Anxiety and depression in the general population

Issues related to assessment, comorbidity, and risk factors

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2. LIST OF PAPERS


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


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/m²)
- 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 ≥ 8 and HADS-D < 8

- **Comorbid disorder**
  - Comorbid anxiety disorder and depression: HADS-A ≥ 8 and HADS-D ≥ 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 ≥ 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 ≤ 80th percentile.

- **Internal consistency**
  - The average inter-item correlation.

- **Persistent cohort**
  - Individuals from the study population in Paper V with ADI-12 scores > 80th 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 multifactorial 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.

![Categorical versus dimensional approach](image)

**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”. Herrmann 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 $\geq 8$ 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.
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-methyltetrahydrofolate (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-methyltetrahydrofolate (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 these 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 80th percentile of ADI-12 at baseline: The incident cohort (N=29,463) was selected by ADI-12 ≤ the 80th percentile; the persistent cohort (N=6,687) was selected by ADI-12 > the 80th 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 ≥ 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 ≥ 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 1 into a mentally healthy sample (the incident cohort) by ADI-12 score ≤ 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 ≥ 30kg/m². 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, ≥ 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 70th-100th 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 \textit{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 format and carried out by a robotic workstation (Micro-lab AT plus 2; Hamilton Bonaduz).

Genotyping of the methylenetetrahydrofolate reductase (MTHFR) 677C\textsuperscript{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\textsuperscript{2} and ≥ 30kg/m\textsuperscript{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, ≥ 30 kg/m².

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

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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 ≥ 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 tranquiliser 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
An 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.

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**Figure 7:** Dose-response relationships between ADI-score at baseline and HADS categories at follow-up 11 years later. The ORs that constitute 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 ≥ 8 and HADS-D ≥ 8; **Unrestricted**, HADS-A ≥ 8 or HADS-D ≥ 8; **Restricted**, HADS-A ≥ 8 and HADS-D < 8, or HADS-D ≥ 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.

<table>
<thead>
<tr>
<th>Identified mediators</th>
<th>Model without mediators</th>
<th>Model with identified mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>INCIDENT COHORT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder:</td>
<td>1.34</td>
<td>1.16-1.55</td>
</tr>
<tr>
<td>Daily smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression:</td>
<td>1.86</td>
<td>1.54-2.25</td>
</tr>
<tr>
<td>Low physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid disorder:</td>
<td>1.97</td>
<td>1.59-2.44</td>
</tr>
<tr>
<td>Daily smoking, low physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PERSISTENT COHORT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder:</td>
<td>1.17</td>
<td>0.92-1.50</td>
</tr>
<tr>
<td>Daily smoking, impaired due to somatic disease, use of analgesics, unemployment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression:</td>
<td>1.80</td>
<td>1.32-2.44</td>
</tr>
<tr>
<td>Lack of social support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid disorder:</td>
<td>1.69</td>
<td>1.33-2.15</td>
</tr>
<tr>
<td>Daily smoking, use of analgesics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) 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 (≥ 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>
<thead>
<tr>
<th>Reasons for non-participation</th>
<th>20-44 years</th>
<th>45-69 years</th>
<th>≥70 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up by physician/hospital</td>
<td>11 (5.8%)</td>
<td>10 (13.7%)</td>
<td>8 (28.6%)</td>
<td>29 (10.0%)</td>
</tr>
<tr>
<td>Long waiting at screening site</td>
<td>8 (4.2%)</td>
<td>4 (5.5%)</td>
<td>0 (0.0%)</td>
<td>12 (4.1%)</td>
</tr>
<tr>
<td>Busy at job</td>
<td>42 (22.1%)</td>
<td>18 (24.7%)</td>
<td>2 (7.1%)</td>
<td>62 (21.3%)</td>
</tr>
<tr>
<td>Immobilised by disease</td>
<td>16 (8.4%)</td>
<td>6 (8.2%)</td>
<td>6 (21.4%)</td>
<td>28 (9.6%)</td>
</tr>
<tr>
<td>Moved, or long time absent</td>
<td>59 (31.1%)</td>
<td>10 (13.7%)</td>
<td>6 (21.4%)</td>
<td>75 (25.8%)</td>
</tr>
<tr>
<td>Forgot/no reason/other</td>
<td>36 (18.9%)</td>
<td>21 (28.8%)</td>
<td>3 (10.7%)</td>
<td>60 (20.6%)</td>
</tr>
<tr>
<td>Unnecessary/unwilling</td>
<td>18 (9.5%)</td>
<td>4 (5.5%)</td>
<td>3 (10.7%)</td>
<td>25 (8.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>190 (100.0%)</td>
<td>73 (100.0%)</td>
<td>28 (99.9%)</td>
<td>291 (100.0%)</td>
</tr>
</tbody>
</table>
Table 3: A comparison between attendees\textsuperscript{a} and nonattendees\textsuperscript{b} in HUNT 1 and HUNT 2.

<table>
<thead>
<tr>
<th>Category</th>
<th>Attended HUNT 1 and HUNT 2</th>
<th>Attended HUNT 1 but not HUNT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)\textsuperscript{c}</td>
</tr>
<tr>
<td>Men</td>
<td>17,706</td>
<td>(47.1)</td>
</tr>
<tr>
<td>20-34 years</td>
<td>10,757</td>
<td>(28.6)</td>
</tr>
<tr>
<td>35-49 years</td>
<td>13,211</td>
<td>(35.2)</td>
</tr>
<tr>
<td>50-69 years</td>
<td>13,611</td>
<td>(36.2)</td>
</tr>
<tr>
<td>Primary school</td>
<td>16,059</td>
<td>(42.9)</td>
</tr>
<tr>
<td>High school</td>
<td>15,536</td>
<td>(41.5)</td>
</tr>
<tr>
<td>College/university</td>
<td>5,863</td>
<td>(15.7)</td>
</tr>
<tr>
<td>ADI-12 score\textsuperscript{e} &gt; the 80\textsuperscript{th} percentile</td>
<td>30,506</td>
<td>(81.2)</td>
</tr>
<tr>
<td>Cardiovascular disease\textsuperscript{f}</td>
<td>972</td>
<td>(2.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>368</td>
<td>(1.0)</td>
</tr>
<tr>
<td>Impaired due to somatic disease</td>
<td>2,265</td>
<td>(6.9)</td>
</tr>
<tr>
<td>Use of analgesics</td>
<td>2,800</td>
<td>(7.7)</td>
</tr>
<tr>
<td>Visit to a physician, last year</td>
<td>28,739</td>
<td>(76.5)</td>
</tr>
<tr>
<td>Hospital admission, last five years</td>
<td>12,394</td>
<td>(33.1)</td>
</tr>
<tr>
<td>Low physical activity</td>
<td>14,798</td>
<td>(40.0)</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>2,277</td>
<td>(6.1)</td>
</tr>
<tr>
<td>BMI \textgreater{} 25 kg/m\textsuperscript{2}</td>
<td>16,119</td>
<td>(42.9)</td>
</tr>
<tr>
<td>BMI \textgreater{} 30 kg/m\textsuperscript{2}</td>
<td>3,249</td>
<td>(8.7)</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>12,686</td>
<td>(34.3)</td>
</tr>
<tr>
<td>High alcohol consumption\textsuperscript{g}</td>
<td>1,081</td>
<td>(2.9)</td>
</tr>
<tr>
<td>Separated or divorced</td>
<td>1,131</td>
<td>(3.0)</td>
</tr>
<tr>
<td>Living alone</td>
<td>2,556</td>
<td>(6.9)</td>
</tr>
<tr>
<td>Lack of social support</td>
<td>6,330</td>
<td>(17.0)</td>
</tr>
<tr>
<td>Loneliness</td>
<td>2,005</td>
<td>(5.4)</td>
</tr>
<tr>
<td>Stressful job</td>
<td>15,766</td>
<td>(49.2)</td>
</tr>
<tr>
<td>Low job control</td>
<td>10,673</td>
<td>(33.2)</td>
</tr>
<tr>
<td>Job dissatisfaction</td>
<td>1,232</td>
<td>(3.6)</td>
</tr>
<tr>
<td>Unemployment</td>
<td>2,393</td>
<td>(7.0)</td>
</tr>
</tbody>
</table>

\textsuperscript{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

\textsuperscript{a} Participated in HUNT 1 and HUNT 2 (age 20-69 years at HUNT 1)

\textsuperscript{b} Participated in HUNT 1, but not in HUNT 2 (age 20-69 years at HUNT 1)

\textsuperscript{c} % within the attendees

\textsuperscript{d} % within the nonattendees

\textsuperscript{e} Anxiety-Depression Index-12 score measured at HUNT 1

\textsuperscript{f} Self-reported present or previous angina pectoris, myocardial infarction, or stroke

\textsuperscript{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 $\geq 8$ 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).
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

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**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.

<table>
<thead>
<tr>
<th>Test result</th>
<th>Anxiety disorder</th>
<th>Major depressive disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Non-cases</td>
</tr>
<tr>
<td>Positive (n)</td>
<td>80</td>
<td>180</td>
</tr>
<tr>
<td>Negative (n)</td>
<td>20</td>
<td>720</td>
</tr>
<tr>
<td>Total (n)</td>
<td>100</td>
<td>900</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>0.80</td>
<td></td>
</tr>
</tbody>
</table>

**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)
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.

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

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**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.)
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](https://example.com/figure11.png)

*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
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.

![Cumulative incidence of anxiety and depression in childhood, adolescence, and early adulthood (200).](image)

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

In the analyses from HUNT 2 (222) impairment due to somatic disease/disabilities, sociodemographic characteristics, health behaviours, somatic diagnoses, somatic symptoms, and physical measurements in a logistic regression analysis.

**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, our 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 irrefutable 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


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.
119. Atack JR. Anxioselective compounds acting at the GABA(A) receptor benzodiazepine binding site. Curr Drug Target CNS Neurol Disord 2003;2:213-32.


APPENDIX I:

HUNT 1

QUESTIONNAIRE 1
Skjemmbildefotograferingen 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 framme fe vil du finne nedenfor.

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

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

Med vennlig hilsen
Statens skjemmbildefotografering
Postboks 8155 Dep, Oslo 1
Fylkeslægen • Helserådet • Statens Institutt For Folkehelse

Født dato Personnr. Kommune
Kreftav.

Møtested Første
bokstav
etternavn Dag og dato
Klokkesslett
A. Hvordan er heisa i for tida?
(Sett kryss i bare en rute.)

