety and Depression Scale: comparing empirically and theoretically derived structures. Br J Clin Psychol 2000; 39:79–94.

[12] Clark LA, Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. J Abnorm Psychol 1991;100:316–36.

[13] Moorey S, Greer S, Watson M, Gorman C, Rowden L, Tunmore R, Robertson B, Bliss J. The factor structure and factor stability of the Hospital Anxiety and Depression Scale in patients with cancer. Br J Psychiatry 1991;158:255–9.

[14] Savard J, Laberge B, Gauthier JG, Ivers H, Bergeron MG. Evaluating anxiety and depression in HIV-infected patients. J Pers Assess 1998; 71:349–67.

[15] Dagnan D, Chadwick P, Trower P. Psychometric properties of the Hospital Anxiety and Depression Scale with a population of members of a depression self-help group. Br J Med Psychol 2000;73:129–37.

[16] Bedford A, Pauw KD, Grant E. The structure of the Hospital Anxiety and Depression Scale (HAD): an appraisal with normal, psychiatric and medical patient subjects. Pers Individ Differ 1997;23:473–8.

[17] Soriano J, Salavert L. The Hospital Anxiety and Depression Scale questionnaire in physical danger and evaluation situations. Couns Psychol Q 1996;9:281–96.

[18] Caplan RP. Stress, anxiety, and depression in hospital consultants, general practitioners, and senior health service managers. BMJ 1994;309:1261–3.

[19] King B, Cotes JE. Relation of lung function and exercise capacity to mood and attitudes to health. Thorax 1989;44:402–9.

[20] Herrmann C, Scholz KH, Kreuzer H. Psychologisches Screening von Patienten einer kardiologischen Akutklinik mit einer deutschen Fassung der ‘‘Hospital Anxiety and Depression (HAD)-Skala’’. Psychother Psychosom Med Psychol 1991;41:83–92.

[21] Leung CM, Ho S, Kan CS, Hung CH, Chen CN. Evaluation of the Chinese version of the Hospital Anxiety and Depression Scale. A cross-cultural perspective. Int J Psychosom 1993;40:29–34.

[22] Watson D, Clark LA, Weber K, Assenheimer JS, Strauss ME, McCormick RA. Testing a tripartite model: II. Exploring the symptom structure of anxiety and depression in student, adult, and patient samples. J Abnorm Psychol 1995;104:15–25.

[23] Bramley PN, Easton AME, Morley S, Snaith RP. The differentiation of anxiety and depression by rating scales. Acta Psychiatr Scand 1988;77:133–8.

[24] Chandarana PC, Eals M, Steingart AB, Bellamy N, Allen S. The detection of psychiatric morbidity and associated factors in patients with rheumatoid arthritis. Can J Psychiatry 1987;32:356–61.

[25] Channer KS, Papouchado M, James MA, Ress JR. Anxiety and depression in patients with chest pain referred for exercise testing. Lancet 1985;820–3.

[26] Farooq S, Gahir MS, Okyere E, Sheikh AJ, Oyebode F. Somatization: a transcultural study. J Psychosom Res 1995;39:883–8.

[27] Jenkins PL, Lester H, Alexander J, Whittaker J. A prospective study of psychosocial morbidity in adult bone marrow transplant recipients. Psychosomatics 1994;35:361–7.

[28] Kurer JR, Watts TL, Weinman J, Gower DB. Psychological mood of regular dental attenders in relation to oral hygiene behaviour and gingival health. J Clin Periodontol 1995;22:52–5.

[29] Lewis G. Observer bias in the assessment of anxiety and depression. Soc Psychiatry Psychiatr Epidemiol 1991;26:265–72.

[30] Martin CR, Thompson DR. A psychometric evaluation of the Hospital Anxiety and Depression Scale in coronary care patients following acute myocardial infarction. Psychol Health Med 2000;5:193–201.

[31] Razavi D, Delvaux N, Farvacques C, Robaye E. Validation de la version francaise du HADS dans une population de patients cancéreux hospitalés. Rev Psychol Appl 1989;39:295–308.

[32] Salkovskis PM, Storer D, Atha C, Warwick C. Psychiatric morbidity in an accident and emergency department characteristics of patients at presentation and one month follow-up. Br J Psychiatry 1990;156: 483–7.

[33] Tauschke E, Helmes E, Merskey H. Evidence that defence mechanisms are more related to personality than to symptoms. Br J Med Psychol 1991;64:137–46.

[34] Botega NJ, Bio MR, Zomignani MA, Garcia C, Pereira WA. Transtornos do humor em enfermaria de clinica medica e validacao de escala de medida (HAD) de ansiedade e depressao. Rev Saude Publica 1995;29:355–63.
[35] el Rufaie OE, Absood GH. Retesting the validity of the Arabic version of the Hospital Anxiety and Depression (HAD) scale in primary health care. Soc Psychiatry Psychiatr Epidemiol 1995;30:26–31.
[36] Hammerlid E, Ahlner-Elmqvist M, Bjordal K, Biorklund A, Evensen J, Boysen M, Jannert M, Kaasa S, Sullivan M, Westin T. A prospective multicentre study in Sweden and Norway of mental distress and psychiatric morbidity in head and neck cancer patients. Br J Cancer 1999;80:766–74.
[37] Wettergren L, Langius A, Bjorkholm M, Bjorvell H. Physical and psychosocial functioning in patients undergoing autologous bone marrow transplantation — a prospective study. Bone Marrow Transplant 1997;20:497–502.
[38] Costantini M, Musso M, Viterbori P, Bonci F, Del Mastro L, Garrone O, Venturini M, Morasso G. Detecting psychological distress in cancer patients: validity of the Italian version of the Hospital Anxiety and Depression Scale. Supportive Care Cancer 1999;7:121–7.
[39] Brandberg Y, Bolund C, Sigurdardottir V. Anxiety and depressive symptoms at different stages of malignant melanoma. Psychooncology 1992;1:71–8.
[40] Martin CR, Thompson DR. Utility of the Hospital Anxiety and Depression Scale in patients with end-stage renal disease on continuous ambulatory peritoneal dialysis. Psychol Health Med 1999;4:369–76.
[41] Abiodun OA. A validity study of the Hospital Anxiety and Depression Scale in general hospital units and a community sample in Nigeria. Br J Psychiatry 1994;165:669–72.
[42] Wilkinson MJ, Barczak P. Psychiatric screening in general practice: comparison of the General Health Questionnaire and the hospital anxiety depression scale. J R Coll Gen Pract 1988;38:311–3.
[43] Lam CL, Pan PC, Chan AW, Chan SY, Munro C. Can the Hospital Anxiety and Depression (HAD) Scale be used on Chinese elderly in general practice? Fam Pract 1995;12:149–54.
[44] Johnson G, Burvill PW, Anderson CS, Jamrozik K, Stewart-Wynne EG, Chakera TM. Screening instruments for depression and anxiety following stroke: experience in the Perth community stroke study. Acta Psychiatr Scand 1995;91:252–7.
[45] Morriss RK, Wearden AJ. Screening instruments for psychiatric morbidity in chronic fatigue syndrome. J R Soc Med 1998;91:365–8.
[46] Hamer D, Sanjeev D, Butterworth E, Barczak P. Using the Hospital Anxiety and Depression Scale to screen for psychiatric disorders in people presenting with deliberate self-harm. Br J Psychiatry 1991;158:782–4.
[47] Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behav Res Ther 1997;35:785–91.
[48] Suàrez-Mendoza AA, Cardiel MH, Caballero-Uribe CV, Ortega-Soto HA, Marquez-Marin M. Measurement of depression in Mexican patients with rheumatoid arthritis: validity of the Beck Depression Inventory. Arthritis Care Res 1997;10:194–9.
[49] Tedman BM, Young CA, Williams IR. Assessment of depression in patients with motor neuron disease and other neurologically disabling illness. J Neurol Sci 1997;152(Suppl 1):75–9.
[50] Watson D, Weber K, Assenheimer JS, Clark LA, Strauss ME, McCormick RA. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. J Abnorm Psychol 1995;104:3–14.
[51] Snaith RP, Baugh SJ, Clayden AD, Husain A, Sipple MA. The Clinical Anxiety Scale: an instrument derived from the Hamilton Anxiety Scale. Br J Psychiatry 1982;141:518–23.
[52] Snaith RP, Taylor CM. Rating scales for depression and anxiety: a current perspective. Br J Clin Pharmacol 1985;19(Suppl 1):17–20.
[53] Upadhyaya AK, Stanley I. Hospital anxiety depression scale. Br J Gen Pract 1993;43:349–50.
[54] Elliott D. Comparison of three instruments for measuring patient anxiety in a coronary care unit. Intensive Crit Care Nurs 1993;9:195–200.
[55] Millar K, Jelicic M, Bonke B, Asbury AJ. Assessment of preoperative anxiety: comparison of measures in patients awaiting surgery for breast cancer. Br J Anaesth 1995;74:180–3.
[56] Spinhoven P, van der Does AJ. Somatization and somatosensory amplification in psychiatric outpatients: an explorative study. Compr Psychiatry 1997;38:93–7.
[57] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–9.
[58] Aylard PR, Gooding JH, McKenna PJ, Snaith RP. A validation study of three anxiety and depression self-assessment scales. J Psychosom Res 1987;31:261–8.
[59] Lepine JP, Godchau M, Brun P, Lemperiere T. Evaluation del'anxiété et de la dépression chez de patients hospitalisés dans un service de médicine interne. Ann Med-Psychol 1985;143:175–89.
[60] Lewis G, Wessely S. Comparison of the General Health Questionnaire and the Hospital Anxiety and Depression Scale. Br J Psychiatry 1990;157:860–4.
[61] O'Rourke S, MacHale S, Signorini D, Dennis M. Detecting psychiatric morbidity after stroke: comparison of the GHQ and the HAD Scale. Stroke 1998;29:980–5.
[62] Clarke DM, Smith GC, Herrman HE. A comparative study of screening instruments for mental disorders in general hospital patients. Int J Psychiatry Med 1993;23:323–37.
[63] Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. Br J Psychiatry 1996;Suppl 30:17–30.
[64] Sartorius N, Ustun TB, Lecrubier Y, Wittchen HU. Depression comorbid with anxiety: results from the WHO study on psychological disorders in primary health care. Br J Psychiatry 1996;38–43 (Suppl).
[65] Mezzich JE, Ahn CW, Fabrega HJ, Pilkonis PA. Patterns of psychiatric comorbidity in a large population presenting for care. In: Maser JD, Cloninger CR, editors. Comorbidity of mood and anxiety disorders. Washington (DC): American Psychiatric Press, 1990. pp. 189–204.
[66] Burns DD, Eidelson RJ. Why are depression and anxiety correlated? A test of the tripartite model. J Consult Clin Psychol 1998;66:461–73.
[67] Campbell D, Fiske D. Convergent and discriminant validation by the multitrait–multimethod matrix. Psychol Bull 1959;56:81–105.
[68] Nunnally J, Bernstein I. Psychometric theory. New York: McGraw-Hill, 1994.
[69] Chaturvedi SK. Asian patients and the HAD scale. Br J Psychiatry 1990;156:133.
[70] Sham T, Farooq S, Gahir M, Okyere E, Sheikh J, Oyebode F. Patterns of somatisation: a cross-cultural study. Eur J Psychiatry 1996;10:69–75.
[71] Johnston M. Mood in chronic disease: questioning the answers. Curr Psychol 1999;18:71–87.
[72] Sigurdardottir V, Bolund C, Brandberg Y, Sullivan M. The impact of generalized malignant melanoma on quality of life evaluated by the EORTC questionnaire technique. Qual Life Res 1993;2:193–203.
[73] Razavi D, Delvaux N, Bredart A, Paesmans M, Debusscher L, Bron D, Stryckmans P. Screening for psychiatric disorders in a lymphoma out-patient population. Eur J Cancer 1992;28A:1869–72.
[74] Barczak P, Kane N, Andrews S, Congdon AM, Clay JC, Betts T. Patterns of psychiatric morbidity in a genitourinary clinic. A validation of the Hospital Anxiety Depression scale (HAD). Br J Psychiatry 1988;152:698–700.
[75] Andersson E. The Hospital Anxiety and Depression Scale. Homogeneity and the subscales. Soc Behav Pers 1993;21:197–204.
[76] Hall A, A'Hern R, Fallowfield L. Are we using appropriate self-report questionnaires for detecting anxiety and depression in women with early breast cancer? Eur J Cancer 1999;35:79–85.

[77] Hopwood P, Howell A, Maguire P. Screening for psychiatric morbidity in patients with advanced breast cancer: validation of two self-report questionnaires. Br J Cancer 1991;64:353–6.
[78] Ibbotson T, Maguire P, Selby P, Priestman T, Wallace L. Screening for anxiety and depression in cancer patients: the effects of disease and treatment. Eur J Cancer 1994;30A:37–40.
[79] Razavi D, Delvaux N, Farvacques C, Robaye E. Screening for adjustment disorders and major depressive disorders in cancer in-patients. Br J Psychiatry 1990;156:79–83.
[80] Kugaya A, Akechi T, Okuyama T, Okamura H, Uchitomi Y. Screening for psychological distress in Japanese cancer patients. Jpn J Clin Oncol 1998;28:333–8.
[81] Silverstone PH. Poor efficacy of the Hospital Anxiety and Depression Scale in the diagnosis of major depressive disorder in both medical and psychiatric patients. J Psychosom Res 1994;38:441–50.
[82] Silverstone PH. Concise assessment for depression (CAD): a brief screening approach to depression in the medically ill. J Psychosom Res 1996;41:161–70.
[83] Berard RM, Boermeester F, Viljoen G. Depressive disorders in an outpatient oncology setting: prevalence, assessment, and management. Psychooncology 1998;7:112–20.
[84] Ramirez AJ, Richards MA, Jarrett SR, Fentiman IS. Can mood disorder in women with breast cancer be identified preoperatively? Br J Cancer 1995;72:1509–12.
[85] Hosaka T, Awazu H, Aoki T, Okuyama T, Yamawaki S. Screening for adjustment disorders and major depression in otolaryngology patients using the Hospital Anxiety and Depression Scale. Int J Psychiatry Clin Pract 1999;3:38–43.
[86] Lepine JP, Godchau M, Brun P, Teherani M. Utilité des échelles d'auto-évaluation de l'anxiété et de la dépression en médicine interne. Acta Psychiatr Belg 1986;86:608–15.

PAPER II

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A dimensional versus a categorical approach to co-occurring anxiety and depression: The HUNT study

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Abstract

Background and Objective: Comorbidity between anxiety and depression and its clinical impact have almost exclusively been studied by a categorical approach in contrast to a dimensional one. Hence, the aim of this study was to explore the occurrence of anxiety and depression as *codimensions* and examine how co-occurring anxiety and depression was associated with impairment in a dimensional approach compared to a categorical one.

Study Design and Setting: In the cross-sectional Nord-Trøndelag Health Study 1995-97 (N=61,216) the relation between anxiety and depression was studied. Associations between continuous anxiety and depression scores and impairment were compared with associations between anxiety and depression categories and impairment by means of generalized and conventional logistic regression analyses.

Results: The relation between anxiety and depression scores was close to linear. Both the dimensional and the categorical approaches demonstrated strong associations between anxiety and depression, respectively, and impairment. The dose-response relation shown by the dimensional approach represented better the impact of co-occurring symptoms, particularly in the lower symptom range.

Conclusion: The dimensional approach is a useful supplement to the categorical one in clinical practice and research addressing comorbid anxiety and depression. By considering both anxiety and depression symptoms their respective contribution is better evaluated.

1. Introduction

In 1987 Goldberg et al [1] reported that the two highly correlated dimensions of anxiety and depression under lied the common mental disorders encountered in primary care. Based on these findings, he proposed a three-dimensional model for common mental disorders, consisting of anxiety, depression, and somatisation [2]. Similar models for milder psychopathology have been developed by other groups, such as the Tripartite Model of anxiety and depression by Clark and Watson [3]. That model was later developed further into the Integrated Hierarchical Model [4]. Krueger's model [5] identified an externalizing and an internalizing dimension, of which the latter encompassed the anxious-misery and fear sub-dimensions.

These models have been counterparts to the categorical classification systems that utilize thresholds of various symptoms to identify diagnostic entities. While the dimensional models mainly have been developed to refine the theoretical constructs of e.g. anxiety and depression, categorical diagnoses are more practically oriented for the clinician as well as for the researcher in need of diagnoses as outcome measures [6]. In the dimensional models anxiety and depression, respectively, are assumed to be conditions distributed on a continuum from minimal to maximal symptom load, as so-called spectrum disorders [7].

When studying the prevalence and consequences of comorbid anxiety and depression the categorical approach have been mostly used. High occurrence of such comorbidity between anxiety disorders and depression have been reported in samples from the general population [8] and primary care [9]. Comorbidity has also been associated with impaired treatment response to antidepressants [10], impaired recovery rate from depression, increased time to recovery, decreased time to relapse [11], as well as increased risk for suicide [12].

The categorical approach has, however, some limitations because of obliged diagnostic thresholds for clinical disorder [13]. Studies have shown that sub-threshold disorders have significant clinical impact regarding both morbidity, functional impairment, mortality, treatment, and prognosis [7, 14-18]. These facts support the notion of anxiety and depression as spectrum disorders consistent with the dimensional model [19]. However, as far as we know, a dimensional approach has not been applied when studying the impact of comorbid anxiety and depression.

Hence, in this study we wanted to examine the association between co-occurring anxiety and depression, and subjective impairment by use of a dimensional approach. To emphasize the dimensional perspective, we introduced the term *codimensionality*, as an equivalent to *comorbidity*. More precisely we asked the following research questions: (I) How is codimensionality between anxiety and depression occurring in the general population as to age, gender and symptom intensity? (II) How is co-occurring anxiety and depression associated with impairment due to chronic mental health problems as seen in a dimensional compared to a categorical approach?

2. Methods

2.1. Study population

Based on updated population register lists all inhabitants aged 20 years and above were invited to take part in the The Nord-Trøndelag Health Study 1995-97 (The HUNT 2 Study) [20]. Nord-Trøndelag County encompasses 3% of the Norwegian population, and except for a lower mean level of education, the County is representative of Norway. Of 92,100 eligible subjects aged 20-89 years, 65,648 (71.3%) participated in the study.

2.2. Assessment of anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) is a self-administered questionnaire consisting of 14 items, seven for anxiety (HADS-A subscale) and seven for depression (HADS-D subscale), each scored from 0 (not present) to 3 (highly present) on a Likert scale formulated in readily understandable language [21, 22]. To increase acceptability and to preclude that individuals felt tested for mental disorders, symptoms of severe psychopathology were not included. HADS-A contains items mainly concerned with restlessness and worry plus one item on panic attacks, while HADS-D focuses mainly on the reduced pleasure response aspect (anhedonia) of depression, as well as psychomotor retardation and depressed mood. The two-dimensional quality of HADS has been demonstrated by several factor analytic studies [22], as well as in the HUNT 2 population where the factors were identical with the sub-scales [23].With a categorical approach, a cut-off value of $\geq$ 8 in both sub-scales has demonstrated optimal screening

properties in identifying anxiety disorders and major depressive disorder, yielding sensitivities and specificities of approximately 0.80 [22]. In the present study sub-scale scores $\geq$ 8 were denoted “high-score” anxiety (or depression) and < 8 “low-score” anxiety (or depression). “Pure high-score anxiety” was restricted to cases without HADS-D scores $\geq$ 8, and “pure high-score depression restricted to cases without HADS-A scores $\geq$ 8. “Comorbid anxiety and depression” was defined by combined HADS-A $\geq$ 8 and HADS-D $\geq$ 8.

A total of 65,344 subjects of HUNT 2 filled in HADS. Valid ratings of the anxiety and depression sub-scales were defined as at least five completed items on HADS-A and HADS-D, respectively. The score of those who filled in five or six items was based on the sum of completed items multiplied with 7/5 or 7/6, respectively. By this procedure [24] the subjects with both valid HADS-A and HADS-D ratings were N = 61,216 (47.3% men). The youngest and oldest age groups were underrepresented (table 1).

2.3. Assessment of impairment

The HUNT questionnaire contained items in which the participants were asked whether they had any chronic (at least for one year) physical or mental diseases or injuries that impaired their daily life functioning. Subjects responding «moderate» or «much» on impairment due to mental problems were defined as impaired (n=1,676), while «no» or «little» was defined as not impaired (n=59,574).

2.4. Statistics

To examine the relation between anxiety and depression in the population the mean of the HADS-A /HADS-D ratio (AD-ratio) in men and women, respectively, was plotted against age strata. The relation between anxiety and depression throughout the symptom score range was demonstrated by plotting the mean HADS-D score and standard deviation (SD) against each score of HADS-A, and vice versa.

Associations between the dimensions of anxiety and depression, respectively, and impairment were examined by a dose-response approach. The effect of anxiety on impairment was evaluated in individuals low-score and high-score depression, respectively. Likewise, the effect of depression was evaluated in

individuals with the corresponding anxiety categories. The associations were estimated by graphical representations of generalized additive logistic regression analyses adjusting for age and gender, based on the generalized additive model (GAM) [25]. The outcome measure of such an analysis is a plot of odds ratios (OR) on a logarithmic scale where the reference value (OR = 1.00) corresponds to the mean value of the explanatory variable. Point-to-point 95% confidence intervals (CI) are demonstrating the relative precision of the point-to-point estimates along the plot.

Using a logistic regression models adjusting for age and gender, OR with CI for impairment due to chronic mental health problems were estimated for five different high-score anxiety/depression categories, compared to the category with combined low-score anxiety and low-score depression. Despite the attempt to define pure anxiety and depression groups by excluding cases with co-occurring high-score depression or anxiety, respectively, the co-occurring low-score depression and anxiety, respectively, might influence the association with impairment. Hence, to examine the effect of such co-occurring low-score symptoms, two models adjusting for HADS-D and HADS-A scores, respectively, were added.

To evaluate effect modification in the categorical analyses, interaction terms between the various anxiety/depression categories and age and gender, respectively, were added separately to all models. A two-sided p-value < 0.05 was chosen to indicate statistical significance. The statistical analyses were conducted using the software package of SPSS 11.0 and S-Plus 6.0.

2.5. Ethics

HUNT-II was approved by the Norwegian Data Inspectorate and Regional Committee for Medical Research Ethics in Health region IV of Norway.

3. Results

3.1. "Prevalence" and consistency of codimensionality

The age and gender stratification of mean anxiety and depression scores and subjective impairment due to mental health problems are shown in table 1 and the AD-ratios in figure 1. The mean anxiety score exceeded the depression score

(AD-ratio >1) in most strata. In general, women had higher anxiety scores, and marginally lower depression scores than men. The proportion of individuals with impairment due to mental health problems varied from 1.3% (men 20-29 years) to 4.3% (women 60-69 years). The younger age groups (20-39 years) and men were less impaired.

The relation between anxiety and depression throughout the symptom score range was close to linear, as demonstrated in figure 2. A tendency towards a more than proportional relation in the higher scores was found. However, the observations at this level were few. The mainly linear pattern was seen in all age and gender strata (data not shown).

3.2. Codimensionality and impairment

The GAM curves demonstrated dose-response relationships between anxiety score and impairment in co-occurring high-score as well as low-score depression (figure 3). Similar, although somewhat weaker, relationships were seen between depression score and impairment in co-occurring low-score and high-score anxiety. The almost linear relationship was demonstrated from the lowest symptom scores.

3.3. Comorbidity and impairment

Comorbid anxiety and depression (OR=32.1; CI: 28.2, 36.5) was more strongly associated with impairment than high-score anxiety and high-score depression alone (figure 4). Pure high-score anxiety (OR=10.5; CI: 9.1-12.1) was less associated with impairment than high-score anxiety without restriction on depressive symptoms (OR=15.2; CI: 13.6, 16.9). Adjusting for depressive symptoms weakened (33%) the association (OR=7.4; CI: 6.4, 8.7). Pure high-score depression (OR=3.9; CI 3.1, 4.8) was, likewise, more weakly associated with impairment than high-score depression without restriction on anxiety symptoms (OR=9.8; CI 8.9, 10.9). The association was further attenuated (55%) after adjusting for anxiety symptoms (OR=2.3; CI 1.9, 2.9). All anxiety/depression categories were more strongly associated with impairment in younger than older age groups. No such effect modification was observed for gender.

4. Discussion

We found that mean anxiety scores in general exceeded mean depression scores in both genders, however, less markedly by increasing age. The relation between anxiety and depression scores was close to linear. A dose-response relationship between anxiety symptoms and impairment was clearly demonstrated in both the low-score and high-score depression categories. A similar relation was found between depression symptoms and impairment in the anxiety categories. All the high-score anxiety/depression categories were associated with subjective impairment, but more so in younger than older age groups. The two high-score anxiety categories were more strongly associated with impairment than the high-score depression categories and the comorbid category still more than the others.

4.1. Strengths and limitations of the study

In a sample from the general population encompassing all adult age groups with a high participation rate, selection bias should not be a major problem. However, despite a high attendance rate (78%) in another Norwegian health survey the prevalence of (hospitalized) psychiatric disorders was 2.5 times higher among nonattenders than attenders [26]. Furthermore, in the younger and older age groups where the participation rates were lower, such bias could not be ruled out. Unfortunately, in the absence of an analysis of non-participation, the effects of an age dependent selection bias was difficult to predict. The observed moderating effect of age on the association between anxiety and depression, respectively, and impairment, might be the result of non-participation of the more impaired individuals in the older age groups. Assuming an overrepresentation of impaired subjects among the participant in the youngest age groups is, however, more questionable.

Due to the cross-sectional design of the study we could not examine the stability of the anxiety and depression symptoms longitudinally, which would be of interest when interpreting the co-occurrence of the symptoms. An unstable relation between anxiety and depression might question the importance of assessing e.g. co-occurring anxiety when depression is addressed. However, the strong associations between symptoms even in the low-score range and impairment suggest that these symptoms are relatively stable.

Moreover, due to the cross-sectional design we could not draw any causal inferences between the anxiety-depression conditions and impairment. However, the participants were asked specifically to report chronic impairment *due to* chronic mental health problems, and not any general impairment that could *cause* anxiety or depression. Furthermore, a study design assuming that the participant were in the very beginning of their «disordered period» at baseline, would be very difficult to perform.

Unlike the categorical approach to psychopathology defined by diagnostic criteria, the dimensional models have no officially accepted common, well-established measure of anxiety or depression. We used HADS, and our findings of the relationship between anxiety and depression must be interpreted with the limitations of that rating scale in mind. Contrary to most prevalence studies, depression assessed by HADS-D is not more common among women and is more prevalent in the older age groups [27, 28]. However, in some studies using the Center for Epidemiologic Studies Depression Scale [29, 30] and Zung Self-Rating Depression Scale [31, 32] the same age effect has been observed. Furthermore, in the US National Comorbidity Survey (NCS) the gender differences in prevalence of depression without somatic symptoms (appetite and sleep disturbances and fatigue), like the “somatic free” HADS-D, were minimal [33].

4.2. The relationship between anxiety and depression symptom scores

The finding that the AD-ratio exceeded 1.0 in most strata emphasizes the major role of anxiety in affective conditions. Also, when using categorical measures, as in the Epidemiological Catchment Area Study [34] or NCS [8] the same leading position of anxiety was demonstrated. In a re-analysis of these two major population studies, the one-year prevalence rates of any anxiety disorder and major depressive episode were estimated to 11.8% and 4.5%, respectively. In NCS anxiety disorders were also more often comorbid with major depression (51.2%) than the opposite (22.1%). Our finding of a decrease in AD-ratio by increasing age in both genders is in accordance with studies demonstrating a temporal pattern where anxiety is dominating in early life, gradually being more mixed up by depression over time [8, 35].

The close to linear relation between HADS-A and HADS-D indicates that the codimensionality between anxiety and depression is independent of score levels, i.e. the relation between HADS-A and HADS-D is the same in low and high symptoms scores. A clinical implication of this finding might be to pay more attention to the occurrence of codimensional conditions in the low-score range.

4.3. Codimensionality and impairment

The dose-response relation between symptom scores and subjective impairment was distinct in our data starting in the sub-threshold area of both sub-scales. That finding was very similar to the results of Angst and Merikangas in the Zürich study [36] and Judd et al in the National Institute of Mental Health Collaborative Depression Study [37] regarding depression and impairment. A dose-response relationship has been found between symptoms of social anxiety [38, 39] and posttraumatic stress disorder [40], respectively, and impairment as well. Hence, our findings support the notion that depression is a spectrum disorder, and suggest that for anxiety, too. The very distinct dose-response relations in the low-score range for both anxiety and depression indicate that the dimensional view of anxiety and depression is not only of theoretical interest, but of clinical importance as well. Patients not fulfilling the diagnostic criteria for either an anxiety disorder or depression might very well be impaired from their symptoms [36].

4.4. Comorbidity and impairment

High-score anxiety and high-score depression without restrictions as to levels of co-occurring depression and anxiety, respectively, were more strongly associated with impairment than pure high-score anxiety and pure high-score depression. The latter ones have by definition a lower total HADS score, which most probably is the cause of the difference. The stronger effect of pure high-score anxiety than pure high-score depression on impairment, indicates that the anxiety component is stronger determinant for impairment. Furthermore, adjusting for anxiety symptoms in pure high-score depression weakened the association with impairment more (55%) than adjustment for depression symptoms in pure high-score anxiety (33%).

We have not found any studies that have examined the possible moderating effect of age on the association between anxiety and depression, respectively, and impairment. This may probably be due to smaller sample sizes and narrower age range in most other studies. However, provided that anxiety disorders and depression in general have a relatively chronic course [41], their reduced effect on subjective impairment by increasing age in our study could be explained by increasingly competent emotion regulation across the life span [42, 43].

4.5. Dimensional versus categorical approach

Both approaches demonstrated that anxiety as well as depression, and in particular the combination of the two, was strongly predictive for impairment. These results are in accordance with the conclusions from the Australian National Survey of Mental Health and Well-Being that the combination of affective (depression and dysthymia) and anxiety disorders was more predictive of disability and service utilization than any other combinations of mental disorders [44]. Moreover, in the Global Burden of Disease Study (GBD) [45], depression was ranked as one of the most important specific cause of global disability-adjusted life year. The impact of anxiety disorders was not addressed in GBD, but other studies have demonstrated considerable impairment associated with anxiety disorders, particularly posttraumatic stress disorder [46], panic disorder [47, 48], social phobia [49] and generalized anxiety disorder [50]. A systematic review of the outcome of anxiety and depressive disorders [51] concluded, consistently with our results, that there is some evidence that anxiety disorders had a worse outcome than depressions.

The dimensional approach demonstrated the impact of co-occurring symptoms throughout the entire range of scores, even in the lower part. That finding indicates that categorical analyses should be performed and interpreted with caution. Our results showed that high-score depression without any anxiety restriction was more than twice as strongly associated with impairment as pure high-score depression. Hence, ignoring the degree of co-occurring anxiety would induce a significant bias. Even in pure high-score depression the co-occurring anxiety symptoms contributed as much as the depression itself to the association with impairment.