[Dårlig, Ikke heit god, God, Svært god]

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

[Almenpraktiserende lege (distriktsslege, privatpraktiserende lege, turnuskandidat), Bedriftslege, Militærlæge, Lege ved sykehus (uten at du var innlagt), Annen lege]

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

[DÅRLIG, IKKE]

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

[Ett tall fra 1 til 7]

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

[Sukkørsyk, Hjerteinfarkt, Angina pectoris, Hjerneskade]

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

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

[Er bevegelseshemmet, Har nedsatt syn, Har nedsatt hørsel, Hemmet pga. kroppssygdom, Hemmet pga. psykiske plager]

G. Har du noen søskene? (Nålevende eller døde)

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

[Sukkørsyk, Hjerteinfarkt/hjertekrampe, Forhøyet blodtrykk]

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

[Svært fornøyd, Meget fornøyd, Ganske fornøyd, Både/og, Nokså misfornøyd, Meget misfornøyd, Svært misfornøyd]
APPENDIX II:

HUNT 1

QUESTIONNAIRE 2
Røykevænker

Røyker du daglig for tiden? ........................................ 17
Hvis du svarte «JA», røyker du DAGLIG for tiden:
   Sigaretter? ......................................................... 18
   Pipe? ............................................................. 19
   Sigarer (eller serutter/sigarillos)? ......................... 20
Hvis du IKKE røyker SIGARETTER daglig for
   tiden: Har du røykt SIGARETTER daglig
   tidligere? .......................................................... 21
Hvis du svarte «JA», hvor lenge er det siden
   du skuttet å røyke sigaretter daglig?
   Mindre enn 3 måneder ............................................. 22
   3 måneder–1 år .................................................... 23
   1–5 år ................................................................... 24
   Mer enn 5 år ........................................................ 25
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 håndduftede) .... 26
Besvares av dem som røyker daglig nå
   eller har røykt daglig tidligere:
   (Gjelder både sigaretten, pipe og sigar-røykmenn)
Hvor gammel var du da du begynte
   å røyke daglig? ...................................................... 27
Hvor mange år tilsammen har du røykt daglig? ........ 28

Alkoholbruk

Hvor ofte har du drikket alkohol (el. vin
   eller brennevin) de SISTE 14 DAGENE?
   Jeg har ikke drikket alkohol, men
   er ikke totalavholdende ........................................ 29
   Jeg har drikket 1–4 ganger .................................... 30
   Jeg har drikket 5–10 ganger .................................. 31
   Jeg har drikket mer enn 10 ganger ......................... 32
   Jeg er totalavholdende, drikker aldri alkohol ......... 33
Dersom du har drikket alkohol de siste 14
dagene, har det ført til at du noen gang har følt
   deg beruset? ......................................................... 34
Har det vært perioder i livet ditt da du har
   drikket for mye, eller i hvert fall i meste laget?
   Nei ................................................................... 35
   Ja ..................................................................... 36

Salt

Hvor ofte bruker du salt kjøtt eller salt
   fisk/sild til middag?
   Aldri, eller sjelden enn en gang i månedene .......... 15
   1–2 ganger i månedene ...................................... 16
   Opp til en gang i uka ...................................... 17
   Opp til to ganger i uka ................................... 18
   Mer enn to ganger i uka .................................. 19
Hvor ofte pleier du å strekke salt på
   middagsmaten?
   Sjelden eller aldri ............................................. 20
   Av og til .......................................................... 21
   Ofte .................................................................. 22
   Alltid eller nesten alltid .................................... 23

Mosjon

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

Hvor ofte driver du mosjon?
   (Ta et gjennomsnitt)
   Aldri, sjeldenere enn en gang i uka ......... 1
   En gang i uka ................................................. 2
   2–3 ganger i uka ............................................ 3
   Omtrent hver dag .......................................... 4

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 andupsten eller svett ............ 13
   Tar meg nesten hett ut ................................... 14

Hvor lenge holder du på hver gang?
   (Ta et gjennomsnitt)
   Mindre enn 15 minutter .................................. 15
   16–30 minutter .............................................. 16
   30 minutter–1 time ..................................... 17
   Mer enn 1 time .............................................. 18

Statens skjemmbildefotografering
Fylkeslaget • Helsesektet • Statens konsultforvaltning
Institutt for anvendt sosialvitenskapelig forskning
Institutt for samfunnsforskning

Navn: .................................................................
Adr: ..................................................................
Postnr. .........................................................
Postkontor: ...................................................
Fnr: .................................................................
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

UTDANNINGEN

Hvilken utdanning har du fullført?
Oppg berøres høyest fullførte utdanning.

7-årig folkeskole eller kortere .................. 40
Framhalds- eller fortsettelsesskole ............... 4
9-årig grunnskole ................................... 4
Real- eller middelskole, grunnskolens 10. år ....... 4
Eitt- eller to-årig videregående skole ............ 4
Artium, økonomisk gymnas eller almenlagt retnin
i videregående skoler ............................. 4
Høyskole eller universitet, mindre enn 4 år .... 4
Høyskole eller universitet, 4 år eller mer .... 4

Har du fullført annen heldags utdanning, og i tilfelle hvor mange år?
Skriv antall år her ........ 41

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 ektelfelle (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.)

Spesialarbeider, utfaglørt arbeider ................ 43,44
Fagarbeider, håndverker, formann ................
Underordnet funksjonær (butikk, kontor,
offentlige tjenester) ..............................
Fagforsorg (f.eks. sykepleier, tekniker, lærer)
Overordnet stilling i offentlig eller privat virksomhet
Gårdbruker eller skogarbeider ..................
Fisker .............................................
Selvstendig i akademisk erverv (f.eks. tatover, advokat)
Selvstendig næringsdrivende (Industi, transport, handel)
Har ikke hatt inntektsgivende arbeid
(f.eks. pga. heltids husarbeid, studier, trygd) ....

Hvis du er i arbeid (sjelder også heltids husarbeid), bor 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
Ganske ofte ....................................... 2
Ganske sjelden .................................... 3
Aldri, eller nesten aldi ............................ 4

Kreer arbeidet ditt så mye konsentrasjon og
oppmærksomhet at du ofte føler deg utsatt etter en arbeidsdag?

Ja, nesten alltid .................................. 46
Ganske ofte ....................................... 2
Ganske sjelden .................................... 3
Aldri, eller nesten aldi ............................ 4

Hvordan trives du alt i alt med arbeidet ditt?

Veldig godt ...................................... 47
Ganske godt ...................................... 2
Gott ................................................ 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
1–2 fast ansatte ................................. 2
3–10 fast ansatte ............................... 3
Mer enn 10 fast ansatte ........................ 4

HVISKONTRASKALSTEMPERATEN

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
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
Sterk og opplagt ............................... 2
Ganske sterk og opplagt ..................... 3
Både - og ........................................ 5
Ganske trett og sliten ......................... 6
Trett og sliten .................................... 7
Svært trett og sliten ............................ 8
### MEDISIN/PLAGER

#### Har du vanligvis:

<table>
<thead>
<tr>
<th>Hoste om morgenen?</th>
<th>51</th>
<th>JA</th>
<th>NEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppsøytt fra brystet om morgenen?</td>
<td>52</td>
<td>JA</td>
<td>NEI</td>
</tr>
</tbody>
</table>

#### Hvor ofte har du brukt smertestillende medisin den siste måneden?

<table>
<thead>
<tr>
<th>Daglig</th>
<th>53</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hver uke, men ikke hver dag</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Sjeldnere enn hver uke</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Aldri</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Daglig</th>
<th>54</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hver uke, men ikke hver dag</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Sjeldnere enn hver uke</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Aldri</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

#### Har du i løpet av siste måned vært plaget av nervøsitet (iritabil, urolig, anspent eller rasles)?

<table>
<thead>
<tr>
<th>Nesten hele tida</th>
<th>55</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofte</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Av og til</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Aldri</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Nesten hver natt</th>
<th>56</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofte</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Av og til</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Aldri</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Nesten hele tida</th>
<th>57</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofte</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Av og til</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Aldri</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

### 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 naboor?

<table>
<thead>
<tr>
<th>Svært sannsynlig</th>
<th>58</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noksa sannsynlig</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Usikkert</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Usannsynlig</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Helt usannsynlig</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

#### Hender det ofte at du føler deg ensom?

<table>
<thead>
<tr>
<th>Meget ofte</th>
<th>59</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofte</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Av og til</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Meget sjelden</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Aldri</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

### 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 |

#### 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 nedstent?

| Svært nedstent | 63 | 1 |
| Nedstent | 2 |
| Noksa nedstent | 3 |
| Både - og | 4 |
| Noksa 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
Personlig innbydelse

Flere steder i skjemaet ber vi deg oppgi din alder da eventuell sykdom inntrådte. Hvis du ikke husker nøysiktig 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 rubrikkene helt til slutt i skjemaet oppgir navnet på den allmenntrektiserende 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

<table>
<thead>
<tr>
<th>Hvordan er helsa di nå?</th>
<th>12</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare ett kryss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dårlig</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ikke helt god</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>God</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Svært god</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### LUFTVEGSPLAGER

<table>
<thead>
<tr>
<th>Hoster du daglig i perioder av året?</th>
<th>14</th>
<th>JA</th>
<th>NEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hvis JA:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Er hosten vanligvis ledsaget av oppsytt?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Har du hatt hoste med oppsytt i minst 3 mnd. sammenhengende i hvert av de to siste åra?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Har du hatt noe anfall med pipende eller tung pest de siste 12 måneder?</td>
<td>16</td>
<td>JA</td>
<td>NEI</td>
</tr>
<tr>
<td>Har du eller har du hatt astma?</td>
<td>17</td>
<td>JA</td>
<td>NEI</td>
</tr>
<tr>
<td>Har du brukt eller bruker du astmamedisiner?</td>
<td>20</td>
<td>JA</td>
<td>NEI</td>
</tr>
</tbody>
</table>

### HJERTE-KARSYKKOMMER, DIABETES

<table>
<thead>
<tr>
<th>Har du, eller har du hatt:</th>
<th>21</th>
<th>JA</th>
<th>NEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hjerteinfarkt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris (hjertekrampe)</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hjerneslag/hjernebladning</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (sukkerykke)</td>
<td>30</td>
<td></td>
<td></td>
</tr>
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</table>

### STOFFSKIFTE

<table>
<thead>
<tr>
<th>Har du noen gang fått påvist:</th>
<th>36</th>
<th>JA</th>
<th>NEI</th>
<th>Ålder første gang</th>
</tr>
</thead>
<tbody>
<tr>
<td>for høyt stoffsifte</td>
<td></td>
<td></td>
<td></td>
<td>år</td>
</tr>
<tr>
<td>for lavt stoffsifte</td>
<td>39</td>
<td></td>
<td></td>
<td>år</td>
</tr>
<tr>
<td>struma</td>
<td>42</td>
<td></td>
<td></td>
<td>år</td>
</tr>
<tr>
<td>annen sykdom i skjoldbruskgjertelen</td>
<td></td>
<td></td>
<td></td>
<td>år</td>
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</table>

<table>
<thead>
<tr>
<th>Bruker du eller har du brukt noen av disse medisinene:</th>
<th>48</th>
<th>JA</th>
<th>NEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroxin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neo-Mercaprole</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Er du operert i skjoldbruskgjertelen</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Har du fått radiojodbehandling</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### MUSKEL/SKJELETT-PLAGER

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

Hvis NEI, gå videre til neste side øverst. Hvis JA, svar på følgende:

### Hvor har du hatt disse plagene?

<table>
<thead>
<tr>
<th>Nakke</th>
<th>61</th>
<th>JA</th>
<th>NEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skuldre (aksler)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Håndledd, hender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bryst/mage</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Øvre del av ryggen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korsryggen</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Høfter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knaer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anker, fetter</td>
<td>70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvis du har hatt plagene i flere områder i minst 3 måneder, sørter du da ring rundt det ja-krysset hvor plagene har vært lengst

<table>
<thead>
<tr>
<th>Hvor lenge har plagene vært sammenhengende?</th>
<th>Antall mnd.</th>
<th>Antall år</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hvis under 1 år, oppgi antall mnd.</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Hvis 1 år eller mer, oppgi antall år.</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

### HAVPAGLEVRED I ARBEIDSEVNE DET SISTE ÅRET?

<table>
<thead>
<tr>
<th>Har plagene redusert din arbeidsnevne det siste året?</th>
<th>76</th>
<th>JA</th>
<th>NEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gjelder også hjemmearbeidende. Bare ett kryss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nei/ubetydelig</td>
<td>I noen grad</td>
<td>I betydelig grad</td>
<td>Vet ikke</td>
</tr>
</tbody>
</table>

Hvis du har vært sykmeldt pga. disse plagene det siste året? | 76 |

| Har plagene fort til redusert aktivitet i fritida? | JA | NEI | IKRET | ARBEID |
RØYKING

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

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

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?

Sigaretter daglig? 130

Sigarer/sigarillos daglig? 131

Pipe daglig? 132

Aldri røykt daglig 133

(Sett kryss)

Antall år

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

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? 136

Hvor gammelt var du da du begynte å røyke daglig? 140

Hvor mange år tilsammen har du røykt daglig? 142

Antall sigaretter

Alder

Antall år

KAFFE/TE/ALKOHOL

Hvor mange koppar kaffe/te drikker du daglig?

Sett 0 hvis du ikke drikker kaffe/te daglig

Kokekaffe 144

Annen kaffe 146

Te 148

Antall kopper

Alkohol:

Er du total avholdsman-kvinne? 150

Antall ganger

Hvor mange ganger i måneden drikker du vanligvis alkohol? 151

Regn ikke med lettet. Sett 0 hvis mindre enn 1 gang i måned.

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

Regn ikke med lettet.

Sett 0 hvis du ikke drikker alkohol 153

Antall glass

FYSISK AKTIVITET

I FRITIDT

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

Arbeidsveg regnes som fritid

Timer pr. uke

Lett aktivitet (ikke svett/andpusten) 159

Under 1 1-2 3 og mer

Hard fysisk aktivitet (svett/andpusten) 160

1 2 3 4

UNDER ARBEID

Hvis du er i lønnet eller uønnnet arbeid:

Hvoredes vil du beskrive arbeidet ditt?

Bare ett kryss

For det meste stillissende arbeid (f.eks. skrivebordsarbeid, montering) 161

Arbeid som krever at du går mye (f.eks. ekspediterarbeit, lett industriarbeid, undervisning) 2

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

Tungt kroppsarbeid (f.eks. skogarbeid, tungt jordbruksarb., tungt bygningsarb.) 4
HVERLEDES FØLER DU DEG?

Har du de siste to ukene følt deg:

Trygg og rolig? ............ 162 □ □ □ □
Glad og optimistisk? ..... 163 □ □ □ □
Har du følt deg:
Nervøs og urolig? .......... □ □ □ □
Plaget av angst? .......... 165 □ □ □ □
Irritabel? ................ □ □ □ □
Nedfor/deprimert? ....... □ □ □ □
Ensom? ................... 168 □ □ □ □

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

Jeg glider meg fortsatt over ting slik jeg pleide før 169
Avgjort like mye .......... □ 1 Bare lite grunn .......... □ 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 ............... 173
Ganske ofte ................ □ 2 En gang i blant ............ □ 3

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

Jeg kan sitte i fred og ro og
ekjenne 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 rastlos 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

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

Tabb for utfyllingen!

Nok en gang:

Velkommen til undersøkelsen!

NORD-TRØNDELAG
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)
Helseundersøkelsen i Nord-Trendelag

Takk for frammetet til undersøkelsen!


All opplysningene er underlagt straks taushetsplikt.

Vennlig hilsen
Helsetjenesten i Nord-Trendelag
Statens Institutt for Folkhelse
Statens helseundersøkelser

UTFYLLING

Dato for uttrykk av skjema: 19

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?
Hvis du ikke bodde i Norge, oppgi land i stedet for kommune.

ARBEID

Nåværende eller tidligere arbeid:
Hva slags inntektsgivende arbeid du har og event. din ektefelle/samboer? Hvis du/dore ikke har inntektsgivende arbeid nå: Oppgi det siste yrket.

Deg Ektesfelle/ selv samboer

Spesialarbeider eller ufaglært arbeidere
Fagarbeider, handverker, formann
Undervisning i fagområde (f.eks. butikk, kontor, off. tjenester)
Fagfunksjonær (f.eks. sykepleier, tekniker, lærer)

Overordnet stilling i off. eller privat virksomhet

Sjåfør
Selvstendig i akademisk erverv (f.eks. tannelege, advokat)

Annen selvstendig næringsvirksomhet

Har ikke vært i inntektsgivende arbeid

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

HAR du i løpet av de siste 12 månedene hatt sykefravær:
med egenmelding
med sykmelding fra lege

Hvis «Ja»: Hvor lenger tilsammen? Bare ett krys
2 uker eller mindre
2-8 uker
Mer enn 8 uker

HAR du i løpet av de siste 12 månedene vurdert å skifte yrke eller arbeidsplass?

ER arbeidet ditt så fysisk anstrengende at du ofte er sliten i kroppen etter en arbeidsdag? Bare ett krys
Ja, nesten alltid
Ganske ofte
Visst ingen

Kever arbeidet ditt så mye konsentrasjon og oppmerksomhet at du ofte føler deg utslitt etter en arbeidsdag?
Ja, nesten alltid
Ganske ofte
Visst ingen

Hvordan trives du i alt med arbeidet ditt?
Veldig godt
Ikke særlig godt
Dårlig

BOLOG

Hvem bor du sammen med?
Ett krys for hver linje og ang av antall

Ektefelle/samboer
Andre personer over 18 år
Personer under 18 år

Hvor mange av barna har plass i barnehage?

Hvilken type bolig bor du i? Bare ett krys

Enebolig/villa
Gårdsbruk
Blokki/terrasseleilighet
Rekkehus/2-4 mannsbolig
Annen bolig

Hvor stor er din boenhed?

Er det heledekkende tepper i stua?
Er det heledekkende tepper på ditt soverom?
Er det kått i boligen?
Er det hund i boligen?
Er det andre pelsklede dyr eller fugler i boligen?

OKONOMI

Mottar du noen av følgende offentlige ytelser?

Sykepenger/sykelynn/rehabiliteringspenger
Ytelser under yrkesrettet attføring
Uførepensjon
Alderspensjon
Sosialstøtte
Arbeidsloshetsstrygd
Overgangsstønad
Etterlattepensjon
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 krys
Ja, ofte
Ja, av og til
Nei, aldri

VENNER

Hvor mange gode venner har du?

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

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

Føler du at du har mange nok gode venner?

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

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

Ja Nei
Svar ut fra nærmiljøet, dvs. nabolaget/grenda.
Ett krys for hvert spørsmål

Jeg føler et sterkt teleesskap med de som bor her 

<table>
<thead>
<tr>
<th>Helt</th>
<th>Delvis</th>
<th>Usikker</th>
<th>Helt</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Selv om noen tar initiativ, er det ingen som blir med på det som settes i gang her

<table>
<thead>
<tr>
<th>Helt</th>
<th>Delvis</th>
<th>Usikker</th>
<th>Helt</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Hvis jeg flytter herfra, vil jeg lengte tilbake

<table>
<thead>
<tr>
<th>Helt</th>
<th>Delvis</th>
<th>Usikker</th>
<th>Helt</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Man kan ikke stole på hverandre her

<table>
<thead>
<tr>
<th>Helt</th>
<th>Delvis</th>
<th>Usikker</th>
<th>Helt</th>
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</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Når noe skal gjøres her, er det lett å få folk med

<table>
<thead>
<tr>
<th>Helt</th>
<th>Delvis</th>
<th>Usikker</th>
<th>Helt</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Det er vanskelig å få kontakt med folk her

<table>
<thead>
<tr>
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<th>Usikker</th>
<th>Helt</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Det er godt samhold her

<table>
<thead>
<tr>
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<th>Delvis</th>
<th>Usikker</th>
<th>Helt</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Ingen orker å ta initiativ til noe lenger her

<table>
<thead>
<tr>
<th>Helt</th>
<th>Delvis</th>
<th>Usikker</th>
<th>Helt</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Folk trives godt her

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Folk her kan ha store problemer uten at naboen vet noe

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Det er alltid noen som tar initiativ til å løse nødvendige oppgaver her

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Folk snakker lite med hverandre her

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Har du selv høysmue eller neseallergi?

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BRUK AV HELSETJENESTER

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

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allmennpraktiserende lege (kommunelege, privatpraktiserende lege, turnusmedisiner)......

bedriftslege

lege ved sykehus (uten at du var innlagt)

annen lege

fysioterapeut

kiropraktor

homeopat.

annen behandler (nattmedisiner, fysioterapeut, håndpåleggere, "healer", "synsk", e.l.)

Har du vært innlagt i sykehus de siste 5 åra?

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ALKOHOL

Hvis du er totalavholdsmann: Gå til KOSTHOLD.

Ett krys for hver spørsmål

Har du noen gang følt at du burde redusere alkoholforbruket ditt?

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Har andre noen gang kritisert alkoholbruken din?

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Har du noen gang følt ubehag eller skystfølelse pga. alkoholbruken din?

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Har det å ta en drink noen gang vært det første du har gjort om morgenen for å roe nervene, kurerere bakrus eller som en oppkvikker?

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KOSTHOLD

Hvor mange måltider spiser du vanligvis daglig (middag og brødmatid)?

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Hvor mange dager i uke spiser du varm middag?

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

Brødtypen ligner ....

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Hva slags fett blir vanligvis brukt i din husholdning?

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MEDISINBRUK

Har du i deler av de siste 12 måneder brukt noen medisiner daglig eller nesten daglig?

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Hvis "Ja":

Angi hvor mange måneder du brukte følgende medisiner: Sett 0 hvis du ikke har brukt medisinerne

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beroligende medisiner

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medisin mot depressjon

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astammedisin ..........

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vitamintillskudd

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tran/fiskeoiljer ....

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Hvor ofte har du brukt avslappende/beroligende medisin eller søvemedisin de siste månedene?

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Daglig .......... 2

Sjeldnere enn hver uke 3

Hver uke, men ikke hver dag 4
HODEPINE

Har du vært plaget av hodepine i løpet av de siste 12 månedene? 209 Ja
Ja, anfallssvis (migrene)........... 2
Ja, alltid plaget av hodepine.... 2
Nei ................. 2

[Neste kolonne]

Omgrenset hvor mange dager i pr. måned har du hodepine?
Mindre enn 7 dager 13
7 til 14 dager 2
Mer enn 14 dager 3

[Hvis «Nei»:] Gå til MUSKEL-/SKJELETTPLAGER

Hvor lenge varer hodepinnen vanligvis hver gang? 215
Mindre enn 4 timer 1
4 timer–3 døgn 2
Mer enn 3 døgn 3

Hvor ofte er hodepinnen preget av eller ledssatt av:

[______________________________________________]

bankende/dunkende smerte 214
pressende smerte 214
halvdisidt, alldidt samme side 214
halvdisidt, vekselsvis h. og v. side 214
smerter i «hete hodet» 214
kalme 219
lyd- og/eller lydslykhet 219
forvevning ved fysisk aktivitet 219
syrnasforstyrrelser før hodepine 222

[Hvis «Ja»:] Gå til MUSKEL-/SKJELETTPLAGER

Hvor mange tabletter/stikpiller har du eventuelt brukt av disse medisinen alt i alt i løpet av den siste månedene?
Skriv 0 hvis du ikke har brukt medisinen.

[______________________________________________]

Kaffert 9
Anervan 219
Imigran 222

MUSKEL-/SKJELETTPLAGER

Har du hatt plaget (smerter, verk, ubehag) i musker og/eller led i den siste månedene? 229
Ja 230
Nei 230

[Hvis «Ja»:] Gå til MUSKEL-/SKJELETTPLAGER

Plager (sett kryss)

[______________________________________________]

Nakke 230
Skulder/aksler 233
Øvre del av ryggen 233
Albuuer 239
Korsrygger 242
Håndled/hendek 246
Hofter 248
Knær 251
Ankler/føtter 254

[Dersom fler kryss: sett ring rundt kryss der plaget var verst]

Har plagen hindret deg i å utføre daglige aktiviteter den siste månedene?
Ja 257
Nei 257

[Hvis «Nei»] Gå til SMERTER I BEINA

I arbeidet 257
I fritiden 256

SMERTER I BEINA

Har du sår på tå, fot eller ankel som ikke vil gro? 299
Ja 299
Nei 299

Har du smerter i det ene eller begge beina når du går? 296
Ja 296
Nei 296

Har du oppsøkt lege p.g.a. smerter i beina? 261
Ja 261
Nei 261

[Hvis «NEI»] Gå til URINVEGS- OG PROSTATAPLAGER

Kan du gå lenger enn 50 meter? 282
Ja 282
Nei 282

Forsvinner smerten når du står stille en stund? 283
Ja 283
Nei 283

Må du se røre deg for at smerten skal gå over? 284
Ja 284
Nei 284

Hvor gjør det mest vondt? Ett kryss 285

Fot 285
Legg 285
Lår 285
Hofte 285

[Hvis «NEI»] Gå til SMERTER I BEINA

[______________________________________________]

Hvis du resten av livet måtte leve med de vannlatingsproblemmene du har nå, hvordan ville du føle deg? 284

Våre meget godt fornøyd 285
Våre for det meste utilfreds 285
Våre fornøyd 285
Våre misfornøyd 285
Våre for det meste tilfreds 285
Ha det forberedelig 285
Ha blandete følelser 285

URINVEGS- OG PROSTATAPLAGER

Etter hvert i løpet av en time.