4.6. Conclusions

The dimensional approach may be a useful supplement to the categorical one in clinical practice and research, giving a more complete description and comprehension of comorbid anxiety and depression. Our data suggest that the degree of symptoms is closely related to the degree of suffering, even in the lower range of the symptom scales. Hence, the clinician should try to apply a dimensional approach when assessing anxiety as well as depression in help-seeking patients, not at least when diagnostic criteria are not fulfilled. For the researcher the reported relations might be a reminder of the importance of considering the level of co-occurring anxiety symptoms when addressing depression, and vice versa. Assuming that anxiety and depression are different, though related conditions, ignoring a codimensional condition may bias the estimates of the associations studied. By setting some restrictions to the degree of co-occurring anxiety and depression and/or adjusting for the other one, their respective contribution may be better evaluated.

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References

[1] Goldberg DP, Bridges K, Duncan-Jones P, Grayson D. Dimensions of neuroses seen in primary-care settings. Psychol Med 1987;17(2):461-70.

[2] Goldberg D. A dimensional model for common mental disorders. Br J Psychiatry 1996;Suppl 30:44-9.

[3] Clark LA, Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. J Abnorm Psychol 1991;100(3):316-36.

[4] Mineka S, Watson D, Clark LA. Comorbidity of anxiety and unipolar mood disorders. Annual Review of Psychology 1998;49:377-412.

[5] Krueger RF. The structure of common mental disorders. Arch Gen Psychiatry 1999;56(10):921-6.

[6] Goldberg D. Plato versus Aristotle: categorical and dimensional models for common mental disorders. Compr Psychiatry 2000;41;2 Suppl 1:8-13.

[7] Angst J, Sellaro R, Merikangas K. Depressive Spectrum Diagnoses. Comprehensive Psychiatry 2000;41:39-47.

[8] Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. Br J Psychiatry 1996;Suppl 30:17-30.

[9] Sartorius N, Ustun TB, Lecrubier Y, Wittchen HU. Depression comorbid with anxiety: results from the WHO study on psychological disorders in primary health care. Br J Psychiatry 1996;Suppl 30:38-43.

[10] Brown C, Schulberg HC, Madonia MJ, Shear MK, Houck PR. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. Am J Psychiatry 1996;153(10):1293-300.

[11] Coryell W, Endicott J, Winokur G. Anxiety syndromes as epiphenomena of primary major depression: outcome and familial psychopathology. Am J Psychiatry 1992;149(1):100-7.

[12] Angst J. Comorbidity of anxiety, phobia, compulsion and depression. Int Clin Psychopharmacol 1993;8 Suppl 1:21-5.

[13] Schotte K, Cooper B. Subthreshold affective disorders: a useful concept in psychiatric epidemiology? Epidemiologia e Psichiatria Sociale 1999;8:255-261.

[14] Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic. Jama 1990;264(19):2524-8.

[15] Johnson J, Weissman MM, Klerman GL. Service utilization and social morbidity associated with depressive symptoms in the community. Jama 1992;267(11):1478-83.

[16] Angst J, Merikangas KR, Preisig M. Subthreshold syndromes of depression and anxiety in the community. J Clin Psychiatry 1997;Suppl 8:6-10.

[17] Maier W, Gansicke M, Weiffenbach O. The relationship between major and subthreshold variants of unipolar depression. J Affect Disord 1997;45(1-2):41-51.

[18] Rapaport MH, Judd LL. Minor depressive disorder and subsyndromal depressive symptoms: functional impairment and response to treatment. J Affect Disord 1998;48(2-3):227-32.

[19] Preisig M, Merikangas KR, Angst J. Clinical significance and comorbidity of subthreshold depression and anxiety in the community. Acta Psychiatr Scand 2001;104:96-103.

[20] Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen T, Bratberg G, et al. The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation. Norsk Epidemiologi 2003;13(1):19-32.

[21] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361-370.

[22] Bjelland I, Dahl AA, Haug T, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An Updated review. J Psychosom Res 2002;52(2):69-77.

[23] Mykletun A, Stordal E, Dahl AA. The Hospital Anxiety and Depression Scale (HADS): Factor Structure, Item Analyses, and Internal Consistency in a Large Population. Br J Psychiatry 2001;179:540-544.

[24] Nunnaly J, Bernstein I. Psychometric Theory. 3 ed. New York, NY: McGraw-Hill; 1994.

[25] Hastie T, Tibshirani R. Generalized Additive Models. 1 ed. London: Chapman & Hall; 1990.

[26] Hansen V, Jacobsen BK, Arnesen E. Prevalence of serious psychiatric morbidity in attenders and nonattenders to a health survey of a general population : the Tromso Health Study. Am J Epidemiol 2001;154(10):891-4.

[27] Stordal E, Krüger MB, Dahl NH, Krüger Ø, Mykletun A, Dahl AA. Depression in relation to age and gender in the general population - the Nord-Trøndelag Health Study (HUNT). Acta Psychiatr Scand 2001;104(3):210-216.

[28] Stordal E, Mykletun A, Dahl AA. The association between age and depression in the general population: a multivariate examination. Acta Psychiatr Scand 2003;107(2):132-41.

[29] Murrell SA, Himmelfarb S, Wright K. Prevalence of depression and its correlates in older adults. Am J Epidemiol 1983;117(2):173-85.

[30] Beekman AT, Deeg DJ, van Tilburg T, Smit JH, Hooijer C, van Tilburg W. Major and minor depression in later life: a study of prevalence and risk factors. J Affect Disord 1995;36(1-2):65-75.

[31] Blumenthal MD. Measuring depressive symptomatology in a general population. Arch Gen Psychiatry 1975;32(8):971-8.

[32] Knight RG, Waal-Manning HJ, Spears GF. Some norms and reliability data for the State-Trait Anxiety Inventory and the Zung Self-Rating Depression scale. Br J Clin Psychol 1983;22 (Pt 4):245-9.

[33] Silverstein B. Gender difference in the prevalence of clinical depression: the role played by depression associated with somatic symptoms. Am J Psychiatry 1999;156(3):480-2.

[34] Regier D, Kaelber C. The Epidemiologic Catchment Area (ECA) Program: Studying the prevalence and incidence of psychopathology. In: Tsuang M, Tohen M, Zahner G, editors. Textbook in Psychiatric Epidemiology. New York: Wiley-Liss; 1995: 135-55.

[35] Wittchen HU, Kessler RC, Pfister H, LIeb M. Why do people with anxiety disorders become depressed? A prospective-longitudinal community study. Acta Psychiatr Scand 2000;Suppl 406:14-23.

[36] Angst J, Merikangas KR. Multi-dimensional criteria for the diagnosis of depression. J Affect Disord 2001;62(1-2):7-15.

[37] Judd LL, Akiskal HS, Zeller PJ, Paulus M, Leon AC, Maser JD, et al. Psychosocial disability during the long-term course of unipolar major depressive disorder. Arch Gen Psychiatry 2000;57(4):375-80.

[38] Merikangas KR, Avenevoli S, Acharyya S, Zhang H, Angst J. The spectrum of social phobia in the Zurich cohort study of young adults. Biol Psychiatry 2002;51(1):81-91.

[39] Stein M, Torgrud L, Walker J. Social Phobia Symptoms, Subtypes, and Severity. Arch Gen Psychiatry 2000;57:1046-1052.

[40] Moreau C, Zisook S. Rationale for a posttraumatic stress spectrum disorder. Psychiatr Clin North Am 2002;25(4):775-90.

[41] Gross JJ, Carstensen LL, Pasupathi M, Tsai J, Skorpen CG, Hsu AY. Emotion and aging: experience, expression, and control. Psychol Aging 1997;12(4):590-9.

[42] Lawton MP, Kleban MH, Rajagopal D, Dean J. Dimensions of affective experience in three age groups. Psychol Aging 1992;7(2):171-84.

[43] Folkman S, Lazarus RS, Pimley S, Novacek J. Age differences in stress and coping processes. Psychol Aging 1987;2(2):171-84.

[44] Andrews G, Slade T, Issakidis C. Deconstructing current comorbidity: data from the Australian National Survey of Mental Health and Well-Being. Br J Psychiatry 2002;181:306-14.

[45] Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349(9063):1436-42.

[46] Warshaw MG, Fierman E, Pratt L, Hunt M, Yonkers KA, Massion AO, et al. Quality of life and dissociation in anxiety disorder patients with histories of trauma or PTSD. Am J Psychiatry 1993;150(10):1512-6.

[47] Markowitz JS, Weissman MM, Ouellette R, Lish JD, Klerman GL. Quality of life in panic disorder. Arch Gen Psychiatry 1989;46(11):984-92.

[48] Candilis PJ, McLean RY, Otto MW, Manfro GG, Worthington JJ, 3rd, Penava SJ, et al. Quality of life in patients with panic disorder. J Nerv Ment Dis 1999;187(7):429-34.

[49] Antony MM, Roth D, Swinson RP, Huta V, Devins GM. Illness intrusiveness in individuals with panic disorder, obsessive-compulsive disorder, or social phobia. J Nerv Ment Dis 1998;186(5):311-5.

[50] Roy-Byrne PP. Generalized anxiety and mixed anxiety-depression: association with disability and health care utilization. J Clin Psychiatry 1996;Suppl 7:86-91.

[51] Emmanuel J, Simmonds S, Tyrer P. Systematic review of the outcome of anxiety and depressive disorders. Br J Psychiatry 1998;Suppl 34:35-41.

TABLE 1

Mean anxiety and depression scores, and individuals with subjective impairment due to mental health problems in the different age and gender strata. The Nord-Trøndelag Health Study 1995-97 (HUNT 2).

				HADS-A [a]		HADS-D [b]		Individuals with impairment [c]	
Age		n [d]	(%)	Mean	(SD)	Mean	(SD)	n	(%)
20-29	Men	3,909	(41.0)	4.1	(2.9)	2.4	(2.4)	50	(1.3)
	Women	4,713	(54.4)	4.5	(3.2)	2.2	(2.4)	77	(1.6)
30-39	Men	5,335	(60.5)	4.2	(3.1)	2.9	(2.7)	83	(1.6)
	Women	6,061	(74.1)	4.6	(3.4)	2.7	(2.8)	131	(2.2)
40-49	Men	6,394	(70.3)	4.2	(3.3)	3.6	(3.0)	165	(2.6)
	Women	6,929	(80.6)	4.6	(3.5)	3.2	(3.0)	205	(3.0)
50-59	Men	5,251	(74.3)	4.0	(3.2)	4.1	(3.2)	167	(3.2)
	Women	5,553	(82.1)	4.8	(3.6)	3.7	(3.1)	209	(3.8)
60-69	Men	4,045	(77.6)	3.5	(3.0)	4.1	(3.1)	131	(3.2)
	Women	4,285	(78.7)	4.7	(3.6)	4.1	(3.2)	182	(4.3)
70-79	Men	3,172	(66.0)	3.3	(3.0)	4.4	(3.3)	86	(2.7)
	Women	3,487	(61.1)	4.3	(3.4)	4.4	(3.3)	97	(2.8)
80-89	Men	824	(39.7)	3.1	(3.0)	4.9	(3.5)	30	(3.6)
	Women	1,162	(34.8)	4.0	(3.6)	4.7	(3.5)	48	(4.1)
Total		61,216	(65.0)	4.3	(3.4)	3.5	(3.1)	1676	(2.7)

[a] Hospital Anxiety and Depression Scale, anxiety sub-scale
[b] Hospital Anxiety and Depression Scale, depression sub-scale
[c] Self-reported impairment due to chronic mental health problems
[d] With valid HADS-A and HADS-D

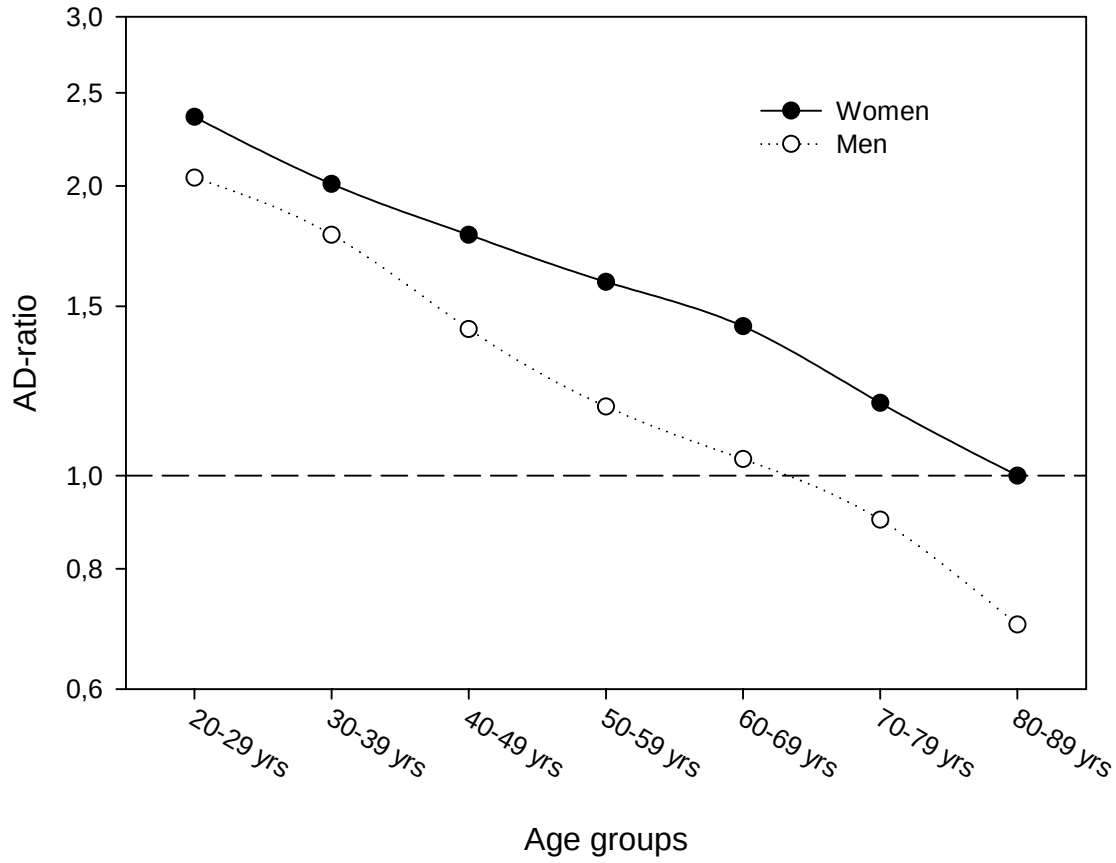

FIGURE 1. The relationship between mean anxiety and depression symptoms in age and gender strata. AD-ratio, mean (HADS-A / HADS-D); HADS-A, anxiety sub-scale of the Hospital Anxiety and Depression Scale; HADS-D, depression sub-scale of the Hospital Anxiety and Depression Scale.

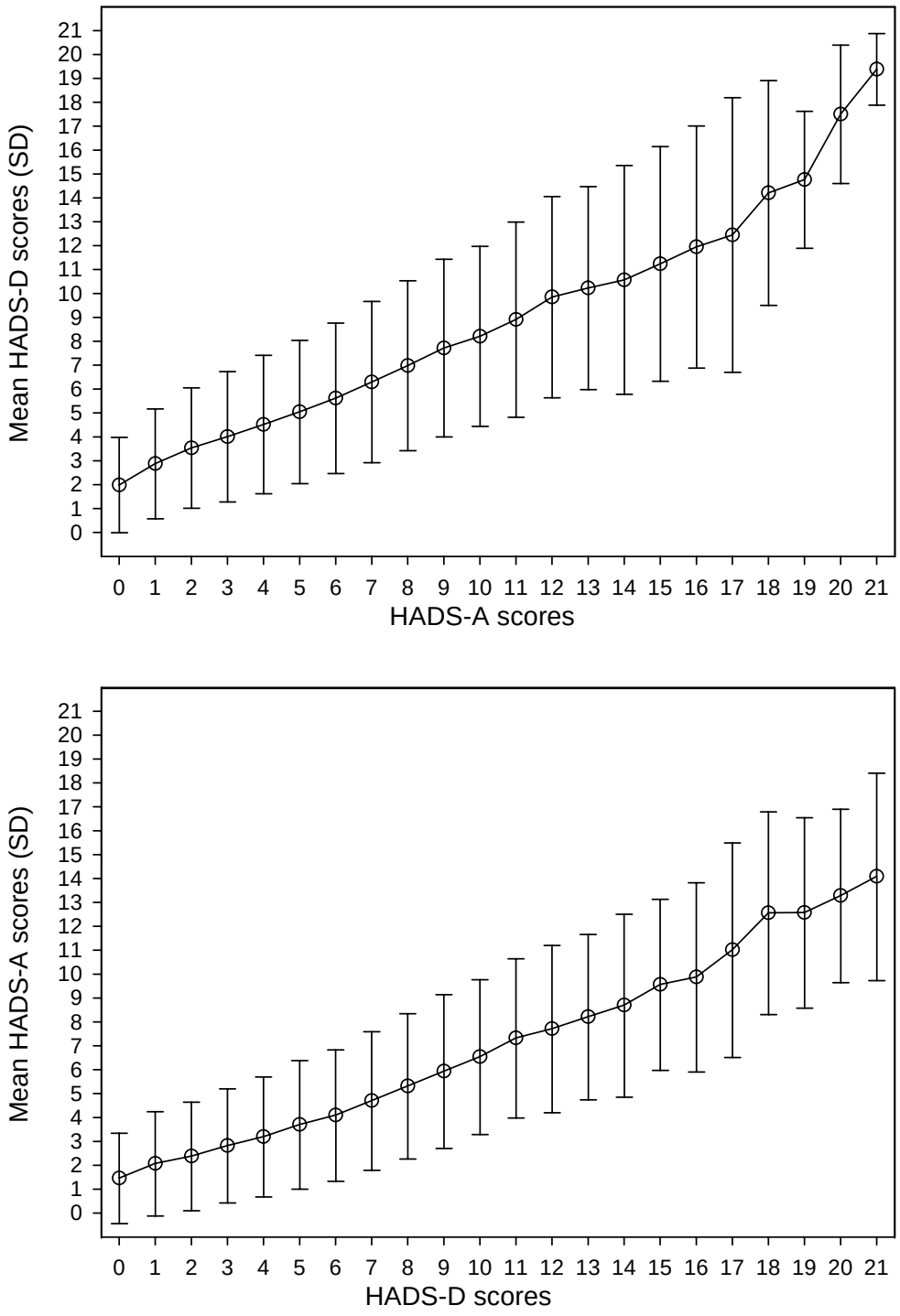

FIGURE 2. Relationship between increasing anxiety scores and mean depression scores, and between increasing depression scores and mean anxiety scores. Standard deviations (SD) are demonstrated by the whiskers. HADS-A, anxiety sub-scale of the Hospital Anxiety and Depression Scale; HADS-D, depression sub-scale of the Hospital Anxiety and Depression Scale.

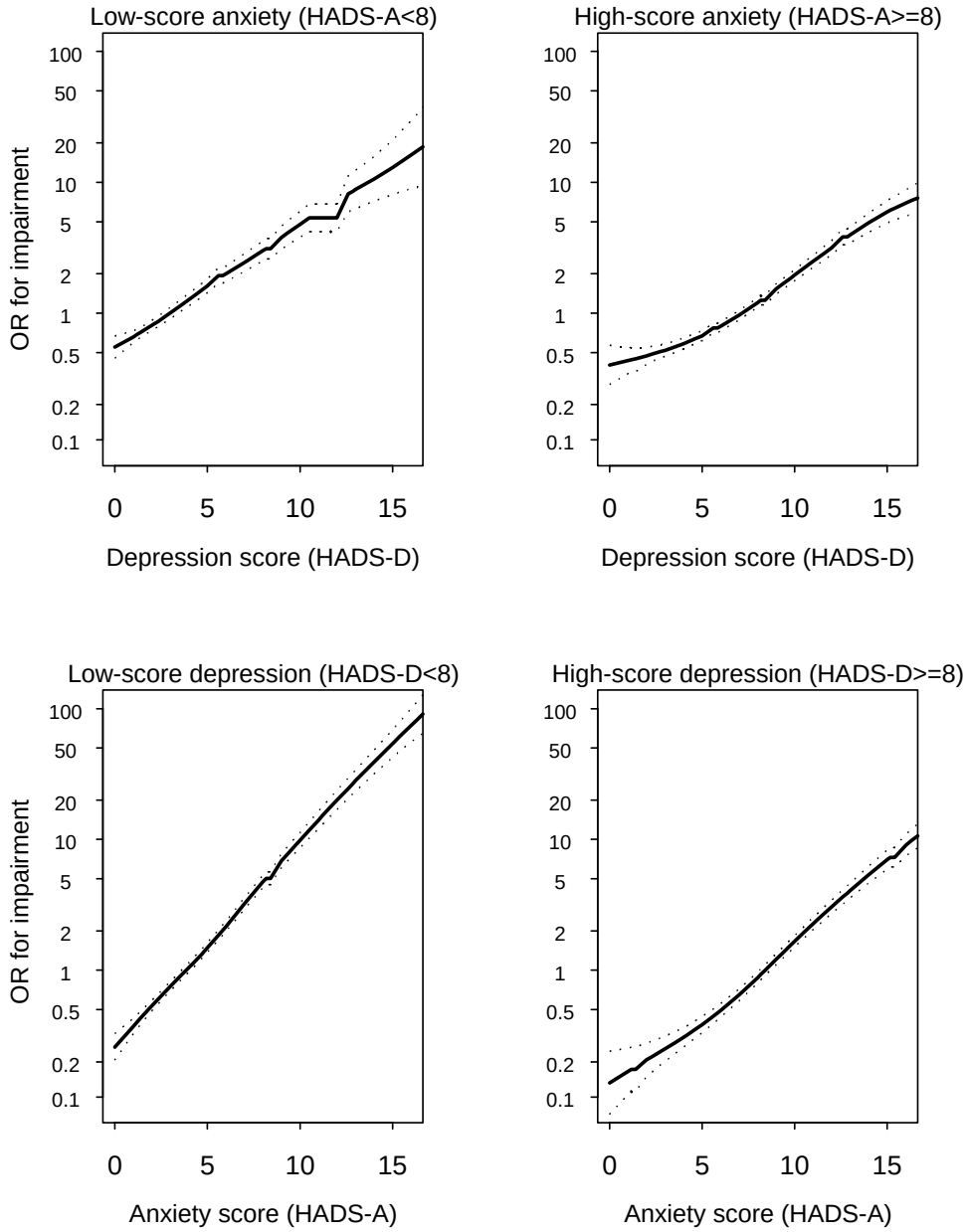

FIGURE 3. Dose-response relationships between anxiety (bottom panels) and depression (top panels) scores, respectively, and subjective impairment due to chronic mental health problems. The presentations are divided according to co-occurring low-score (left panels) and high-score (right panels) depression and anxiety, respectively. The curves were constructed by using generalized additive regression analyses adjusting for age and gender. The dotted lines indicate 95% pointwise confidence intervals. HADS-A, anxiety sub-scale of the Hospital Anxiety and Depression Scale; HADS-D, depression sub-scale of the Hospital Anxiety and Depression Scale.

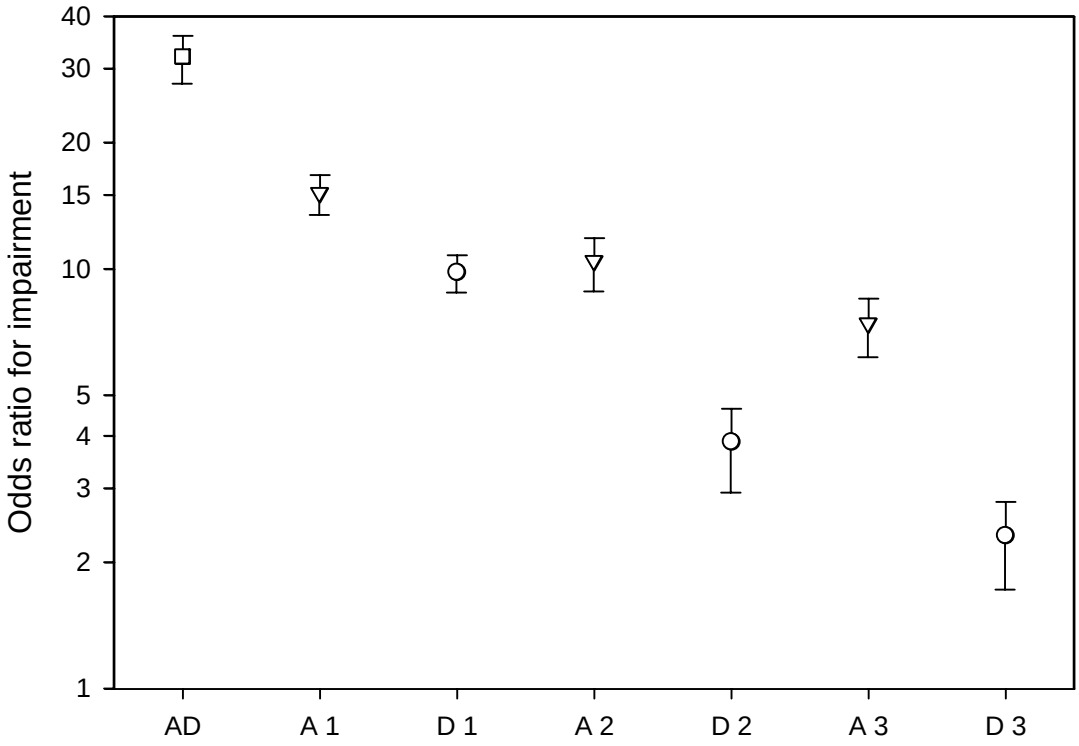

FIGURE 4. Associations between the different anxiety-depression categories and subjective impairment due to chronic mental health problems. 95% confidence intervals are indicated by whiskers. All odds ratios are adjusted for age and gender. AD, Comorbid anxiety and depression (HADS-A≥8; HADS-D≥8); A1, High-score anxiety (HADS-A≥8); D1, High-score depression (HADS-D≥8); A2, Pure high-score anxiety (HADS-A≥8; HADS-D<8); D2, Pure high-score depression (HADS-D≥8; HADS-A<8); A3, Pure high-score anxiety adjusted for depression symptoms (HADS-D score); D3, Pure high-score depression adjusted for anxiety symptoms (HADS-A score). HADS-A, anxiety sub-scale of the Hospital Anxiety and Depression Scale; HADS-D, depression sub-scale of the Hospital Anxiety and Depression Scale.

PAPER III

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healthsciences

Anxiety and depression in individuals with somatic health problems. The Nord-Trøndelag Health Study (HUNT)

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Objective **– To examine the relationship between anxiety disorders and depression and various somatic health problems in the general population.**
Design **– Cross-sectional study with survey methods and clinical examinations.**
Setting **– The Health Study of Nord-Trøndelag, Norway (the HUNT study).**
Participants **– 60 869 individuals aged 20–89 years.**
Main outcome measures **– Anxiety disorder, depression and their comorbidity are categorized based on scores on the Hospital Anxiety and Depression Scale. All somatic health variables are self-reported, while blood pressure, height and weight are measured. Multivariate nominal logistic regression analyses are used to investigate the relationship between somatic variables and the anxiety/depression categories.**
Results **– Most somatic health variables show a stronger association with comorbid anxiety disorder/depression than with anxiety disorder or depression alone. About one-third of individuals reporting somatic health problems also have anxiety disorder and/or depression.**
Conclusion **– Somatic health problems carry a high risk of both anxiety disorder and depression. Active identification and treatment of these co-occurring mental disorders are of practical importance.**

Key words: **anxiety, comorbidity, depression, somatic health problems.**

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Several studies have reported a high occurrence of depressive symptoms in patients with various somatic health problems (1,2). However, the occurrence of anxiety symptoms in these patients is less well examined (3). Epidemiological and clinical studies have shown that states of anxiety and depression frequently coexist (4–6). Patients with comorbid anxiety disorder and depression show more impairment (7), lower treatment response (8) and poorer long-term outcome (9) compared to those with only one disorder. The relationship between somatic health problems and comorbid states of anxiety and depression has been given little attention in the literature. One reason could be that in most studies self-rating instruments have been used that measure only one of these affects or general mental distress alone. In addition, most studies of the relationship between somatic health problems and these affective states have been performed on selected samples of patients from hospitals or primary care. Selection bias is a frequent occurrence in such studies and can be reduced by studying population-based samples.

The aim of this study was to investigate the relationship between somatic health problems and comorbid states of anxiety and depression (contrasted to the 'pure' states) in a cross-sectional study of a general population.

MATERIAL AND METHODS

Participants

Of the total population of Nord-Trøndelag County of Norway aged 20 to 89 years, 71.3% (n = 65 648) participated in the HUNT study 1995–1997. Of these, 60 869 (66.1%) had the somatic variables examined and had valid ratings of anxiety and depression. Details of the data collection procedure and characteristics of the study population have been published

There is a high occurrence of depressive symptoms in patients with somatic health problems.

- About one-third of individuals with somatic health problems have anxiety disorders and/or depression.
- Comorbid anxiety disorder and depression are found to be more strongly associated with somatic health problems than pure anxiety disorder and pure depression.

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Table I. Sample characteristic.[1]

	Men		Women		p
	n	%	n	%	
Gender	28 808	100.0	32 061	100.0	
Age groups					
20–29 years	3 867	20.5	4 661	19.5	< 0.001
30–39 years	5 322	21.2	6 042	19.5	
40–49 years	6 377	20.4	6 915	18.8	
50–59 years	5 235	14.0	5 546	13.3	
60–69 years	4 033	11.3	4 279	11.5	
70–79 years	3 158	9.2	3 474	11.2	
80–89 years	816	3.4	1 144	6.1	
Impairment	4 009	12.7	4 586	14.0	0.170
Myocardial infarction	1 333	4.0	455	1.5	< 0.001
Stroke	527	1.6	492	1.7	0.005
Diabetes	827	2.6	811	2.7	0.009
Migraine	861	3.0	1 173	3.6	< 0.001
Fibromyalgia	266	0.8	1 723	4.8	< 0.001
Musculoskeletal	8 143	26.4	10 818	32.6	< 0.001
Cardiovascular	5 035	16.8	7 379	22.5	< 0.001
Smoking	7 727	26.5	9 435	28.4	< 0.001
Alcohol problems	5 530	20.2	1 977	6.3	< 0.001
Low physical activity	3 959	13.3	5 327	17.3	< 0.001
Hypertension	5 406	16.4	4 331	13.1	< 0.001
High BMI	4 117	13.6	5 727	17.5	< 0.001

[1] Absolute numbers and statistical tests are based on unweighted data and percentages on weighted data.

elsewhere (10,11). The sample characteristics are given in Table I.