Har du noen gang blitt fortalt av lege at du har:
Ja 272
Nei 272

forstørret prostata 272
prostatakreft 272

Har du gjennomgått noe av følgende:
Ja 274
Nei 274
sterilisering 274
tatt vevsprøve (biopsi) av prostata 275
kurigje fra smertene i nakken (helt eller delvis) 276

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

[Hvis «Ja»:] Gå til SMERTER I BEINA

Hvor ofte har du hatt følelsen av at blæren ikke er blitt fullstendig tømt etter avsluttet vannlatning? 217
Ja 217
Nei 217

Aldri 217
1 om til 2 av 3 ganger 4
Om tre av 5 ganger 5

Hvor ofte har du mottatt late vannet på nytt mindre enn 2 timer etter forrige vannlatning? 217
Ja 217
Nei 217

Hvor ofte har du mottatt stoppe og starte flere ganger under vannlatningen? 218
Ja 218
Nei 218

Aldri 218
1 om til 2 av 3 ganger 5
Om tre av 5 ganger 6

Hvor ofte syns du det har vært vanskelig å holde igjen når du har felt trang til å late vannet? 219
Ja 219
Nei 219

Aldri 219
1 om til 2 av 3 ganger 4
Om tre av 5 ganger 5

Hvor ofte har du hatt svak urinstråle? 261
Ja 261
Nei 261

Aldri 261
1 om til 2 av 3 ganger 4
Om tre av 5 ganger 5

Hvor ofte har du mottatt trykke eller presser for å begynne vannlatningen? 262
Ja 262
Nei 262

Aldri 262
1 om til 2 av 3 ganger 4
Om tre av 5 ganger 5

Hvor mange ganger har du vanligvis mottatt stø opp i løpet av natta før å late vannet? 263
Ja 263
Nei 263

Ingen 263
1 ganger 263
2 ganger 263
3 ganger 263
4 ganger 263
5 ganger 263
6 ganger 263

Hvis du resten av livet måtte leve med de vannlatingsproblemmene du har nå, hvordan ville du føle deg? 264

Våre meget godt fornøyd 264
Våre for det meste utilfreds 264
Våre fornøyd 264
Våre misfornøyd 264
Våre for det meste tilfreds 264
Ha det forberedelig 264
Ha blandete følelser 264

[Neste kolonne]
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 ........................................ 1 0 3 5 i dårlig humør ........................................ 0 2 3 5

Er du rask til å oppfatte et humoristisk poeng? 287

Svært treg Ganske treg Ganske rask Svært rask

Er du en i at det er noe ansvarsløst over folk som stadig prøver å være morsomme? 286

Nei, slett ikke ........................................ 0 2 3 5 Ganske enig ........................................ 3 0 2 5

I noen grad ........................................ 0 3 2 5 Ja, absolutt ........................................ 3 0 2 5

Er du en munter person? 289

Nei, slett ikke ........................................ 0 2 3 5 Ganske munter ........................................ 3 0 2 5

I noen grad ........................................ 0 3 2 5 Ja, absolutt ........................................ 3 0 2 5

INNE

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

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

Nesten aldri ........................................ 0 2 3 5 Ganske ofte ........................................ 3 0 2 5

Noen ganger ........................................ 0 3 2 5 Nesten altid ........................................ 3 0 2 5

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

Nesten aldri ........................................ 0 2 3 5 Ganske ofte ........................................ 3 0 2 5

Noen ganger ........................................ 0 3 2 5 Nesten altid ........................................ 3 0 2 5

HVILE OG AVSLAPPNING

Hvor mange timer tilbringer du vanligvis i liggende stilling i løpet av ett døgn? (nattesøvn, middagshvit) ........................................ 292

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

Hvor ofte er du plaget av søvnløshet? 295

Aldri, eller noen få ganger i året ........................................ 0 2 3 5 1–2 ganger i måneden ........................................ 0 3 2 5

Omreint 1 gang i uka ........................................ 0 3 2 5 Mer enn en gang i uka ........................................ 0 3 2 5

Har du siste år vært plaget av søvnløshet slik at det har gått ut over arbeidsetten? 297

Ja Nei

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

Nesten hver natt ........................................ 0 2 3 5 Av og til ........................................ 0 3 2 5

Ofte ........................................ 0 3 2 5 Aldri ........................................ 3 0 2 5

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

Nesten hver natt ........................................ 0 2 3 5 Av og til ........................................ 0 3 2 5

Ofte ........................................ 0 3 2 5 Aldri ........................................ 3 0 2 5

Har du i løpet av siste måned vært plaget av nervøsitet (irritabel, urolig, anspelet eller rastløs)? 290

Nesten hele tida ........................................ 0 2 3 5 Ofte ........................................ 0 3 2 5

Av og til ........................................ 0 3 2 5 Aldri ........................................ 3 0 2 5

HVORDAN DU HAR HATT DET

Har det noen gang i løpet av ditt liv vært sammenhengende perioder på 2 uker eller mer da du: falt deg deprimert, trist og nedfor ........................................ 3 1 0 2 hadde problemer med matulyset eller spiste alt for lite ........................................ 3 0 2 5 var plaget av kraftløshet eller mangel på overskudd virkelig bebreidet deg selv og følte deg verdslig ... hadde problemer med å konsentrere deg eller vanskelig for å ta beslutninger ........................................ 3 0 2 5 hadde minst tre av de problemerne som er nevnt ovenfor samtidig ........................................ 3 0 2 5

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

Jeg har en positiv holdning til meg selv ........................................ 3 0 2 5

Jeg føler meg virkelig ubrukkelig til tider ........................................ 3 0 2 5

Jeg føler at jeg ikke har mye å være stolt av ........................................ 3 0 2 5

Jeg føler at jeg er en verdifull, i allefall på lik linje med andre ........................................ 3 0 2 5

Synes du at du har funnet et virkelig betydningsfullt innhold i livet ditt? 310

Ja Nei

Føler du at du lever fullt ut ........................................ 3 0 2 5

HVORDAN DU FØLER DEG NA

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 ........................................ 0 3 2 5

Nedstemt ........................................ 0 3 2 5

Nokså nedstemt ........................................ 3 0 2 5

Både – og ........................................ 0 3 2 5

Nokså glad ........................................ 3 0 2 5

Glad ........................................ 0 3 2 5

Svært glad ........................................ 3 0 2 5

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

Nesten hele tida ........................................ 0 3 2 5

Ofte ........................................ 0 3 2 5

Av og til ........................................ 0 3 2 5

Aldri ........................................ 3 0 2 5

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

Meget sterk og opplagt ........................................ 0 3 2 5

Sterk og opplagt ........................................ 0 3 2 5

Ganske sterk og opplagt ........................................ 3 0 2 5

Både – og ........................................ 0 3 2 5

Ganske trøtt og sliten ........................................ 3 0 2 5

Trøtt og sliten ........................................ 3 0 2 5

Svært trøtt og sliten ........................................ 3 0 2 5

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

Hjertelig takk for hjelpa!
APPENDIX V:

HUSK

QUESTIONNAIRE 1
1. EGEN HELESE

<table>
<thead>
<tr>
<th>Symptomer</th>
<th>Ja</th>
<th>Nei</th>
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<tr>
<td>Anvikkelser</td>
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Med vennlig hilsen
1.5. helseundersøkelsen i Hordaland

2. Hvor må deg de fleste antall hitta skjøvet (ned, klingende, sår og sprukken hud):

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<thead>
<tr>
<th>Symptomer</th>
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<tbody>
<tr>
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<td>Andre steder på kroppen</td>
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Med trenting sees mer på plager i form av at en eller flere fingre blir hvite og at man samtidig mister følelser i de små boksene setter du kryss for det svaret som passer best for deg.

3. SYKDOM I FAMILIEN

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4. MUSKEL- OG SKÆLETTPLAGER

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5. MOSJON

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6. KAFFEE / TE / ALKOHOL

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7. RØYKING

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8. ENDRING AV HELSEVANTER

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9. UTDANNING

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10. HELSE OG TRIVSEL

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11. EKSTRA AVSPANNING

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1. EGEN SELJE

Evaluering av fylte 60

NEIJA Antall mnd.

Alder i Bokstaver: 

Har plagene redusert din arbeidsevne det siste i de store boksene skriver du tall eller blokkbokstaver

NEIJA Antall sigaretter 3 og mer 

i de små boksene setter du kryss for det svaret som passer best for deg

• Eksempler:

3. SYKDOM I FAMILIEN

1. EGEN HELSE 4. MUSKEL- OG SKJELETTPLAGER

ø Har du de siste to ukene føtt hjerteinfarkt (som f.eks. "hvite fingre")?

ø Angina pectoris (hjertekrampe)?

ø Hvordan har din fysiske aktivitet i fritiden vært de siste 4 ukene?

ø Hvor lenge er du vanligvis daglig

ø Hvordan er helset i familien?

ø Hvordan har du fylte 60

ø Diabetes (ukjent)?

ø Hvis NEI, gis alt av tekst 5. 

ø Hvis JA, svar på følgende:

ø Hvis under 1

ø Meder

ø Amer

ø Diabetes

ø Blodtrykk

ø Angina pectoris

ø Hard fysisk aktivitet

ø Litt aktivitet

ø Aldri

ø Nei

ø Ja

ø Litt

ø Nei

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11. BRUK AV MEDISINER
Medisiner mens vi har alle slags mediciner: både
• med og uten resept, naturmedisin, vitaminer og mineraler
• medisiner som sykdom, alvorlige sykdommer, sterkefjer, salver, kremmer eller slipper.

Tikk du noen slags medicin i GÅR?.................

Hele tiden: .............................................
Nesten hele tiden: ...................................
Mye av tiden: ........................................ En del av tiden: ........................................ Litt av tiden: ........................................ Ikke i det hele talt: .....................................

Hvor ofte har du hatt overskudd? Sett siste svangerskap...

Møtt flere ganger av søkte medisiner...

12. ARBEID
Besvar av dem som har hatt inntektsgivende arbeid i minst 120 timer det siste året.
Beskriv virksomheten på det arbeidet der du utførte innenfølgende arbeid i lengst til de siste 12 mod. (Oblige f.eks. jordbruk, barneverd, sykehus, anektesykepleier, anerkjener e.l.).

13. SAMLIV
Oppgi antall egne barn (eventuelt f) av hvert kjønn:

Antall gutter: ........................................ Antall jenter: ........................................

Har du noen gang hatt regelmessig samleie uten prevensjon i sitt år eller mer uten at det døde først til graviditet?

Noen gang:         Velkommen til undersøkelsen

Oppgi antall mener det tok med regelmessig samleie uten prevensjon eller ett, om lag er av anektesykepleier og andre oppgave.

14. ETTERUNDESDERKELSE
Hvis denne helsetilrådelsen viser at du bør undersøkes nærmere, vil denne helsetilrådelsen vise at du bør undersøkes nærmere.
APPENDIX VI:

HUSK

QUESTIONNAIRE 2
FOR THE
HOMOCYSTEINE
COHORT
## TRIVSEL OG HELSE

Hvor kommer noen spennemå om hvordan du føler deg.