Measures of anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) is a questionnaire that is widely used to measure anxiety and depression in somatic and psychiatric patients as well as in general populations (12,13). HADS has 7 items for depression and 7 for anxiety, and each item is scored from 0 to 3, so that the maximum score is 21 on each of the HADS subscales (HADS-D and HADS-A). Factor analyses of HADS in the HUNT material resulted in a two-factor solution consistent with the two subscales (14). Optimal cut-off levels for anxiety disorders and depressive disorders are at scores ≥ 8 for both subscales, resulting in sensitivities and specificities of approximately 0.80 for both HADS-A and HADS-D (13). This cut-off was applied to define four categories of anxiety and depression (Table II): neither depression nor anxiety disorder (group 00), pure anxiety disorder (group A), pure depression (group D), and comorbid anxiety disorder and depression (group AD).

Somatic health problems

In the HUNT questionnaire, somatic diseases were asked for by the standard formulation: "Do you have or have you ever had the following disease?" Confirmations of these diagnoses were not obtained from hospitals or GPs. Five somatic diseases were included: myocardial infarction, stroke, diabetes, migraine and fibromyalgia. Impairment due to somatic diseases was based entirely on the subjective reports of the respondents. Smoking was defined as daily consumption of any cigarettes. Alcohol problems implied at least one

Table II. Categories of anxiety and depression by gender.[1]

Categories	HADS-A range	HADS-D range	n	% of men	% of women
Pure depressive disorder (D)	0–7	8–21	2 988	5.4	4.0
Comorbid anxiety-depressive disorder (AD)	8–21	8–21	3 610	4.9	6.3
Pure anxiety disorders (A)	8–21	0–7	5 827	7.6	11.6
Neither anxiety nor depressive disorder	0–7	0–7	48 444	82.1	78.0

Gender by comorbidity groups: Pearson chi-square 510.97; d.f. = 3; $p < 0.001$.
[1] Absolute numbers and statistical tests are based on unweighted data and percentages on weighted data.

positive response to the five items of the CAGE screening instrument (15). Musculoskeletal symptoms were reported as pain and/or stiffness in muscles for at least 3 months in the past year, and cardiovascular symptoms implied reports of palpitations or breathlessness in recent years. Hypertension was defined as systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90, based on the mean of the second and third measurements at the HUNT examination. High body mass index (BMI) was given by an index value of 30 or above. Low physical activity was defined as self-reported infrequent physical activity. Somatic variables that could be seen as expressions of anxiety or depression (such as insomnia) were excluded because of the risk of circularity.

Statistics

Analyses were performed with weighting to adjust for differences in response rate according to age and gender, and for age and gender differences between the population of Nord-Trøndelag County and the total population of Norway. The weighting procedure was based on the National population statistics of 1996, and was identical to the procedure used in the National Comorbidity Survey (16) and in several of our previous studies (10,11). All statistics except crude numbers were based on weighted data.

Gender differences in prevalences of health problems (Tables I and II) were tested with the Pearson chi-square test. Multinominal logistic regression analysis was used to model the associations between the somatic health problem variables and the categories of anxiety and depression. The somatic variables were dichotomized and entered as independent variables, and the anxiety and depression categories as the dependent variable (Table III, Fig. 1). The category with neither anxiety nor depressive disorder was used as reference group. Age, gender and age by gender interaction were included in all the regression models reported. The level of significance was set at $p = 0.05$ and two-sided tests were used.

Ethics

The National Data Inspectorate and the Board of Medical Research Ethics in Health region IV of Norway approved the HUNT study.

RESULTS

Several thousand participants reported somatic health problems (from 1019 (stroke) to 18 961 (musculoskeletal symptoms)). All somatic symptoms and diagnoses were reported as more prevalent among women than among men, except myocardial infarction and hypertension. Alcohol problems, too, were more prevalent in men, but more women reported smoking and low physical activity. Subjective impairment due to somatic health problems, however, were equally frequent in men and women.

The numbers of participants in the categories of anxiety and depression are displayed in Table II. Those who had an anxiety and/or depressive disorder

Table III. Adjusted[1] odds ratios (OR) for somatic health problems according to anxiety and depression.

	Depression			Comorbid depression and anxiety disorder			Anxiety disorder			Total[2]
	%[3]	OR	95% CI	%[3]	OR	95% CI	%[3]	OR	95% CI	%[3]
Impairment[4]	8.9	1.95	1.78–2.14	12.4	3.05	2.81–3.30	13.2	2.03	1.88–2.19	34.5
Myocardial infarction	11.9	1.31	1.11–1.54	8.6	1.50	1.25–1.81	6.7	1.19	0.97–1.46	27.2
Stroke	15.7	2.10	1.75–2.52	10.8	1.98	1.60–2.44	9.8	1.64	1.32–2.05	36.3
Diabetes	9.2	1.14	0.96–1.37	8.1	1.27	1.06–1.54	8.4	1.12	0.93–1.35	25.7
Migraine	4.0	1.38	1.09–1.74	9.6	2.13	1.82–2.49	15.5	1.73	1.53–1.97	29.1
Fibromyalgia	6.2	2.02	1.64–2.49	17.8	4.02	3.50–4.61	18.7	2.44	2.14–2.78	42.7
Musculo-skeletal	6.8	1.78	1.64–1.93	10.4	3.11	2.90–3.35	13.3	2.11	1.99–2.24	30.5
Cardio-vascular	6.5	1.88	1.73–2.06	12.9	4.27	3.97–4.59	18.4	3.34	3.15–3.54	37.8
Smoking	4.3	1.20	1.10–1.31	7.8	1.82	1.69–1.96	12.1	1.45	1.37–1.54	24.2
Alcohol problems	4.2	1.46	1.29–1.66	7.1	1.88	1.70–2.08	14.2	1.97	1.82–2.12	25.5
Low physical activity	3.9	1.68	1.53–1.84	5.1	1.74	1.59–1.91	9.6	1.28	1.19–1.39	18.6
Hypertension	6.9	0.93	0.85–1.03	6.3	0.92	0.83–1.01	7.8	0.93	0.85–1.02	21.0
High BMI	6.2	1.21	1.10–1.33	7.0	1.18	1.08–1.29	8.9	0.94	0.87–1.02	22.1

[1] Adjusted for age and gender.
[2] Total percent having depression, comorbid depression and anxiety disorder, or anxiety disorder within health problem group (e.g. stroke).
[3] Proportion of all subjects within a health problem group (e.g. stroke).
[4] Impairment due to somatic health problems.
Reference group (OR = 1.00): Neither depression nor anxiety disorder (HADS-A and D both < 8).

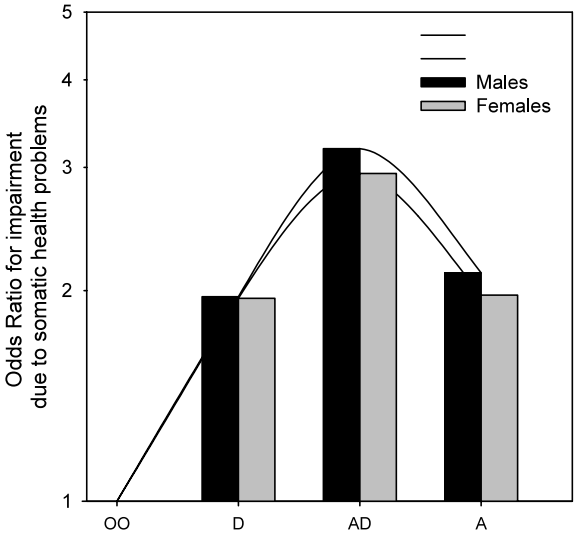

Fig. 1. Impairment due to somatic health problems in relation to depression and anxiety disorder. The estimates are obtained from multinominal logistic regression analysis adjusted for age. OO = No anxiety disorder or depression (HADS-A and D scores < 8): reference group. D = Depression without anxiety disorder (HADS-A score < 8, HADS-D score ≥ 8). AD = Comorbid anxiety disorder and depression (HADS-A and HADS-D scores ≥ 8). A = Anxiety disorder without depression (HADS-A score ≥ 8, HADS-D score < 8).

numbered 12 425 (20.4%), while 48 444 (79.6%) had no disorders of these types (Group 00). The prevalence of depression with comorbid anxiety disorder was approximately the same as the prevalence of pure depression. Anxiety disorder without depression was more prevalent than depression without anxiety disorder, especially among women. Among those reporting somatic health problems, about one-third also had anxiety disorder and/or depression. This prevalence varied between different health problems; details are given in the right column in Table III.

As a main tendency, comorbid anxiety disorder and depression were found to be more strongly associated with somatic health problems than pure anxiety disorder and pure depression (Fig. 1). This main tendency was found in both men and women. Fig. 1 illustrates this for subjective impairment due to somatic symptoms, and the same tendency was found for myocardial infarction, diabetes, migraine, fibromyalgia, musculoskeletal symptoms, cardiovascular symptoms, smoking and low physical activity (Table III). There were a few exceptions, however; stroke and high BMI were more strongly associated with pure depression than the comorbid condition, and alcohol problems were more strongly associated with anxiety disorder. For details on the estimates, see Table III.

DISCUSSION

Statement of principal findings

We have three main findings: (a) There was an increased occurrence of comorbid anxiety disorder and depression in individuals who currently had somatic health problems compared to those with pure anxiety disorder or depression only. (b) Such comorbidity was frequent and represented 28% of all cases with anxiety disorder and depression in our sample. (c) In persons reporting somatic health problems commonly in focus in primary health care settings, depression, anxiety disorder and comorbid conditions were highly frequent. In about one of three persons with a somatic health problem, anxiety and depression were present as well.

We could not find any studies in the literature where the association between somatic health problems and the comorbid anxiety/depression state had been examined, and therefore our results cannot be compared with other samples. Intuitively, it makes sense that those with the more severe comorbid mental disorders are more represented among those who have somatic health problems.

The cross-sectional design of HUNT does not allow for any assumptions about the causal relation between the somatic health problems and anxiety or depression.

Strengths and weaknesses

Our study has several strengths. The attendance rate of the HUNT study was high, probably because it was carried out in the local communities, the participation fee was low, and the study had been run once before and was well announced in the local media. As a general health study, HUNT did not focus on mental health problems in particular and thereby avoided selection biases inherent in mental health surveys. The general population approach also avoided the selection biases frequently occurring in special or primary care samples. The large sample size made possible examination of many somatic health problems with a high number of participants, which allowed for multivariate statistical modelling.

The HADS subscale specificity of approximately 0.80 at cut-off ≥ 8 introduced a certain risk of false-positive cases. However, a higher cut-off yielding a better specificity excluding more false-positives would increase the risk of false-negatives, which clinically could be more questionable. Ideally we should have interviewed a random sample of the participants with scores around cut-off in order to get good prevalence

estimates. Such a procedure, however, was not part of the HUNT design. The point prevalence we observed for anxiety disorder and depression was in good accordance with those reported by Kringlen et al. from their recent survey of the population of Oslo, Norway (17).

A limitation of this study was a 29% non-participant rate. We tried to compensate for this by using a weighting procedure. Based on findings from other studies (18) we can assume that persons with severe somatic and mental health problems were underrepresented in HUNT. Another weakness is that most of our data on somatic health problems were based on self-report. Practical, economic and ethical reasons precluded validation by GPs or hospitals. The time frames of the somatic questions differed considerably, and could influence the prevalences of anxiety and depression. In this cross-sectional study the causality sequence between several somatic health variables and anxiety and depression is unclear. However, our purpose was rather to compare different anxiety and depression states in somatic health problems than to study the mechanisms of the relationships.

Participants with clinically significant levels of anxiety and depression might have reported more somatic health problems and impairment due to their mental state. This possible information bias could have led to minor overestimates of the associations between the mental disorders and impairment and somatic symptoms.

Meaning of the study

In conclusion, the clinical implication of our findings is that clinicians should pay attention to anxiety and depression in patients with somatic health problems as about one in three patients consulting a general practitioner for somatic health problems also has anxiety disorder and/or depression. In some somatic health-problem groups, anxiety disorder and/or depression is even more frequent (Table III). Diagnosis and treatment of anxiety and/or depressive disorder can be quite efficient (19), and thereby contribute to better subjective well-being and quality of life in patients with long-standing somatic health problems.

Unanswered questions and future research

Is the burden of somatic health problems the cause of the increased occurrence of anxiety and depression in these individuals? Or are anxiety disorder and depression risk factors for the development of such health problems? These questions can only be answered by well-designed longitudinal studies, or even clinical trials examining the long-term effects of treating both somatic and psychiatric patients.

ACKNOWLEDGEMENTS

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REFERENCES

1. Stewart R, Prince M, Richards M, Brayne C, Mann A. Stroke, vascular risk factors and depression. Cross-sectional study in a UK Caribbean-born population. Br J Psychiatry 2001;178:23–8.
2. Kivelä S-L, Kongäs-Saviro P, Kimmo P, Kesti E, Laippala P. Health, health behavior and functional ability predicting depression in old age: a longitudinal study. Int J Geriatr Psychiatry 1996;11:871–7.
3. de Beurs E, Beekman ATF, Deeg DJH, van Dyck R, van Tilburg W. Predictors of change in anxiety symptoms of older persons: results from the Longitudinal Aging Study Amsterdam. Psychol Med 2000;30:515–27.
4. Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. Comorbidity of DSM-III-R major depressive disorders in the general population: Results from the US National Comorbidity Survey. Br J Psychiatry 1996;168 (Suppl 30):17–30.
5. Sartorius N, Ustun TB, Lecrubier Y, Wittchen H-U. Depression comorbid with anxiety: results from the WHO study on psychological disorders in primary health care. Br J Psychiatry 1996;168(Suppl 30):38–43.
6. Brown TA, Campbell LA, Lehman CL, Grisham JR, Mancill RB. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. J Abnorm Psychol 2001;110:585–99.
7. Sherbourne CD, Wells KB. Course of depression in patients with comorbid anxiety disorders. J Affect Disord 1997;43:245–50.
8. Brown C, Schulberg HC, Madonia MJ, Shear MK, Houck MS. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. Am J Psychiatry 1996;153:1293–300.
9. Coryell W, Endicott J, Winocur G. Anxiety syndromes as epiphenomena of primary major depression: outcome and familial psychopathology. Am J Psychiatry 1992;149:100–7.
10. Stordal E, Krüger MB, Dahl NH, Krüger Ø, Mykletun A, Dahl AA. Depression in relation to age and gender in the general population: The Nord-Trøndelag Health Study (HUNT). Acta Psychiatr Scand 2001;104:210–16.
11. Stordal E, Mykletun A, Dahl AA. The association between age and depression in the general population: A multivatiate examination. Acta Psychiatr Scand 2003;107:132–41.
12. Herrmann C. International experiences with the Hospital anxiety and depression scale: A review of validation data and clinical results. J Psychosom Res 1997;42:17–41.
13. Bjelland I, Dahl AA, Tangen Haug T, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002;52:69–77.
14. Mykletun A, Stordal E, Dahl AA. The Hospital Anxiety and Depression Scale (HADS): Factor Structure, Item

Analyses, and Internal Consistency in a Large Population. Br J Psychiatry 2001;179:540–4.
15. Ewing A. Detecting alcoholism – the CAGE questionnaire. JAMA 1984;252:1905–7.
16. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19.
17. Kringlen E, Torgersen S, Cramer V. A Norwegian epidemiological study. Am J Psychiatry 2002;158:1091–8.
18. Eaton WW, Holzer CE, von Korff M, Anthony JC, Helzer JE, Georg L, et al. The design of epidemiological catchment surveys: the control and measurement error. Arch Gen Psychiatry 1984;41:941–8.
19. Thompson C, Ostler K, Peveler RC, Baker N, Kinmonth A-L. Dimensional perspective on the recognition of depressive symptoms in primary care. Br J Psychiatry 2001;179:317–23.