Jeg føler meg nervøs og urolig
- Mesteparten av tiden
- I et par til en annen
- Bare sjelden
- Ikke i det hele tatt

Jeg føler meg fortsatt i bevegelse, sjelden jeg står stille
- Avgjort ofte
- Fra tid til annen
- Uten tvil
- Ikke sår derimot

Jeg har en utrolig, som om noe farlig vil skje
- Ja, og noe svært lite
- Litt, bekymringer meg ikke
- Ikke i det hele tatt

Jeg kan le og se det morsomme i situasjoner
- Avgjort
- Fra tid til annen
- Ofte
- Ikke sår

Jeg har en urolig følelse av panikk
- Avgjort mindre enn før
- Nokre ganger
- Veldig ofte
- Ikke i det hele tatt

Jeg er rastløs
- Avgjort
- Fra tid til annen
- Ofte
- Ikke i det hele tatt

Jeg kan sitte i fred og ro og kjenne meg avslappet
- Avgjort
- Fra tid til annen
- Ofte
- Ikke i det hele tatt

Jeg har hodet fullt av bekymringer
- Avgjort
- Fra tid til annen
- Ofte
- Ikke i det hele tatt

Jeg har en urofullt værende tanke, som beskriver dine følelser
- Avgjort
- Fra tid til annen
- Ofte
- Ikke i det hele tatt

Svare口号 for hvert avsnitt.

## INNTEKT

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

<table>
<thead>
<tr>
<th>Prisområde</th>
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<tr>
<td>Ikke sår</td>
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## SINNSSTEMMING


Sætt ett kryss for hver avsnitt.

Jeg er vant til folkes påvirkning:  
- Avgjort
- Fra tid til annen
- Ofte
- Ikke i det hele tatt

Jeg er i god humør:  
- Avgjort
- Fra tid til annen
- Ofte
- Ikke i det hele tatt

Jeg er i godt humør:  
- Avgjort
- Fra tid til annen
- Ofte
- Ikke i det hele tatt

Jeg er glad for å jobbe:  
- Avgjort
- Fra tid til annen
- Ofte
- Ikke i det hele tatt

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- Fra tid til annen
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- Avgjort
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- Ofte
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## SYMPTOMER PÅ HJERTE- OG KARSYKDOM

Hvor er du noen gang siden 1992 hatt store smerten i brytet som varer i mer enn 30 minutter?

Dersom JA, angi år:  
- Avgjort
- Fra tid til annen
- Ofte
- Ikke i det hele tatt

## HELSEUNDERSØKELSEN I HORDALAND 1997-99

Takk for at du har tatt deg tid til å komme til en ny helseundersøkelse i Hordaland. Dere som inviteres til deltakelse i Helseundersøkelsen i Hordaland finner du i HUSK brosjyren og i eget informasjonsskriv.

Alle svar vil bli behandlet strengt fortrolig.

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

<table>
<thead>
<tr>
<th>Prisområde</th>
<th>T</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikke sår</td>
<td>T</td>
<td>T</td>
</tr>
<tr>
<td>Ikke i det hele tatt</td>
<td>T</td>
<td>T</td>
</tr>
</tbody>
</table>

## Vennlig hilsen

Blii du kortlempet når du skynder deg (gjør fort) på flat mark, eller går opp en liten bakke? T

Hvordan NEI, på andre avsikt. Hvis JA, fortsett med de neste spørsmålene.

Blii du kortlempet når du spaserer på flat mark sammen med mennesker på din egen alder? JA NEI

Hender det at du må stoppe for å få igjen pusten mens du spaserer i åttid øg tempo på flat mark? NEI

Får du pustevansker i forbindelse med stoff og påkledning? NA

Har du pustevansker når du ligger stille, f.eks. i sengen? NEI

Bruker du ekstra puter om natten p.g.a. pustevansker? NEI

**ANNEN SYKDOM**

*Har du noen gang haft følgende sykdommer?*** T

**Sekruefor Øverfor av spørsmålstegn**

**Hvis ja, vil du angi årene de oppstod.**

**Hvis ne, vil du fortsette med de neste spørsmålene.**

- Hjerneslag/Hjernedrypp
- Blodpropp i legg/lunge
- Blodpropp i hjerte
- Blodpropp i øyeblikk
- Skade som følge av ryggeavlapp

- Ja
- Nei

**HJERTE- OG KARSYKDOM SIDEN 1992**

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

**Hvis ja, vil du angi årene.**

**Hvis ne, vil du fortsette med de neste spørsmålene.**

**Hvis NEI, fortsett med de neste spørsmålene.**

**Hvis JA, fortsett med de neste spørsmålene.**

- Blodpropp i legg/lunge
- Blodpropp i hjerte
- Blodpropp i øyeblikk
- Skade som følge av ryggeavlapp

- Ja
- Nei

**SKAL BARE BESVARE AV KVINNER**

*Bruker du eller har du brukt:***

**Hvis ne, vil du fortsette med de neste spørsmålene.**

**Hvis ja, vil du fortsette med de neste spørsmålene.**

**Hvis NEI, fortsett med de neste spørsmålene.**

- P-pille (også mepipil)
- Hormonpare
- Dødegrind (fattige eller plastater)
- Dødegrind (revrav eller slippgrind)
- Skade som følge av ryggeavlapp

- Ja
- Nei

**SENKEN DEPRESJON**

*Hvordan synes du at du sover totalt sett?***

**Hvis ja, vil du fortsette med de neste spørsmålene.**

**Hvis ne, vil du fortsette med de neste spørsmålene.**

**Hvis NEI, fortsett med de neste spørsmålene.**

- Veldig bra
- Praktisk
- Anntakelig

- Ja
- NEI

**KONTAKT MED ANDRE MENSSEKSER**

*Hvor ofte tar du del i foreningsvirksomhet som f.eks. idrettslag, arbeid eller i fritiden?***

**Hvis ja, vil du fortsette med de neste spørsmålene.**

**Hvis ne, vil du fortsette med de neste spørsmålene.**

**Hvis NEI, fortsett med de neste spørsmålene.**

**Hvis JA, fortsett med de neste spørsmålene.**

- Over 1 gang i uken
- I blant
- I liten grad

- Ja
- NEI

**SØVN**

*Har du mørket felles sysner stile 3 måneder?***

**Hvis ja, vil du fortsette med de neste spørsmålene.**

**Hvis ne, vil du fortsette med de neste spørsmålene.**

**Hvis NEI, fortsett med de neste spørsmålene.**

**Hvis JA, fortsett med de neste spørsmålene.**

**Når slappers du?**

- I morgenen
- Fra midnatt
- I nattens ende

- Ja
- NEI

**SMOKING**

*Smoking (farge andre)***

**Hvis ja, vil du fortsette med de neste spørsmålene.**

**Hvis ne, vil du fortsette med de neste spørsmålene.**

**Hvis NEI, fortsett med de neste spørsmålene.**

**Hvis JA, fortsett med de neste spørsmålene.**

- Ja
- NEI

**GÅR» KONTAKT MED ANDRE MENSSEKSER**

*Hvor ofte tar du del i foreningsvirksomhet som f.eks. idrettslag, arbeid eller i fritiden?***

**Hvis ja, vil du fortsette med de neste spørsmålene.**

**Hvis ne, vil du fortsette med de neste spørsmålene.**

**Hvis NEI, fortsett med de neste spørsmålene.**

**Hvis JA, fortsett med de neste spørsmålene.**

- I morgenen
- Fra midnatt
- I nattens ende

- Ja
- NEI

**SØVN**

*Har du mørket felles sysner stile 3 måneder?***

**Hvis ja, vil du fortsette med de neste spørsmålene.**

**Hvis ne, vil du fortsette med de neste spørsmålene.**

**Hvis NEI, fortsett med de neste spørsmålene.**

**Hvis JA, fortsett med de neste spørsmålene.**

**Når slappers du?**

- I morgenen
- Fra midnatt
- I nattens ende

- Ja
- NEI

**SMOKING**

*Smoking (farge andre)***

**Hvis ja, vil du fortsette med de neste spørsmålene.**

**Hvis ne, vil du fortsette med de neste spørsmålene.**

**Hvis NEI, fortsett med de neste spørsmålene.**

**Hvis JA, fortsett med de neste spørsmålene.**

- Ja
- NEI

**GÅR» KONTAKT MED ANDRE MENSSEKSER**

*Hvor ofte tar du del i foreningsvirksomhet som f.eks. idrettslag, arbeid eller i fritiden?***

**Hvis ja, vil du fortsette med de neste spørsmålene.**

**Hvis ne, vil du fortsette med de neste spørsmålene.**

**Hvis NEI, fortsett med de neste spørsmålene.**

**Hvis JA, fortsett med de neste spørsmålene.**

- I morgenen
- Fra midnatt
- I nattens ende

- Ja
- NEI
**SKAL BARE BESVARE AV KVINNER**

Bruker du eller har du brukt:

- P-pille (også minipille) ...........................................  
- Hormonpille ..........................................................  
- Dihydroprogesteron (tabletter eller plaster) .................  
- Dihydroprogesteron (krem og stkpk) ..........................  
- Skade som førte til sykehusinleggingsuavhengighet .........

**ANNEN SYKDOM**

**Hvor lenge varte disse plagene?**

- Lårheisbludd............................. JA NEI
- Brust ved håndeldsunderarm.............. JA NEI
- Nackesøk (skipskar).......................... JA NEI
- Skade som førte til sykehusinleggingsuavhengighet ........

**HJA ER OG KARSYKDOM SIDEN 1992**

**Hvor du haft hjuemelag, blodspropp, hjertetekt, hjertes ødelægnelse eller kannoner i 1992 eller senere?**

- JA NEI. Hvis NEI, på hvilket nivå?

**Hvilken smerte avhengighet ble de mest uavhengige?**

- Det finnes en viktig person i livet mitt som ønsker å støtte meg, men som ofte rører meg i stedet (ikke i det hele tatt)
- Det finnes mennesker som jeg må være sammen med nesten daglig som ofte bakker på meg (ikke i det hele tatt)
- Det finnes mennesker som jeg ikke trenger det (ikke i det hele tatt)

**SØVN**

**Har du merket følgende besvær stile 3 måneder?**

- Knættelavn ...........................................  
- Utvikkesvake ...........................................  
- Angst ...........................................  

**Gode venner**

- Stemmer helt ...........................................  
- Stemmer ganske bra .................................  
- Stemmer lidt ...........................................  
- Stemmer slett ikke .................................  

**Har du merket følgende besvær stile 3 måneder?**

- Smånet er vanskelig fordi de normale rutene har forandret seg, eller andre foreninger?
- Felder du at du har nok gode venner?

**KONTAKT MED ANDRE MENSER**

- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikke i det hele tatt)
- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikke i det hele tatt)
- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikke i det hele tatt)

**Hva er hjertekrav eller hensyn som ville kunne lave meg penger for en kortere tid?**

- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikke i det hele tatt)

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

- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikke i det hele tatt)
- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikke i det hele tatt)

**Hvis du ikke har noen jeg bryr meg om, kan du snakke med et annet hjertekrav eller hensyn som ville kunne lave meg penger for en kortere tid?**

- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikke i det hele tatt)

**Hva er hjertekrav eller hensyn som ville kunne lave meg penger for en kortere tid?**

- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikke i det hele tatt)

**Hvis du ikke har noen jeg bryr meg om, kan du snakke med et annet hjertekrav eller hensyn som ville kunne lave meg penger for en kortere tid?**

- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikke i det hele tatt)

**Hva er hjertekrav eller hensyn som ville kunne lave meg penger for en kortere tid?**

- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikne i det hele tatt)

**Hvordan synes du at du sover totalt sett?**

- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikke i det hele tatt)

**Hvordan synes du at du sover totalt sett?**

- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikne i det hele tatt)

**Hvordan synes du at du sover totalt sett?**

- Jeg synes at jeg har nok kontakt med mennesker som bryr seg om meg (ikne i det hele tatt)
**TRIVSEL OG HELSE**

Hver kommer noen spørsmål om hvordan du føler deg. For hvert spørsmål setter du kryss for det som passer best for deg. Ikke tenk for lenge - i de små boksene setter du kryss for det svaret som passer best for deg.

Jeg felter meg nervøs og urolig: 
- Ikke i det hele tatt
- Nesten hele tiden
- Sjelden
- Aldri

Jeg føler meg som om jeg har sommerfulgler i magen: 
- Ikke i det hele tatt
- Nesten hele tiden
- Sjelden
- Aldri

Jeg har en urofullende bakrele ondskap, som om alt går langsomme: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg tunge: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg blekk: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg utvikler: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler megrst: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg oppmerksom: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg entusiastisk: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg irritabel: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg oppmerksom: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg overvektig: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg svært oppmerksom: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg overvektig: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg forvirret: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg paralysert: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

Jeg føler meg uværet: 
- Ikke sannsynlig
- Sannsynlig
- Fullt sannsynlig

**SINNSSTEMNING**


Jeg er vanligvis: 
- Bare litt
- Litt
- Fullt
- Alt

**INNTEKT**

Hva er for tiden husholdsholdings årsinntekt (lønn ogrente) før skatt?

<table>
<thead>
<tr>
<th>Kr.</th>
<th>0 – 9.999</th>
<th>10.000 – 19.999</th>
<th>20.000 – 29.999</th>
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<th>450.000 – 499.999</th>
<th>500.000 – 549.999</th>
<th>550.000 – 599.999</th>
</tr>
</thead>
</table>

**HELSEUNDERSØKELSEN I HORDALAND 1997-99**

Takk for at du har tatt deg tid til å komme til en ny helsetilundersøkelse i Hordaland. Dette er sannsynlig det eneste som er gjort i løpet av noen tiår i Hordaland.

**SYMPTOMER PÅ HJERTE- OG KARSKYDOM**

Hvordan føler du deg? 
- Full av energi
- Appr normale
- Låg

**Vennlig hilsen**

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. © 2002 Elsevier Science Inc. All rights reserved.

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 nonpsychiatric 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
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. Spinhowen 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 Spinhowen et al. [8] and Lisspers et al. [9] based on data from the general population both reported a two-factor structure (total $N = 6017$). Spinhowen 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).
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 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Version of HADS</th>
<th>Method of factor analysis</th>
<th>Number of factors</th>
<th>Cronbach’s α</th>
</tr>
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<tbody>
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<td>Swedish</td>
<td>PCA</td>
<td>4</td>
<td>.83 .86</td>
</tr>
<tr>
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<td>English</td>
<td>PCA</td>
<td>2</td>
<td>.85 .81</td>
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<tr>
<td>Brandberg et al. [39]</td>
<td>Swedish</td>
<td>PCA</td>
<td>3</td>
<td>.85 .89</td>
</tr>
<tr>
<td>Costantini et al. [38]</td>
<td>Italian</td>
<td>PCA</td>
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<td>.84 .83</td>
</tr>
<tr>
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<td>English</td>
<td>PCA</td>
<td>2</td>
<td>.84 .83</td>
</tr>
<tr>
<td>Dunbar et al. [11]</td>
<td>English</td>
<td>CFA</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hammerlid et al. [36]</td>
<td>Norwegian Swedish</td>
<td>PCA</td>
<td>2</td>
<td>.89 .82</td>
</tr>
<tr>
<td>Hermann et al. [3]</td>
<td>German</td>
<td>PCAa</td>
<td>2</td>
<td>.80 .81</td>
</tr>
<tr>
<td>Leung et al. [21]</td>
<td>English</td>
<td>PCA</td>
<td>3</td>
<td>.81 .74</td>
</tr>
<tr>
<td>Lewis [29]</td>
<td>English</td>
<td>PCA</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Lispens et al. [9]</td>
<td>Swedish</td>
<td>PCA</td>
<td>2</td>
<td>.84 .82</td>
</tr>
<tr>
<td>Martin and Thompson [40]</td>
<td>English</td>
<td>MLA</td>
<td>4</td>
<td>.82 .78</td>
</tr>
<tr>
<td>Martin and Thompson [30]</td>
<td>English</td>
<td>MLA</td>
<td>3</td>
<td>.76 .72</td>
</tr>
<tr>
<td>Moorey et al. [13]</td>
<td>English</td>
<td>PCA</td>
<td>2</td>
<td>.93 .90</td>
</tr>
<tr>
<td>Razavi et al. [31]</td>
<td>French</td>
<td>PCA</td>
<td>3</td>
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<tr>
<td>Savard et al. [14]</td>
<td>French Canadian</td>
<td>PCA</td>
<td>2</td>
<td>.89 .89</td>
</tr>
<tr>
<td>Sigurdardottir et al. [72]</td>
<td>Swedish</td>
<td>PCA</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Soriano and Salavert [17]</td>
<td>Spanish</td>
<td>PCA</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Spinhoven et al. [8]</td>
<td>Dutch</td>
<td>PCA</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Botega et al. [34]</td>
<td>Portuguese</td>
<td></td>
<td>.68 .67</td>
<td></td>
</tr>
<tr>
<td>el Rufaie et al. [35]</td>
<td>Arabic</td>
<td></td>
<td>.78 .88</td>
<td></td>
</tr>
<tr>
<td>Wettergren et al. [37]</td>
<td>Swedish</td>
<td></td>
<td>.88 .86</td>
<td></td>
</tr>
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</table>

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.*
Table 2
Estimated sensitivity specificity of the HADS at optimal cut-off values

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnostic system</th>
<th>Diagnostic instrument</th>
<th>Diagnosis</th>
<th>Patient population</th>
<th>Optimal cut-off values</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>el-Rufaie et al. [35]</td>
<td>DSM-III</td>
<td>CIS</td>
<td>Anxiety, depression</td>
<td>Primary care</td>
<td>217</td>
<td>9+</td>
<td>0.66</td>
</tr>
<tr>
<td>Lam et al. [43]</td>
<td>DSM-III?</td>
<td>CIS</td>
<td>Anxiety, depression</td>
<td>Primary care</td>
<td>100</td>
<td>3+</td>
<td>0.67</td>
</tr>
<tr>
<td>Wilkinson and Barczak [42]</td>
<td>DSM-III</td>
<td>SCID</td>
<td>Anxiety, depression</td>
<td>General medical</td>
<td>80</td>
<td>9+</td>
<td>0.94</td>
</tr>
<tr>
<td>Botega et al. [34]</td>
<td>DSM-III</td>
<td>DIS</td>
<td>Anxiety, depression</td>
<td>Breast Cancer</td>
<td>197</td>
<td>10+</td>
<td>0.84</td>
</tr>
<tr>
<td>Hall et al. [76]</td>
<td>DSM-III</td>
<td>PSE</td>
<td>Anxiety, depression</td>
<td>Breast cancer</td>
<td>266</td>
<td>7+</td>
<td>0.72</td>
</tr>
<tr>
<td>Hopwood et al. [77]</td>
<td>DSM-III</td>
<td>CIS</td>
<td>Anxiety, depression</td>
<td>Breast cancer</td>
<td>81</td>
<td>11+</td>
<td>0.75</td>
</tr>
<tr>
<td>Ibbotson et al. [78]</td>
<td>DSM-III</td>
<td>DIS</td>
<td>Adjustment disorders + MDD</td>
<td>MDD only cancer</td>
<td>210</td>
<td>11+</td>
<td>0.54</td>
</tr>
<tr>
<td>Johnson et al. [44]</td>
<td>DSM-III</td>
<td>PAS</td>
<td>Anxiety, depression</td>
<td>Poststroke</td>
<td>93</td>
<td>4+</td>
<td>0.95</td>
</tr>
<tr>
<td>Clarke et al. [62]</td>
<td>DSM-III-R</td>
<td>SCID-R</td>
<td>MDD</td>
<td>General hospital</td>
<td>179</td>
<td>10+</td>
<td>0.71</td>
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<tr>
<td>Kugaya et al. [80]</td>
<td>DSM-III-R</td>
<td>SCID</td>
<td>Adjustment disorders + MDD</td>
<td>MDD only cancer</td>
<td>128</td>
<td>8+</td>
<td>0.75</td>
</tr>
<tr>
<td>Razavi et al. [73]</td>
<td>DSM-III-R</td>
<td>DIS</td>
<td>Adjustment disorders, depression, anxiety</td>
<td></td>
<td>117</td>
<td>10+</td>
<td>0.94</td>
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<tr>
<td>Hosaka et al. [85]</td>
<td>DSM-IV</td>
<td>‘Structured interview’</td>
<td>Adjustment disorders + MDD</td>
<td>Cancer</td>
<td>50</td>
<td>12+</td>
<td>0.93</td>
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<tr>
<td>Silverstone [81]</td>
<td>DSM-III-R</td>
<td>SCAN</td>
<td>Modified MDD</td>
<td>General medical</td>
<td>153</td>
<td>8+</td>
<td>0.68</td>
</tr>
<tr>
<td>Silverstone [82]</td>
<td>DSM-IV</td>
<td>SCAN</td>
<td>MDD</td>
<td>General medical</td>
<td>153</td>
<td>8+</td>
<td>0.91</td>
</tr>
<tr>
<td>Berard et al. [83]</td>
<td>DSM-IV</td>
<td>SCID</td>
<td>Adjustment disorders</td>
<td>Cancer</td>
<td>100</td>
<td>8+</td>
<td>0.91</td>
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<tr>
<td>Ramirez et al. [84]</td>
<td>Bedford Criteria</td>
<td>PSE</td>
<td>Anxiety, depression</td>
<td>Breast cancer</td>
<td>91</td>
<td>11+</td>
<td>0.84</td>
</tr>
<tr>
<td>Spinhoven et al. [8]</td>
<td>ICD-8</td>
<td>PSE</td>
<td>Depression</td>
<td>General medical</td>
<td>169</td>
<td>10+</td>
<td>0.54</td>
</tr>
<tr>
<td>Abiodun [41]</td>
<td>ICD-9</td>
<td>PSE</td>
<td>Anxiety, depression</td>
<td>Medical and surgical</td>
<td>275</td>
<td>8+</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gynecological</td>
<td>233</td>
<td>8+</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antenatal</td>
<td>169</td>
<td>10+</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Community</td>
<td>330</td>
<td>8+</td>
<td>0.88</td>
</tr>
</tbody>
</table>

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.

* For example, 8+ means equal to or above 8.
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-D 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

---

**Table 3**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Compared questionnaire</th>
<th>Correlation coefficients between HADS and the other questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck et al. [47]</td>
<td>BDI-PC</td>
<td>.62</td>
</tr>
<tr>
<td>Lisspers et al. [9]</td>
<td>BDI</td>
<td>.64</td>
</tr>
<tr>
<td>Suárez-Mendosa et al. [48]</td>
<td>BDI</td>
<td>.83</td>
</tr>
<tr>
<td>Savard et al. [14]</td>
<td>BDI</td>
<td>.68</td>
</tr>
<tr>
<td>Tedman et al. [49]</td>
<td>BDI</td>
<td>.61</td>
</tr>
<tr>
<td>Watson et al. [50]</td>
<td>BDI</td>
<td>.69</td>
</tr>
<tr>
<td>Lewis and Wessely [60]</td>
<td>GHQ-12</td>
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<tr>
<td>Caplan [18]</td>
<td>GHQ-28</td>
<td>.68</td>
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<tr>
<td>Chardarana et al. [24]</td>
<td>GHQ-28</td>
<td>.50</td>
</tr>
<tr>
<td>Elliot [54]</td>
<td>STAI</td>
<td>.64</td>
</tr>
<tr>
<td>Hermann et al. [20]</td>
<td>STAI</td>
<td>.66</td>
</tr>
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<td>Lisspers et al. [9]</td>
<td>STAI-S</td>
<td>.64</td>
</tr>
<tr>
<td></td>
<td>STAI-T</td>
<td>.66</td>
</tr>
<tr>
<td>Millar et al. [55]</td>
<td>STAI-S</td>
<td>.81</td>
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<tr>
<td>Savard et al. [14]</td>
<td>STAI-S</td>
<td>.78</td>
</tr>
<tr>
<td>Lepine et al. [59]</td>
<td>MADRS</td>
<td>.78</td>
</tr>
<tr>
<td>Snauth and Taylor [52]</td>
<td>MADRS</td>
<td>.37</td>
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<tr>
<td>Upadhyaya and Stanley [53]</td>
<td>MADRS</td>
<td>.37</td>
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<tr>
<td>Aylard et al. [58]</td>
<td>MADRS (item 3)</td>
<td>.37</td>
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<tr>
<td>Snauth and Taylor [52]</td>
<td>CAS</td>
<td>.69</td>
</tr>
<tr>
<td>Upadhyaya and Stanley [53]</td>
<td>CAS</td>
<td>.75</td>
</tr>
<tr>
<td>Spinohon and van der Does [56]</td>
<td>SCL-90, Anxiety, Depression</td>
<td>.49</td>
</tr>
<tr>
<td>Watson et al. [50]</td>
<td>SCL-90, Anxiety, Depression</td>
<td>.73</td>
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<tr>
<td>Lepine et al. [59]</td>
<td>HAMA-S, HAMA-P, HAMA-T</td>
<td>.34</td>
</tr>
<tr>
<td>Millar et al. [55]</td>
<td>VAS</td>
<td>.74</td>
</tr>
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</table>

**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.
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 Zignmond and Snith 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


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;12:49–54.