PAPER IV

Archives of General Psychiatry 60, Bjelland, I.; Tell, G. S.; Vollset, S. E.; Refsum, H.; Ueland, P. M., Folate, Vitamin B12, Homocysteine, and the MTHFR 677ÇT Polymorphism in Anxiety and Depression: The Hordaland Homocysteine Study.

Folate, Vitamin B12, Homocysteine, and the MTHFR 677C→T Polymorphism in Anxiety and Depression. The Hordaland Homocysteine Study

Abstract

Background: An association between depression and folate status has been demonstrated in clinical studies, whereas data are sparse on the relationship between depression and other components of 1-carbon metabolism such as vitamin B12, homocysteine, and the methylenetetrahydrofolate reductase 677C→T polymorphism. The relationship between anxiety and these components is less well known. This study examined the associations between folate, total homocysteine, vitamin B12, and the methylenetetrahydrofolate reductase 677C→T polymorphism, and anxiety and depression in a large population-based study.

Methods: Anxiety and depression, measured by the Hospital Anxiety and Depression Scale, were assessed in 5948 subjects aged 46 to 49 years (mean, 47.4 years) and 70 to 74 years (mean, 71.9 years) from the Hordaland Homocysteine Study cohort. By means of logistic regression models, anxiety and depression scores were examined in relation to the factors listed above.

Results: Overall, hyperhomocysteinemia (plasma total homocysteine level ≥15.0 μmol/L [≥ 2.02 mg/dL]) (odds ratio, 1.90; 95% confidence interval, 1.11-3.25) and T/T methylenetetrahydrofolate reductase genotype (odds ratio, 1.69; 95% confidence interval, 1.09-2.62), but not low plasma folate or vitamin B12 levels, were significantly related to depression without comorbid anxiety disorder. Plasma folate level was inversely associated with depression only in the subgroup of middle-aged women. None of the investigated parameters showed a significant relationship to anxiety.

Conclusion: Our results provide further evidence of a role of impaired 1-carbon metabolism in depression.

PAPER V

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Education as predictor for anxiety and depression - A population based cohort study.

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Abstract

In the paucity of prospective studies we aimed to examine the associations between educational level and later anxiety disorder and depression among individuals with and without mental distress at baseline. We also wanted to identify factors that explained eventual associations. 36,150 individuals aged 20-69 years from the Nord-Trøndelag Health Study 1984-1986 were followed up after 11 years. The analyses were performed in an incident and a persistent cohort defined by a low and a high mental distress level at baseline, respectively. Using logistic regression models, the association between educational level and anxiety/depression categories at follow-up were examined. Covariates related to somatic health, health behaviors, psychosocial status, and sociodemographic and work characteristics were included in the analyses.

Significant gradients (trend test: $p < 0.001$) from the highest to the lowest educational level were observed in the association with anxiety disorder, depression, and comorbid disorder in the incident cohort, and with depression and comorbid disorder in the persistent cohort. The depression component at follow-up was more related to educational level than the anxiety one. The other covariates influenced the observed associations to a lesser degree.

In conclusion the lower educational levels predicted new as well as chronic cases of depression, with and without comorbid anxiety disorder.

A recent meta-analysis (1) found higher prevalence and incidence as well as persistence of depression in subjects within the lowest group of socioeconomic status (SES) compared to those in the highest. However, in the few studies not addressing education, which is the most frequently used SES indicator, the results of incidence (2, 3) and persistence (3-5) were inconsistent.

The majority of published studies addressing SES and depression have a cross-sectional design. To our knowledge the number of longitudinal studies on this topic is limited to four (2-5), and these differ in sample size, measure of depression, follow-up time and covariates examined. Only one of these focused on SES, including education, as the main predictor of depression (5).

Although anxiety disorders are closely related to depression (6, 7), we are not aware of longitudinal studies of their relation to education. The association between education and comorbid anxiety disorder and depression (comorbid disorder) has hardly been addressed at all.

The association between SES and depression is not fully understood. In contrast to e.g. schizophrenia, there is most evidence for low SES as a predictor of depression, at least in women (1, 8). Some studies (9, 10), however, support the selection theory (11) as well that depression hinders upward and promotes downward social mobility.

In a cross-sectional study (12) using occupational grade as a proxy for SES, work characteristics, including skill discretion and decision authority, explained most of the SES-depression gradient. Economic situation was used as the measure of SES in a prospective study (13), where health behavior (smoking, alcohol consumption, physical activity) and body-mass index rather than physical disease, explained the SES-depression gradient. However, physical and psychological functioning w assessed only at follow-up and the different health behaviors were not evaluated separately. One of the prospective studies (3) addressed somatic health and health behaviors, but the effects of specific variables were not evaluated. Nor was the effect of unfavorable psychosocial status, such as living alone (3, 4), being socially isolated (3), or being unemployed (3, 4) examined.

The aims of our study were to examine, in a prospective study of 36,150 individuals followed for 11 years, whether low education is a predictor of new and chronic cases of anxiety disorder, depression and comorbid disorder; and if so, whether somatic illness, use of health services, health behaviors, or sociodemographic or work characteristics may explain the relationships.

MATERIALS AND METHODS

The cohorts

All inhabitants of Nord-Trøndelag County of Norway, aged 20 years and above (N=87,285) were invited to participate in the Nord-Trøndelag Health Study 1984-1986 (HUNT 1) (14). Nord-Trøndelag County encompasses 3 percent of the Norwegian population. In the age group of 20-69 years, which was examined in the current study, 64,443 (89.5%) participated. Valid scores of an Anxiety-Depression Index (ADI-12, described under "*Assessment of anxiety and depression"*) were obtained from 51,295 individuals (71.3 percent) in that group. Among these, 44,585 (61.9 percent) individuals were invited to take part in the Nord-Trøndelag Health Study 1995-1997 (HUNT 2) (14, 15) 11 years later and 37,579 (84.3 percent) participated. However, non-valid scores of anxiety or depression were observed in 1,335 subject and missing information of education in further 121, reducing the current total cohort to 36,150 individuals (81.1 percent of those invited to HUNT 2).

Incidence of anxiety disorder and depression was examined among the participants who had ADI-12 scores $\leq$ the 80^{th} percentile (N= 29,463) at baseline (the incident cohort). Persistence of anxiety disorder and depression was studied in the remaining participants (n=6,687) (the persistent cohort).

Assessment of mental distress at baseline (ADI-12)

Because no specific measure for anxiety or depression was used at HUNT 1, an Anxiety-Depression Index (ADI-12) was composed of 12 HUNT 1 questions addressing different aspects of anxiety, depression, life satisfaction, and personality. Individuals having answered at least eight of the 12 ADI questions, were given valid ADI-12 scores calculated as the mean of the z-scores of the 12 ADI questions. Each z-score was weighted with its loading on the one factor extracted from a principal component analysis of the 12 questions. Low ADI-12 scores indicated good mental health. In a four year follow-up after HUNT 1 where these 12 questions were repeated, the ADI-12 scores predicted 67 percent of the variance of the Hopkins Symptom Checklist (SCL-25) scores (16).

Assessment of anxiety and depression at follow-up

At follow-up anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS), a self-administered questionnaire consisting of 14 items, seven for anxiety (HADS-A subscale) and seven for depression (HADS-D subscale), each scored from

0 (not present) to 3 (maximally present) on a Likert scale formulated in readily understandable language (17). To increase acceptability and to preclude that individuals feel tested for mental disorders, symptoms of severe psychopathology were not included. HADS-A contains items mainly concerned with restlessness and worry, as in generalized anxiety disorder, plus one item on panic attacks. HADS-D focuses mainly on the reduced pleasure response aspect (anhedonia) of depression, as well as psychomotor retardation and depressed mood. With a categorical approach, a cut-off value of ≥ 8 in both subscales has demonstrated optimal screening properties in identifying anxiety disorders and major depressive disorder, with sensitivities and specificities of approximately 0.80 (18). The two-dimensional quality of HADS has been demonstrated by several factor analytic studies (18), as well as in the HUNT 2 population where the factors were identical with the subscales (19).

Valid ratings of HADS-A and HADS-D were defined as at least five completed items on each subscale. Those who only had filled in five or six items got their score based on the sum of completed items multiplied with 7/5 or 7/6, respectively.

HADS-A and HADS-D are inter-correlated, most often in the range of 0.50 - 0.60 (18). Hence, in order to identify more homogenous groups with anxiety disorders or depressions, restrictions were put on the other subscale when cases were defined. Thus, anxiety disorder was defined as HADS-A ≥ 8, and HADS-D < 8 in order to avoid comorbidity. Accordingly, depression was defined as HADS-D ≥ 8, and HADS-A < 8. Cases with comorbid disorder was defined as both HADS-A and HADS-D scores ≥ 8.

Education

Education was divided into three levels: Primary school (<10 years), high school (10-12 years), and college or university (>12 years). Considering that not all participants had finished their education at baseline, we composed a common educational level for HUNT 1 and HUNT 2, using the highest reported level. When information on education was missing at one time point, information from the other was used.

Potential mediators

At baseline there was self-reported information on somatic health, use of health services, health behavior, and sociodemographic and work characteristics. Whether they should be considered as confounders or intermediate variables (mediators) in the association between education and anxiety/depression was not obvious. Nevertheless, we included them

in the analyses to examine their influence on that association and denoted them “potential mediators”.

At baseline, current or former diabetes, mycardial infarction, angina pectoris and stroke were reported. The three latter were combined to denote cardiovascular disease. Daily impairment due to chronic physical illness or injury was dichotomized into “Not impaired” and “Impaired”. Use of analgesics was defined as daily or weekly use the last month. Having visited a general practitioner or other physician during the last 12 months and having been hospitalized during the last five years, were the two measures of health services use. Problems of falling asleep or sleep problems almost every night or frequently were characterized as “Sleep problems”. Calculation of Body Mass Index (kg/m^2) was based on data from the clinical examinations and categorized by two cut-offs, $\geq 25kg/m^2$ and $\geq 30kg/m^2$, respectively. Health behaviors were dichotomized like this: Physical exercise $\geq$ weekly practicing; smoking $\geq$ one cigarette daily; alcohol consumption $\geq$ ten days with alcohol use during the last two weeks. Psychosocial status included whether the respondents felt lonely and/or had available social support in case of long-lasting illness in need of bed rest. Sociodemographic characteristics included whether the respondents were living alone and/or were separated or divorced. Work characteristics included dichotomized variables as to whether the respondents considered their job to be stressful, whether the job allowed influence on the planning of the work, whether they were satisfied with their job, and whether they were unemployed.

Statistics

Most analyses were performed separately for the incident and persistent cohorts. Logistic regression analyses were used to estimate odds ratios (OR) with corresponding 95 percent confidence intervals (CI) for being a case of anxiety disorder, depression, or comorbid disorder at follow-up, comparing the two lower educational levels separately to the highest. The representation of the three educational levels as indicator variables was used to allow for assessment of non-linear dose-response relationships, while a linear (1 df) representation was used to test for linear trends.

To examine the effect of education on HADS scores at follow-up, two logistic regression models were used, one with adjustment for age and gender (Model 1) and one with additional adjustment for anxiety/depression (ADI-12 score) at baseline (Model 2). The purpose of the latter was to adjust for the variation in ADI-12 within the cohorts. To examine whether “sub-threshold” depression (HADS < 8) in anxiety disorder would influence the association between educational level and anxiety disorder, the HADS-D score was added to

the model, and vice versa regarding “sub-threshold” anxiety (HADS-A < 8) in depression. Further, to evaluate possible effect modification of age and gender, product terms between these variables and educational level were added separately to the models.

To examine the effect of the potential mediators, the logistic regression analyses were performed in three steps. First, all the mediator variables were added one by one separately to Model 2 above for the three anxiety/depression outcome variables. Second, those mediators reducing the odds ratio (OR) for being a case at the lowest versus to the highest educational level with at least 5 percent, were included in the analyses to evaluate the combined effect of all the mediators by adding each variable to the model after the other(s) were already in. Third, the mediators still reducing the OR in the preliminary model, were included in the final model.

One aspect of the selection hypothesis was addressed by examining whether a high anxiety/depression score at baseline determined less educational attainment during the follow-up period in the younger age group. To do so a logistic regression analysis adjusting for age and gender, which estimated the OR for an unchanged educational level at follow-up for individuals in the high-ADI-12 group (persistent cohort) compared to the low ADI-12 group (incident cohort) was performed as well. Product terms for interaction between ADI-12 group, gender or age were added to the model.

The causation hypothesis could be supported if lower educational attainment was associated with anxiety/depression at follow-up. Hence, a logistic regression analysis adjusting for age, gender, and ADI-12 score was performed, estimating the OR for being a case at follow-up among those with unchanged educational level between baseline and follow-up compared to those with an increased level.

A two-sided p-value < 0.05 was chosen to indicate statistical significance. The statistical analyses were conducted using the software package of SPSS 11.5.

Ethics

The Norwegian Data Inspectorate and the Regional Committee for Medical Research Ethics in Health region IV of Norway approved HUNT 2. These agencies were not established in Norway when HUNT 1 was planned and performed. Each participant in the HUNT 2 study was asked to sign an informed consent, stating that his or her data could be used for medical research (15).

RESULTS

There were more similarities than differences in the findings from the two cohorts. Hence instead of reporting and discussing them separately, they will be treated together.

Characteristics of the cohorts at baseline

The age and gender distribution of educational level, anxiety and depression categories, and potential mediators are presented in tables 1 and 2. The educational level was lowest in the older and highest in the younger age groups in both genders. Men had a higher educational level than women in the middle aged (35-49 years) and older age groups (50-69 years), while there was no gender difference among the youngest (20-34 years). In the incident cohort the educational level was somewhat higher than in the persistent cohort. Most indicators of somatic health, health behaviors, psychosocial status, and work characteristics showed a more unfavorable in the persistent cohort. Rates of anxiety disorder, depression and comorbid disorder were approximately two, three and four times higher, respectively, in the persistent cohort compared with the incident cohort, but the distribution by age and gender was similar. In the incident cohort the rates of anxiety disorder at follow-up were generally higher in women, highest among younger women (10.6 percent) and lowest among older men (3.2 percent). The oldest age groups had lower rates of anxiety disorder than the younger ones. Contrary to anxiety disorder, rates of depression were somewhat higher in men, and highest among the oldest (2.1 percent in younger women and 10.2 percent in older men in the incident cohort). Rates of comorbid disorder showed no clear patterns in terms of age or gender, the rates were approximately 4 percent in all groups (incident cohort).

Attendees versus nonattendees

Baseline characteristics were compared between those attending and not attending HUNT 2. Characteristics of attendees aged 20-69 years were compared to participants in HUNT 1 not attending HUNT 2, but in the same age. Among the nonattendees there were significantly more men, more individuals in the youngest and oldest age groups, they were less educated and had higher ADI-12 scores. Except for a self-reported stressful job and low job control, the nonattendees had significantly more unfavorable characteristics as to somatic health, health behaviors, psychosocial factors, and sociodemographic characteristics.

Unadjusted associations

The rates of depression and comorbid disorder increased with lower educational levels in both cohorts, while the rates of anxiety disorder were less clearly related to educational level (figure 1). However, by further stratification on age group and gender, rates of anxiety disorder in the incident cohort showed the same gradient as depression and comorbid disorder among the youngest (20-34 years) and oldest (50-69 years) women (data not shown). Rates of all the anxiety/depression categories were in general more than three times higher in the persistent cohort than in the incident cohort.

Adjusted analyses

All outcome measures of anxiety and depression, except anxiety disorder in the persistent cohort, were significantly associated with lower levels of education (table 3), with significant gradients from the lowest to the highest educational level. ORs for comorbid disorder were comparable with those for depression, and markedly higher than for anxiety disorder. The ORs in the incident cohort were in general higher than in the persistent cohort. Adjustments for ADI-12 scores at baseline influenced the estimates only marginally. There was no significant interaction between educational level and age or gender, except for anxiety disorder in the incident cohort, which corresponded to the finding in the unadjusted, age and gender stratified analyses. A subsequent logistic regression analysis stratified by age group and gender showed a significant association between educational level and anxiety disorder in the incident cohort only in the women between 20-34 years (OR=1.93; 95 percent CI: 1.42, 2.63). Adjusting for HADS-D and HADS-A scores at follow-up in the analyses of anxiety disorder and depression, respectively, resulted in a major reduction in OR for anxiety disorder (lowest educational level: from 1.35 (95 percent CI: 1.17, 1.56) to 1.18 (95 percent CI: 1.01, 1.37)) and a minor for depression (lowest educational level: from 1.89 (95 percent CI: 1.56, 2.28) to 1.83 (95 percent CI: 1.51, 2.22).

Associations related to educational attainment during the follow up period

OR for having an unchanged educational level at follow-up among those in the high-ADI-12 group at baseline compared to the low-ADI-12 group was 0.79 (95 percent CI: 0.68-0.92). The interaction terms between baseline ADI-12 group and gender or age were not significant. There were no significant associations between increased educational level during the observational period and any of the anxiety-depression categories at follow-up (data not shown).

Potential mediators

The effects of the various potential mediators on the association between educational level and the outcome variables were in general small. In the incident cohort adjustment for smoking status reduced the OR for anxiety disorder in the lowest educational group from 1.34 (95 percent CI: 1.16, 1.55) to 1.28 (95 percent CI: 1.11, 1.49); adjustment for physical activity reduced the OR for depression in the lowest educational group from 1.86 (95 percent CI: 1.54, 2.25) to 1.81 (95 percent CI: 1.49, 2.19); and adjustments for smoking status plus physical activity reduced the OR for comorbid disorder in the lowest educational group from 1.97 (95 percent CI: 1.59, 2.44) to 1.88 (95 percent CI: 1.51, 2.33). In the persistent cohort adjustments for smoking status, impairment due to somatic illness, use of analgesics, and employment status reduced the OR for anxiety disorder in the lowest educational group from 1.17 (95 percent CI: 0.92, 1.50) to 1.15 (95 percent CI: 0.89, 1.48). Adjustments for social support status reduced the OR for depression in the lowest educational group from 1.80 (95 percent CI: 1.32, 2.44) to 1.75 (95 percent CI: 1.29, 2.38). Finally, adjustments for smoking status and use of analgesics reduced the OR in the lowest educational group for comorbid disorder from 1.69 (95 percent CI: 1.33, 2.15) to 1.62 (95 percent CI: 1.28, 2.07).

DISCUSSION

This cohort study showed that during a follow-up period of 11 years, educational level was negatively associated with depression and comorbid disorder at follow-up, in both the incident and persistent cohort, and with anxiety disorder in the incident cohort. The latter association was significant only among younger women. A high mental distress score (ADI-12) at baseline was inversely but weakly associated with unchanged educational level during follow-up period. An increase in educational level during the observation period was not significantly associated with incidence of anxiety/depression at follow-up. The associations between low educational level and anxiety/depression at follow-up were only modestly affected by the potential mediators.

Strengths and limitations of the study

This is the largest prospective study ever examining the association between educational level and subsequent anxiety and depression. The cohorts were population-based with a wide age range. Information regarding both somatic and mental health, as well as health behaviors, psychosocial status, and sociodemographic and work characteristics was collected, and the follow-up period was long. Mental health was not assessed by diagnostic

inventories at neither baseline nor follow-up. However, according to Dohrenwend the use of rating scales for mental health are welcomed in this field, because "…until diagnosis is less dependent on interviews, it is important to use a variety of methods…"(20). The use of HADS enabled us to study the effect of education on not only depression, but on anxiety as well, a focus lacking in most previous studies. The ADI-12 index is not specific as to anxiety or depression. Hence, in the persistent cohort individuals with anxiety disorder, depression or comorbid disorder at follow-up might not have had the same mental health condition at baseline. However, the purpose of the stratification was just as much to define a mentally healthy cohort at baseline. A possible selection bias indicated by the lower educational level and more disadvantageous characteristics among nonattendees versus the cohort participants with regard to mental health and the potential mediators might in fact have attenuated the true association between education and anxiety/depression and the effect of the potential mediators.

Depression

Lower educational levels were consistently predictive of depression in both cohorts, which is in accordance with the results of Kaplan et al (3) who followed 4,864 individuals for 9 years. In their cohorts the ORs for being depressed at follow-up in the lowest compared to the highest educational groups were 1.59 in the incident cohort and 1.60 in the persistent cohort. However, our results were mainly inconsistent with the few other comparable studies: Eaton et al (2) did not find such an association after 15 years in their rather small incident cohort (N=693). Bracke (4) reported an association between low educational level and depression in men only after three years follow-up of a persistent cohort (N=2,223), but after adjustment for baseline depression severity, the association was not present. Likewise, Sargeant et al (5) estimated a significant effect of low education on depression after one year in their small persistent cohort (N=423), which was not present after adjustments for number and length of former depressive episodes and symptom severity at baseline. In our analyses the association between education and depression was only weakly influenced by adjustments for a variety of covariates including baseline mental health, somatic illness, use of health services, health behaviors, psychosocial status, and work characteristics. Hence, our results support that education is predictive for incident as well as persistent cases of depression.

Anxiety disorder

Educational level was not a strong predictor of anxiety disorder, except among younger women (20-34 years) in the incident cohort. The marked attenuating effect of adjusting for “sub-threshold” depression on the education-anxiety association further emphasized that anxiety, compared to depression, was not very influenced by education. This discrepancy between anxiety and depression may be due to some fundamental differences between the two conditions. The occurrence of depression is often delayed temporally compared to anxiety disorders (6), suggesting that depression is a more secondary phenomenon than anxiety (21-23).

Comorbid disorder

Despite a higher total symptom level in comorbid disorder than in depression, education was not a stronger predictor of comorbid disorder than depression in either of the cohorts. These results further support the notion that education primarily predicts the depression component compared to the anxiety component.

Causation or selection?

The findings from the incident cohort support the causation theory. However, educational level did not only “cause” new cases of depression, but predicted maintenance of mental distress as well. Furthermore, high levels of mental distress at baseline did not predict less additional education in the younger age group during the follow up period, which weakens the support for the selection hypothesis. However, getting additional education during the follow-up period was not predictive of having less anxiety or depression at follow up. Furthermore, there might be a common factor, e.g. belonging to a lower social class, or personality, predicting both low educational attainment and depression.

How does education predict depression?

Whether the potential mediators are viewed as either true mediators or confounders, they did not explain much of the effects exerted by education on anxiety/depression. The examined variables included a variety of factors suggested to mediate the effects of SES on health in general (24). The effect of other SES indicators on depression, such as occupational grade, economic situastion, and income have been partly explained by work characteristics (13), economic situation (14), and psychosocial factors (3), respectively. The effect of

education on follow-up depression has mainly been explained by depressive symptoms at baseline (4, 5) and prior to baseline (5) in longitudinal studies.

In the predominant absence of measured mediators of the education-anxiety/depression relationship, education might be hypothesized to induce resilience to stress in an individual. In addition to attaining knowledge and competence, which probably influences attitudes and important choices in early adult life, education might positively influence coping strategies buffering the harmful effects of later life incidents. Being highly educated often implies belonging to a higher social class as well, which is associated with access to more interpersonal, material, and public resources. The individual physiologic and behavioral responses to chronic stress, allostatic load (25), is associated with anxiety and depression (26), which is suggested to be related to SES as well (27).

The psychological pain of low SES has been suggested to cause feelings of shame, social anxiety and depression (28) more directly. Social anxiety is characterized by a feeling of being devaluated, which may be more pronounced on the lower rung of the hierarchical ladder. Finally, from an evolutionary point of view depression has been considered as an adaptive response to situations dominated by others where the consequences of opposition could be harmful (29). Thus, psychological effects of being low down on the social ladder may have detrimental effects on mental health, whatever the actual material condition of life. Again, in the absence of other explanatory factors for the association between education and anxiety/depression these mechanism might deserve further attention.

Conclusion

Our study supports the notion that lower educational level may predict new as well as chronic cases of depression, with or without comorbid anxiety disorder. This association is mainly unexplained by baseline anxiety/depression, somatic illness, health behaviors, psychosocial status, or work characteristics.

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TABLE 1: Characteristics of the incident cohort*. The Nord-Trøndelag Health Study 1984-86 (HUNT 1) and 1995-97 (HUNT 2).

	20-34 years				35-49 years				50-69 years				Total cohort	
	Men n=4,411		Women n=4,880		Men n=5,261		Women n=5,396		Men n=4,923		Women n=4,877		N=29,748	
Variables	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Primary school	649	(14.8)	778	(16.0)	1,706	(32.6)	2,255	(42.3)	2,713	(55.7)	3,534	(74.0)	11,635	(39.5)
High school	2,860	(65.1)	2,930	(60.4)	2,325	(44.4)	2,119	(39.7)	1,670	(34.3)	959	(20.1)	12,863	(43.7)
College/university	881	(20.1)	1,141	(23.5)	1,205	(23.0)	963	(18.0)	491	(10.1)	284	(5.9)	4,965	(16.9)
Anxiety disorder†	316	(7.7)	477	(10.5)	286	(6.1)	463	(9.5)	131	(3.2)	282	(7.1)	1,955	(7.4)
Depression‡	124	(3.2)	87	(2.1)	298	(6.3)	182	(4.0)	454	(10.2)	286	(7.2)	1,431	(5.5)
Comorbid disorder§	140	(3.2)	199	(4.1)	213	(4.1)	207	(3.9)	127	(2.6)	186	(3.9)	1,072	(3.6)
Cardio-vascular disease#	5	(0.1)	7	(0.1)	43	(0.8)	15	(0.3)	346	(7.1)	147	(3.1)	563	(1.9)
Diabetes	13	(0.3)	9	(0.2)	33	(0.6)	29	(0.5)	79	(1.6)	87	(1.8)	250	(0.8)
Impaired due to somatic disease	81	(2.0)	52	(1.1)	162	(3.3)	151	(3.0)	430	(10.6)	267	(6.5)	1,143	(4.3)
Use of analgesics	83	(1.9)	179	(3.7)	157	(3.0)	323	(6.2)	227	(4.7)	384	(8.4)	1,353	(4.7)
Visit to a physician, last year	3,053	(69.5)	4,071	(84.0)	3,693	(70.5)	4,034	(75.6)	3,577	(73.4)	3,546	(74.2)	21,974	(74.6)
Hospital admission, last five years	860	(19.6)	2,634	(54.6)	974	(18.6)	1,892	(35.5)	1,368	(28.1)	1,387	(29.1)	9,115	(31.0)
Sleep problems	35	(0.8)	60	(1.2)	41	(0.8)	49	(0.9)	61	(1.3)	166	(3.6)	412	(1.4)
BMI** $\geq$ 25 kg/m^2	1,437	(32.7)	926	(19.1)	2,609	(49.8)	1,687	(31.7)	2,889	(59.3)	2,826	(59.3)	12,374	(42.0)
BMI**$\geq$ 30 kg/m^2	130	(3.0)	189	(3.9)	341	(6.5)	396	(7.4)	432	(8.9)	814	(17.1)	2,302	(7.8)
Low physical activity	1,946	(44.4)	1,842	(38.1)	2,171	(41.7)	2,077	(39.2)	2,967	(62.4)	1,485	(32.0)	11,309	(38.8)
Daily smoking	1,459	(33.4)	2,022	(42.0)	1,725	(33.2)	1,759	(33.4)	1,628	(33.9)	1,005	(21.7)	9,598	(33.0)
High alcohol consumption††	107	(2.4)	62	(1.3)	200	(3.8)	103	(2.0)	248	(5.2)	92	(2.0)	812	(2.8)
Separated or divorced	65	(1.5)	113	(2.4)	159	(3.0)	196	(3.7)	100	(2.1)	93	(2.0)	726	(2.5)
Living alone	329	(7.5)	217	(4.5)	197	(3.8)	89	(1.7)	279	(5.7)	556	(11.7)	1,667	(5.7)
Lack of social support	154	(3.5)	309	(6.4)	418	(8.0)	730	(13.7)	802	(16.6)	1,404	(29.7)	3,817	(13.0)
Loneliness	48	(1.1)	78	(1.6)	68	(1.3)	72	(1.4)	65	(1.3)	105	(2.2)	436	(1.5)
Stressful job	2,174	(53.1)	1,859	(44.2)	3,051	(59.9)	2,224	(44.6)	1,892	(47.0)	1,135	(30.5)	12,335	(47.2)
Low job control	1,504	(34.3)	1,459	(30.1)	1,496	(29.4)	1,787	(35.8)	1,078	(26.7)	1,001	(26.6)	8,325	(31.8)
Job dissatisfaction	114	(2.7)	65	(1.4)	107	(2.1)	69	(1.3)	81	(1.9)	39	(0.9)	475	(1.7)
Unemployment	46	(1.1)	448	(9.8)	4	(0.1)	342	(6.9)	34	(0.7)	703	(19.1)	1,577	(5.8)

* Participants at or below the 80th percentile of the Anxiety-Depression 12 Index (ADI-12) at baseline (HUNT 1)
† The Hospital Anxiety and Depression Scale, Anxiety subscale (HADS-A) score $\geq$8; Depression subscale (HADS-D) <8
‡ HADS-D $\geq$8; HADS-A <8
§ HADS-A $\geq$8; HADS-D $\geq$8
# Self-report of present or previous angina pectoris, heart infarction or stroke
** Body Mass Index
†† Self-report of $\geq$ 10 days of alcohol use during the last two weeks

TABLE 2: Characteristics of the persistent cohort*. The Nord-Trøndelag Health Study 1984-86 (HUNT 1) and 1995-97 (HUNT 2).