PAPER II
Submitted to Journal of clinical Epidemiology:

**A dimensional versus a categorical approach to co-occurring anxiety and depression: The HUNT study**

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**Running title:** A dimensional versus a categorical approach to anxiety and depression  
**Key words:** Anxiety, depression, categorical, dimensional, comorbidity, impairment.

**Word count:**  
Main text: 3,098  
Abstract: 198
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 ≥ 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 ≥ 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 ≥ 8, and “pure high-score depression restricted to cases without HADS-A scores ≥ 8. “Comorbid anxiety and depression” was defined by combined HADS-A ≥ 8 and HADS-D ≥ 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 subscales. 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.

Acknowledgements

The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between The HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Verdal, The National Institute of Public Health, The National Health Screening Service of Norway and Nord-Trøndelag County Council. The Norwegian Research Council and Glaxo SmithKline (Norway) supported the present study. H. Lundbeck Ltd (Norway) and Upjohn Ltd. (Norway) gave research grants to the first author. We are very grateful to professor Grethe S. Tell, for her advice in writing up this paper.
References


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).

<table>
<thead>
<tr>
<th>Age</th>
<th>n d  (%)</th>
<th>HADS-A a</th>
<th>HADS-D b</th>
<th>Individuals with impairment c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>n (%)</td>
</tr>
<tr>
<td>20-29</td>
<td>Men 3,909 (41.0)</td>
<td>4.1 (2.9)</td>
<td>2.4 (2.4)</td>
<td>50 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Women 4,713 (54.4)</td>
<td>4.5 (3.2)</td>
<td>2.2 (2.4)</td>
<td>77 (1.6)</td>
</tr>
<tr>
<td>30-39</td>
<td>Men 5,335 (60.5)</td>
<td>4.2 (3.1)</td>
<td>2.9 (2.7)</td>
<td>83 (1.6)</td>
</tr>
<tr>
<td></td>
<td>Women 6,061 (74.1)</td>
<td>4.6 (3.4)</td>
<td>2.7 (2.8)</td>
<td>131 (2.2)</td>
</tr>
<tr>
<td>40-49</td>
<td>Men 6,394 (70.3)</td>
<td>4.2 (3.3)</td>
<td>3.6 (3.0)</td>
<td>165 (2.6)</td>
</tr>
<tr>
<td></td>
<td>Women 6,929 (80.6)</td>
<td>4.6 (3.5)</td>
<td>3.2 (3.0)</td>
<td>205 (3.0)</td>
</tr>
<tr>
<td>50-59</td>
<td>Men 5,251 (74.3)</td>
<td>4.0 (3.2)</td>
<td>4.1 (3.2)</td>
<td>167 (3.2)</td>
</tr>
<tr>
<td></td>
<td>Women 5,553 (82.1)</td>
<td>4.8 (3.6)</td>
<td>3.7 (3.1)</td>
<td>209 (3.8)</td>
</tr>
<tr>
<td>60-69</td>
<td>Men 4,045 (77.6)</td>
<td>3.5 (3.0)</td>
<td>4.1 (3.1)</td>
<td>131 (3.2)</td>
</tr>
<tr>
<td></td>
<td>Women 4,285 (78.7)</td>
<td>4.7 (3.6)</td>
<td>4.1 (3.2)</td>
<td>182 (4.3)</td>
</tr>
<tr>
<td>70-79</td>
<td>Men 3,172 (66.0)</td>
<td>3.3 (3.0)</td>
<td>4.4 (3.3)</td>
<td>86 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Women 3,487 (61.1)</td>
<td>4.3 (3.4)</td>
<td>4.4 (3.3)</td>
<td>97 (2.8)</td>
</tr>
<tr>
<td>80-89</td>
<td>Men 824 (39.7)</td>
<td>3.1 (3.0)</td>
<td>4.9 (3.5)</td>
<td>30 (3.6)</td>
</tr>
<tr>
<td></td>
<td>Women 1,162 (34.8)</td>
<td>4.0 (3.6)</td>
<td>4.7 (3.5)</td>
<td>48 (4.1)</td>
</tr>
<tr>
<td>Total</td>
<td>61,216 (65.0)</td>
<td>4.3 (3.4)</td>
<td>3.5 (3.1)</td>
<td>1676 (2.7)</td>
</tr>
</tbody>
</table>

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.
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. 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.
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

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**Table I. Sample characteristic.**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Men</th>
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<tr>
<td>Gender</td>
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<tr>
<td>20–29 years</td>
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<td>30–39 years</td>
<td>5322</td>
<td>6042</td>
<td>19.5</td>
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<td>40–49 years</td>
<td>6377</td>
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<td>80–89 years</td>
<td>816</td>
<td>1144</td>
<td>6.1</td>
</tr>
<tr>
<td>Impairment</td>
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<td>4586</td>
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<tr>
<td>Myocardial infarction</td>
<td>1333</td>
<td>455</td>
<td>1.5</td>
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<tr>
<td>Stroke</td>
<td>527</td>
<td>492</td>
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<td>Diabetes</td>
<td>827</td>
<td>811</td>
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<tr>
<td>Migraine</td>
<td>861</td>
<td>1173</td>
<td>3.6</td>
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<td>Fibromyalgia</td>
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<td>Low physical activity</td>
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<tr>
<td>Hypertension</td>
<td>5406</td>
<td>4331</td>
<td>13.1</td>
</tr>
<tr>
<td>High BMI</td>
<td>4117</td>
<td>5727</td>
<td>17.5</td>
</tr>
</tbody>
</table>

1 Absolute numbers and statistical tests are based on unweighted data and percentages on weighted data.

---

**Table II. Categories of anxiety and depression by gender.**

<table>
<thead>
<tr>
<th>Categories</th>
<th>HADS-A range</th>
<th>HADS-D range</th>
<th>n</th>
<th>% of men</th>
<th>% of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure depressive disorder (D)</td>
<td>0–7</td>
<td>8–21</td>
<td>2988</td>
<td>5.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Comorbid anxiety-depressive disorder (AD)</td>
<td>8–21</td>
<td>8–21</td>
<td>3610</td>
<td>4.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Pure anxiety disorders (A)</td>
<td>8–21</td>
<td>0–7</td>
<td>5827</td>
<td>7.6</td>
<td>11.6</td>
</tr>
<tr>
<td>Neither anxiety nor depressive disorder</td>
<td>0–7</td>
<td>0–7</td>
<td>48444</td>
<td>82.1</td>
<td>78.0</td>
</tr>
</tbody>
</table>

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.

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.

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Comorbid depression and anxiety disorder</th>
<th>Anxiety disorder</th>
<th>Total(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%(^3)</td>
<td>OR 95% CI</td>
<td>%(^3)</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Impairment(^4)</td>
<td>8.9</td>
<td>1.95 1.78–2.14</td>
<td>12.4</td>
<td>3.05 2.81–3.30</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11.9</td>
<td>1.31 1.11–1.54</td>
<td>8.6</td>
<td>1.50 1.25–1.81</td>
</tr>
<tr>
<td>Stroke</td>
<td>15.7</td>
<td>2.10 1.75–2.52</td>
<td>10.8</td>
<td>1.98 1.60–2.44</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9.2</td>
<td>1.14 0.96–1.37</td>
<td>8.1</td>
<td>1.27 1.06–1.54</td>
</tr>
<tr>
<td>Migraine</td>
<td>4.0</td>
<td>1.38 1.09–1.74</td>
<td>9.6</td>
<td>2.13 1.82–2.49</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>6.2</td>
<td>2.02 1.64–2.49</td>
<td>17.8</td>
<td>4.02 3.50–4.61</td>
</tr>
<tr>
<td>Musculo-skeletal</td>
<td>6.8</td>
<td>1.78 1.64–1.93</td>
<td>10.4</td>
<td>3.11 2.90–3.35</td>
</tr>
<tr>
<td>Cardio-vascular</td>
<td>6.5</td>
<td>1.88 1.73–2.06</td>
<td>12.9</td>
<td>4.27 3.97–4.59</td>
</tr>
<tr>
<td>Smoking</td>
<td>4.3</td>
<td>1.20 1.10–1.31</td>
<td>7.8</td>
<td>1.82 1.69–1.96</td>
</tr>
<tr>
<td>Alcohol problems</td>
<td>4.2</td>
<td>1.46 1.29–1.66</td>
<td>7.1</td>
<td>1.88 1.70–2.08</td>
</tr>
<tr>
<td>Low physical activity</td>
<td>3.9</td>
<td>1.68 1.53–1.84</td>
<td>5.1</td>
<td>1.74 1.59–1.91</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.9</td>
<td>0.93 0.85–1.03</td>
<td>6.3</td>
<td>0.92 0.83–1.01</td>
</tr>
<tr>
<td>High BMI</td>
<td>6.2</td>
<td>1.21 1.10–1.33</td>
<td>7.0</td>
<td>1.18 1.08–1.29</td>
</tr>
</tbody>
</table>

\(^1\) 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).

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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-participation 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 under-represented 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
The Nord-Trøndelag Health Study (HUNT study) is a collaboration between the HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Verdal, the National Institute of Public Health, the National Health Screening Service of Norway, and Nord-Trøndelag County Council. The Norwegian Research Council, Glaxo-SmithKline (Norway) and H. Lundbeck (Norway) supported the study financially.

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PAPER IV
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
Submitted to American Journal of Epidemiology:

**Education as predictor for anxiety and depression -
A population based cohort study.**

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⁴Department of Clinical Cancer Research, The Norwegian Radium Hospital, University of Oslo

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**Key words:** Anxiety, cohort studies, comorbidity, depression, education, mediator,
prospective studies, socioeconomic status

**Word count**
Abstract: 195
Main text: 3,936
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 were 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 ≤ the 80th 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 $\geq 8$ 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 $\geq 8$, and HADS-D $< 8$ in order to avoid comorbidity. Accordingly, depression was defined as HADS-D $\geq 8$, 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, 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 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/m²) was based on data from the clinical examinations and categorized by two cut-offs, ≥25kg/m² and ≥30kg/m², respectively. Health behaviors were dichotomized like this: Physical exercise ≥ weekly practicing; smoking ≥ one cigarette daily; alcohol consumption ≥ 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 situation, 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.