	20-34 years				35-49 years				50-69 years				Total cohort	
	Men n=565		Women n=846		Men n=967		Women n=1,437		Men n=1,028		Women n=1,844		N=6,687	
Variables	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Primary school	128	(22.7)	166	(19.6)	338	(35.0)	697	(48.5)	624	(60.7)	1,439	(78.0)	3,392	(50.7)
High school	327	(57.9)	524	(61.9)	419	(43.3)	533	(37.1)	324	(31.5)	320	(17.4)	2,447	(36.6)
College/university	110	(19.5)	156	(18.4)	210	(21.7)	207	(14.4)	80	(7.8)	85	(4.6)	848	(12.7)
Anxiety disorder†	112	(19.8)	215	(31.8)	142	(21.3)	333	(32.4)	106	(16.1)	307	(26.4)	1,215	(26.3)
Depression‡	44	(7.8)	36	(7.2)	129	(13.3)	94	(11.9)	162	(22.7)	184	(17.7)	649	(16.0)
Comorbid disorder§	470	(83.2)	129	(15.3)	165	(17.1)	293	(20.5)	161	(15.9)	348	(19.4)	1,191	(18.0)
Cardio-vascular disease#	4	(0.7)	0	(0.0)	16	(1.7)	17	(1.2)	125	(12.2)	145	(7.9)	307	(4.6)
Diabetes	2	(0.4)	1	(0.1)	9	(0.9)	8	(0.6)	25	(2.4)	35	(1.9)	80	(1.2)
Impaired due to somatic disease	45	(9.6)	38	(5.2)	103	(13.4)	155	(13.7)	248	(34.8)	390	(29.1)	972	(19.0)
Use of analgesics	48	(8.7)	123	(14.9)	108	(11.5)	304	(22.2)	194	(20.3)	508	(30.5)	1,285	(20.4)
Visit to a physician, last year	449	(79.5)	765	(90.4)	779	(80.6)	1,232	(85.7)	847	(82.4)	1,637	(88.8)	5,709	(85.4)
Hospital admission, last five years	149	(26.5)	494	(58.5)	291	(30.1)	711	(49.6)	428	(41.6)	753	(41.1)	2,826	(42.4)
Sleep problems	117	(20.9)	155	(18.5)	208	(21.7)	324	(22.9)	249	(24.6)	672	(37.6)	1,725	(26.3)
BMI**$\geq$ 25 kg/m^2	173	(30.6)	172	(20.4)	452	(46.8)	483	(33.7)	604	(58.8)	1,039	(56.5)	2,923	(43.8)
BMI**$\geq$ 30 kg/m^2	28	(5.0)	37	(4.4)	77	(8.0)	130	(9.1)	107	(10.4)	326	(17.7)	705	(10.6)
Low physical activity	259	(46.0)	406	(48.4)	481	(50.2)	661	(46.2)	416	(41.5)	699	(39.4)	2,967	(45.2)
Daily smoking	252	(44.8)	475	(56.5)	429	(44.7)	622	(44.0)	401	(40.0)	533	(29.9)	2,712	(41.3)
High alcohol consumption††	22	(3.9)	23	(2.7)	48	(5.0)	30	(2.1)	63	(6.3)	39	(2.2)	225	(3.4)
Separated or divorced	20	(3.5)	43	(7.0)	60	(6.2)	121	(8.4)	44	(4.3)	73	(4.0)	361	(5.4)
Living alone	74	(13.2)	57	(7.0)	68	(7.1)	51	(3.7)	123	(12.0)	311	(16.9)	684	(10.4)
Lack of social support	67	(11.9	176	(20.8)	199	(20.7)	489	(34.2	293	(28.9)	866	(47.6)	2,090	(31.5)
Loneliness	126	(22.3)	222	(26.2)	170	(17.7)	315	(22.0)	171	(16.8)	448	(24.5)	1,452	(21.8)
Stressful job	342	(70.4)	443	(61.4)	686	(78.5)	718	(59.7)	452	(66.2)	480	(43.5)	3,121	(61.6)
Low job control	265	(46.9)	296	(40.9)	348	(39.8)	514	(42.7)	270	(39.5	369	(32.8)	2,062	(40.4)
Job dissatisfaction	85	(16.6)	86	(10.9)	148	(16.3)	127	(9.5)	128	(16.9)	148	(10.4)	722	(12.6)
Unemployment	9	(1.7)	76	(9.7)	8	(0.8)	167	(12.8)	27	(2.8)	355	(25.7)	642	(10.8)

* Participants scoring above the 80th percentile of the Anxiety-Depression 12 Index (ADI-12) at baseline (HUNT 1)
† The Hospital Anxiety and Depression Scale, Anxiety subscale (HADS-A) score $\geq$8, Depression subscale (HADS-D) <8
‡ HADS-D $\geq$8, HADS-A <8
§ HADS-A $\geq$8, HADS-D $\geq$8
# Self-report of present or previous angina pectoris, heart infarction or stroke
** Body Mass Index
†† Self-report of $\geq$ 10 days of alcohol use during the last two weeks

TABLE 3: Odds ratios for having anxiety disorder, depression or comorbid disorder, measured by the Hospital Anxiety and Depression Scale (HADS†) at follow-up at different educational levels. Model 1 is adjusted for age and gender and model 2 is adjusted for age, gender and anxiety/depression level‡ at baseline. The Nord-Trøndelag Health Study 1984-86 (HUNT 1) and 1995-97 (HUNT 2).

	Cases		**Model 1**			**Model 2**		
	n	%	OR	95% CI	P	OR	95% CI	p
INCIDENT COHORT§ (N=29,748)								
Anxiety disorder#								
College / University	317	6.8	**1**			**1**		
High school	901	7.7	**1.15**	1.00-1.31		**1.18**	1.03-1.35	
Primary school	737	7.4	**1.33**	1.15-1.53		**1.35**	1.17-1.56	
Test for trend					**			**
Depression† †								
College / University	143	3.2	**1**			**1**		
High school	536	4.7	**1.48**	1.22-1.78		**1.50**	1.24-1.82	
Primary school	752	7.5	**1.86**	1.54-2.25		**1.89**	1.56-2.28	
Test for trend					**			**
Comorbid disorder‡‡								
College / University	121	2.4	**1**			**1**		
High school	463	3.6	**1.50**	1.22-1.84		**1.52**	1.24-1.87	
Primary school	488	4.2	**1.92**	1.55-2.36		**1.92**	1.56-2.37	
Test for trend					**			**
PERSISTENT COHORT§§ (N=6,687)								
Anxiety disorder								
College / University	161	23.7	**1**			**1**		
High school	492	27.6	**1.21**	0.99-1.49		**1.13**	0.95-1.44	
Primary school	562	26.1	**1.21**	0.98-1.50		**1.33**	0.91-1.40	
Test for trend					*			*
Depression								
College / University	58	10.1	**1**			**1**		
High school	218	14.4	**1.50**	1.10-2.04		**1.48**	1.09-2.02	
Primary school	373	19.0	**1.82**	1.34-2.48		**1.80**	1.32-2.44	
Test for trend					**			**
Comorbid disorder								
College / University	103	12.2	**1**			**1**		
High school	399	16.4	**1.41**	1.12-1.78		**1.34**	1.06-1.69	
Primary school	689	20.8	**1.91**	1.52-2.41		**1.73**	1.37-2.19	
Test for trend					**			**

* $p > 0.05$
** $p < 0.001$
† Consists of an anxiety subscale (HADS-A) and a depression subscale (HADS-D)
‡ Anxiety Depression Index-12. The adjustment is performed due to variation in ADI-12 at baseline within each cohort.
§ Cohort with Anxiety Depression Index-12 at or below the 80th percentile at baseline (HUNT 1).
# HADS-A$\geq$8‡‡‡, HADS-D§§§ <8.
†† HADS-D$\geq$8, HADS-A <8.
‡‡ HADS-A$\geq$8, HADS-D $\geq$8.
§§ Cohort with Anxiety Depression Index-12 above the 80th percentile at baseline (HUNT 1).

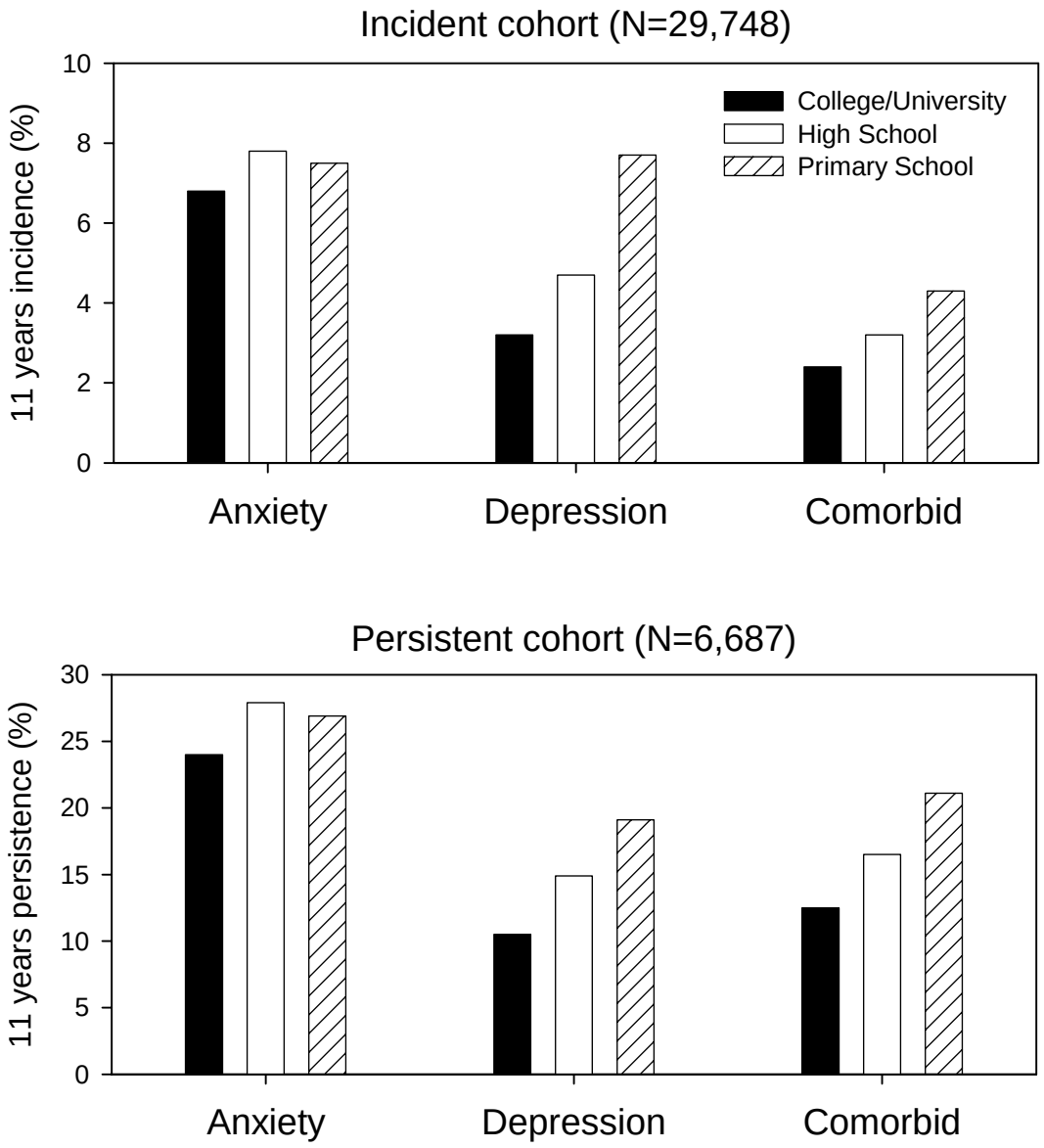

FIGURE 1: The Nord-Trøndelag Health Study 1984-86 (HUNT 1) and 1995-97 (HUNT 2):

11 years incidence and persistence rates of anxiety disorder, depression, and comorbid disorder, respectively, at the three educational levels. Incidence cohort, Individuals with Anxiety Depression Index-12 $\leq 80^{th}$ percentile at baseline; Persistence cohort, Individuals with Anxiety Depression Index-12 $>80^{th}$ percentile at baseline; Anxiety disorder, the Hospital Anxiety and Depression Scale, Anxiety subscale (HADS-A) score $\geq$8, Depression subscale (HADS-D) <8; Depression, HADS-D$\geq$8 and HADS-A <8; Comorbid, HADS-A$\geq$8, HADS-D $\geq$8.

References

1. Lorant V, Deliege D, Eaton W, et al. Socioeconomic inequalities in depression: a meta-analysis. Am J Epidemiol 2003;157:98-112.
2. Eaton WW, Muntaner C, Bovasso G, et al. Socioeconomic status and depressive syndrome: the role of inter- and intra-generational mobility, government assistance, and work environment. J Health Soc Behav 2001;42:277-94.
3. Kaplan GA, Roberts RE, Camacho TC, et al. Psychosocial predictors of depression. Prospective evidence from the human population laboratory studies. Am J Epidemiol 1987;125:206-20.
4. Bracke P. The three-year persistence of depressive symptoms in men and women. Soc Sci Med 2000;51:51-64.
5. Sargeant JK, Bruce ML, Florio LP, et al. Factors associated with 1-year outcome of major depression in the community. Arch Gen Psychiatry 1990;47:519-26.
6. Kessler RC, Nelson CB, McGonagle KA, et al. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. Br J Psychiatry 1996;Suppl 30:17-30.
7. Sartorius N, Ustun TB, Lecrubier Y, et al. Depression comorbid with anxiety: results from the WHO study on psychological disorders in primary health care. Br J Psychiatry 1996;Suppl 30:38-43.
8. Dohrenwend BP, Levav I, Shrout PE, et al. Socioeconomic status and psychiatric disorders: the causation-selection issue. Science 1992;255:946-52.
9. Kessler RC, Foster CL, Saunders WB, et al. Social consequences of psychiatric disorders, I: Educational attainment. Am J Psychiatry 1995;152:1026-32.
10. Johnson JG, Cohen P, Dohrenwend BP, et al. A longitudinal investigation of social causation and social selection processes involved in the association between socioeconomic status and psychiatric disorders. J Abnorm Psychol 1999;108:490-9.
11. West P. Rethinking the health selection explanation for health inequalities. Soc Sci Med 1991;32:373-84.
12. Stansfeld SA, Head J, Marmot MG. Explaining social class differences in depression and well-being. Soc Psychiatry Psychiatr Epidemiol 1998;33:1-9.
13. Lynch JW, Kaplan GA, Shema SJ. Cumulative impact of sustained economic hardship on physical, cognitive, psychological, and social functioning. N Engl J Med 1997;337:1889-95.

14. HUNT. The Nord-Trøndelag Health Study, Norway. http://www.hunt.folkehelsa.no/english/index.asp, 2004.
15. Holmen J, Midthjell K, Krüger Ø, et al. The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation. Norsk Epidemiologi 2003;13:19-32.
16. Tambs K, Moum T. Low genetic effect and age-specific family effect for symptoms of anxiety and depression in nuclear families, halfsibs and twins. J Affect Disord 1993;27:183-95.
17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-370.
18. Bjelland I, Dahl AA, Haug T, et al. The validity of the Hospital Anxiety and Depression Scale. An Updated review. J Psychosom Res 2002;52:69-77.
19. Mykletun A, Stordal E, Dahl AA. The Hospital Anxiety and Depression Scale (HADS): Factor Structure, Item Analyses, and Internal Consistency in a Large Population. Br J Psychiatry 2001;179:540-4.
20. Dohrenwend BP. A psychosocial perspective on the past and future of psychiatric epidemiology. Am J Epidemiol 1998;147:222-31.
21. Boyer P. Do anxiety and depression have a common pathophysiological mechanism? Acta Psychiatr Scand 2000;102 (suppl 406):24-9.
22. Regier D, Kaelber C. The Epidemiologic Catchment Area (ECA) Program: Studying the prevalence and incidence of psychopathology. In: Tsuang M, Tohen M, Zahner G, eds. Textbook in Psychiatric Epidemiology. New York: Wiley-Liss, 1995:135-55.
23. Wittchen HU, Kessler RC, Pfister H, et al. Why do people with anxiety disorders become depressed? A prospective-longitudinal community study. Acta Psychiatr Scand 2000;102 (Suppl 406):14-23.
24. Adler NE, Ostrove JM. Socioeconomic status and health: what we know and what we don't. Ann N Y Acad Sci 1999;896:3-15.
25. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med 1993;153:2093-101.
26. McEwen BS. Mood disorders and allostatic load. Biol Psychiatry 2003;54:200-7.
27. McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. Ann N Y Acad Sci 1999;896:30-47.
28. Wilkinson RG. Health, hierarchy, and social anxiety. Ann N Y Acad Sci 1999;896:48-63.
29. Nesse RM. Is depression an adaptation? Arch Gen Psychiatry 2000;57:14-20.