Acknowledgements

The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between The HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Verdal, The Norwegian Institute of Public Health, and Nord-Trøndelag County Council. The Norwegian Research Council and Glaxo SmithKline (Norway) supported the present study. H. Lundbeck Ltd (Norway) and Upjohn Ltd. (Norway) gave research grants to the first author.
### TABLE 1: Characteristics of the incident cohort*. The Nord-Trøndelag Health Study 1984-86 (HUNT 1) and 1995-97 (HUNT 2).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men n=4,411</th>
<th>Women n=4,880</th>
<th>Men n=5,261</th>
<th>Women n=5,396</th>
<th>Men n=4,923</th>
<th>Women n=4,877</th>
<th>Total cohort N=29,748</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary school</td>
<td>649 (14.8)</td>
<td>778 (16.0)</td>
<td>1,706 (32.6)</td>
<td>2,255 (42.3)</td>
<td>2,713 (55.7)</td>
<td>3,534 (74.0)</td>
<td>11,635 (39.5)</td>
</tr>
<tr>
<td>High school</td>
<td>2,860 (65.1)</td>
<td>2,930 (60.4)</td>
<td>3,235 (44.4)</td>
<td>2,119 (39.7)</td>
<td>1,670 (34.3)</td>
<td>959 (20.1)</td>
<td>12,863 (43.7)</td>
</tr>
<tr>
<td>College/university</td>
<td>881 (20.1)</td>
<td>1,141 (23.5)</td>
<td>1,205 (23.0)</td>
<td>963 (18.0)</td>
<td>491 (10.1)</td>
<td>284 (5.9)</td>
<td>4,965 (16.9)</td>
</tr>
<tr>
<td>Anxiety disorder†</td>
<td>316 (7.7)</td>
<td>477 (10.5)</td>
<td>286 (6.1)</td>
<td>463 (9.5)</td>
<td>131 (2.6)</td>
<td>282 (7.1)</td>
<td>1,955 (6.8)</td>
</tr>
<tr>
<td>Depression‡</td>
<td>124 (3.2)</td>
<td>87 (2.1)</td>
<td>298 (6.3)</td>
<td>182 (4.0)</td>
<td>454 (10.2)</td>
<td>286 (7.2)</td>
<td>1,431 (5.1)</td>
</tr>
<tr>
<td>Cardiovascular disease§</td>
<td>140 (3.2)</td>
<td>199 (4.1)</td>
<td>213 (4.1)</td>
<td>207 (3.9)</td>
<td>127 (2.6)</td>
<td>186 (3.9)</td>
<td>1,072 (3.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (0.1)</td>
<td>7 (0.1)</td>
<td>43 (0.8)</td>
<td>15 (0.3)</td>
<td>346 (7.1)</td>
<td>147 (3.1)</td>
<td>563 (1.9)</td>
</tr>
<tr>
<td>BMI** &gt; 25 kg/m²</td>
<td>1,437 (32.7)</td>
<td>926 (19.1)</td>
<td>2,609 (48.8)</td>
<td>1,687 (31.7)</td>
<td>2,889 (59.3)</td>
<td>2,826 (59.3)</td>
<td>12,374 (42.0)</td>
</tr>
<tr>
<td>BMI** &gt; 30 kg/m²</td>
<td>130 (3.0)</td>
<td>189 (3.9)</td>
<td>341 (6.5)</td>
<td>396 (7.4)</td>
<td>432 (9.2)</td>
<td>814 (17.1)</td>
<td>2,302 (7.8)</td>
</tr>
<tr>
<td>Low physical activity§</td>
<td>1,946 (44.4)</td>
<td>1,842 (38.3)</td>
<td>2,171 (41.7)</td>
<td>2,077 (39.2)</td>
<td>2,967 (62.4)</td>
<td>1,485 (32.0)</td>
<td>11,309 (38.8)</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>1,459 (33.4)</td>
<td>2,022 (42.0)</td>
<td>1,725 (33.2)</td>
<td>1,759 (33.4)</td>
<td>1,628 (33.9)</td>
<td>1,005 (21.7)</td>
<td>9,598 (32.0)</td>
</tr>
<tr>
<td>Alcohol drinking†</td>
<td>65 (1.5)</td>
<td>113 (2.4)</td>
<td>159 (3.0)</td>
<td>196 (3.7)</td>
<td>100 (2.1)</td>
<td>93 (2.0)</td>
<td>726 (2.5)</td>
</tr>
<tr>
<td>Living alone</td>
<td>329 (75.5)</td>
<td>217 (4.5)</td>
<td>197 (3.8)</td>
<td>89 (1.7)</td>
<td>279 (5.7)</td>
<td>556 (11.7)</td>
<td>1,667 (57.7)</td>
</tr>
<tr>
<td>Low job control</td>
<td>154 (3.5)</td>
<td>309 (6.4)</td>
<td>418 (8.0)</td>
<td>730 (13.7)</td>
<td>802 (16.6)</td>
<td>1,404 (29.7)</td>
<td>3,817 (130)</td>
</tr>
<tr>
<td>Low social support</td>
<td>65 (1.1)</td>
<td>78 (1.6)</td>
<td>68 (1.3)</td>
<td>72 (1.4)</td>
<td>65 (1.3)</td>
<td>105 (2.2)</td>
<td>436 (1.5)</td>
</tr>
<tr>
<td>Stressful job</td>
<td>2,174 (53.1)</td>
<td>1,859 (44.2)</td>
<td>3,051 (59.9)</td>
<td>2,224 (44.6)</td>
<td>1,892 (47.0)</td>
<td>1,135 (23.5)</td>
<td>12,335 (42.2)</td>
</tr>
<tr>
<td>Low job control</td>
<td>1,504 (34.3)</td>
<td>1,459 (33.4)</td>
<td>1,496 (29.4)</td>
<td>1,787 (35.8)</td>
<td>1,078 (26.7)</td>
<td>1,001 (21.7)</td>
<td>8,325 (31.8)</td>
</tr>
<tr>
<td>Unemployment</td>
<td>114 (2.7)</td>
<td>65 (1.4)</td>
<td>107 (2.1)</td>
<td>69 (1.3)</td>
<td>81 (1.9)</td>
<td>39 (0.9)</td>
<td>475 (1.7)</td>
</tr>
</tbody>
</table>

* 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 ≥ 8; Depression subscale (HADS-D) < 8
‡ HADS-D ≥ 8; HADS-A < 8
§ HADS-A ≥ 8; HADS-D ≥ 8
# Self-report of present or previous angina pectoris, heart infarction or stroke
** Body Mass Index
†† Self-report of ≥ 10 days of alcohol use during the last two weeks
<table>
<thead>
<tr>
<th>Variables</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>N=6,687</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-34 years</td>
<td>35-49 years</td>
<td>50-69 years</td>
<td>Total cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>128 (22.7)</td>
<td>166 (19.6)</td>
<td>338 (35.0)</td>
<td>697 (48.5)</td>
<td>624 (48.5)</td>
<td>1,439 (78.0)</td>
<td>3,392 (50.7)</td>
</tr>
<tr>
<td>High school</td>
<td>327 (57.9)</td>
<td>524 (61.9)</td>
<td>419 (43.3)</td>
<td>533 (37.1)</td>
<td>324 (31.5)</td>
<td>320 (17.4)</td>
<td>2,447 (36.6)</td>
</tr>
<tr>
<td>College/university</td>
<td>110 (19.5)</td>
<td>156 (18.4)</td>
<td>210 (21.7)</td>
<td>207 (14.4)</td>
<td>80 (7.8)</td>
<td>85 (4.6)</td>
<td>2,599 (37.2)</td>
</tr>
<tr>
<td>Anxiety disorder†</td>
<td>112 (19.8)</td>
<td>215 (31.8)</td>
<td>142 (13.1)</td>
<td>333 (23.2)</td>
<td>105 (15.2)</td>
<td>184 (10.6)</td>
<td>649 (16.0)</td>
</tr>
<tr>
<td>Depression‡</td>
<td>44 (7.8)</td>
<td>36 (7.2)</td>
<td>129 (13.3)</td>
<td>94 (11.9)</td>
<td>162 (22.7)</td>
<td>184 (10.6)</td>
<td>649 (16.0)</td>
</tr>
<tr>
<td>Comorbid disorder§</td>
<td>4 (0.7)</td>
<td>1 (0.1)</td>
<td>16 (1.7)</td>
<td>17 (1.2)</td>
<td>125 (12.3)</td>
<td>145 (7.9)</td>
<td>307 (4.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (0.4)</td>
<td>1 (0.1)</td>
<td>9 (0.9)</td>
<td>8 (0.6)</td>
<td>25 (2.4)</td>
<td>35 (1.9)</td>
<td>50 (0.8)</td>
</tr>
<tr>
<td>Impaired due to somatic disease</td>
<td>45 (9.6)</td>
<td>38 (5.2)</td>
<td>103 (13.4)</td>
<td>155 (13.7)</td>
<td>248 (19.4)</td>
<td>390 (29.1)</td>
<td>972 (19.0)</td>
</tr>
<tr>
<td>Use of analgesics</td>
<td>48 (8.7)</td>
<td>123 (14.9)</td>
<td>108 (11.5)</td>
<td>304 (22.2)</td>
<td>307 (26.4)</td>
<td>1,215 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Visit to a physician, last year</td>
<td>449 (79.5)</td>
<td>765 (90.4)</td>
<td>779 (80.6)</td>
<td>1,232 (85.7)</td>
<td>847 (88.8)</td>
<td>1,637 (88.8)</td>
<td>5,709 (85.4)</td>
</tr>
<tr>
<td>Hospital admission, last five years</td>
<td>149 (26.5)</td>
<td>494 (58.5)</td>
<td>291 (30.1)</td>
<td>711 (49.6)</td>
<td>428 (41.6)</td>
<td>753 (41.1)</td>
<td>2,826 (42.4)</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>117 (20.9)</td>
<td>155 (18.5)</td>
<td>208 (21.7)</td>
<td>324 (22.9)</td>
<td>249 (24.6)</td>
<td>672 (37.6)</td>
<td>1,725 (26.3)</td>
</tr>
<tr>
<td>BMI**&gt; 25 kg/m²</td>
<td>173 (30.6)</td>
<td>172 (20.4)</td>
<td>452 (46.8)</td>
<td>483 (33.7)</td>
<td>604 (58.8)</td>
<td>1,039 (66.5)</td>
<td>2,923 (43.8)</td>
</tr>
<tr>
<td>Low physical activity</td>
<td>28 (5.0)</td>
<td>37 (4.4)</td>
<td>77 (8.0)</td>
<td>130 (9.0)</td>
<td>107 (10.4)</td>
<td>326 (17.7)</td>
<td>705 (10.6)</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>252 (44.8)</td>
<td>475 (56.5)</td>
<td>429 (44.7)</td>
<td>622 (44.0)</td>
<td>401 (40.0)</td>
<td>533 (29.9)</td>
<td>2,712 (41.3)</td>
</tr>
<tr>
<td>High alcohol consumption††</td>
<td>22 (3.9)</td>
<td>23 (2.7)</td>
<td>48 (5.0)</td>
<td>30 (2.1)</td>
<td>63 (6.3)</td>
<td>39 (2.2)</td>
<td>225 (3.4)</td>
</tr>
<tr>
<td>Separated or divorced</td>
<td>20 (3.5)</td>
<td>43 (7.0)</td>
<td>60 (6.2)</td>
<td>121 (8.4)</td>
<td>44 (4.3)</td>
<td>73 (4.0)</td>
<td>361 (5.4)</td>
</tr>
<tr>
<td>Living alone</td>
<td>74 (13.2)</td>
<td>57 (7.0)</td>
<td>68 (7.1)</td>
<td>51 (3.7)</td>
<td>123 (12.0)</td>
<td>311 (16.9)</td>
<td>684 (10.4)</td>
</tr>
<tr>
<td>Lack of social support</td>
<td>67 (11.9)</td>
<td>176 (20.8)</td>
<td>199 (20.7)</td>
<td>489 (34.2)</td>
<td>293 (28.9)</td>
<td>866 (47.6)</td>
<td>2,090 (31.5)</td>
</tr>
<tr>
<td>Loneliness</td>
<td>126 (22.3)</td>
<td>222 (26.2)</td>
<td>170 (17.7)</td>
<td>315 (22.0)</td>
<td>171 (16.8)</td>
<td>448 (24.5)</td>
<td>1,452 (21.8)</td>
</tr>
<tr>
<td>Stressful job</td>
<td>342 (70.4)</td>
<td>443 (61.4)</td>
<td>686 (78.5)</td>
<td>718 (59.7)</td>
<td>542 (46.2)</td>
<td>480 (45.5)</td>
<td>3,121 (46.6)</td>
</tr>
<tr>
<td>Low job control</td>
<td>265 (46.9)</td>
<td>296 (40.9)</td>
<td>348 (39.8)</td>
<td>514 (42.7)</td>
<td>270 (39.5)</td>
<td>369 (32.8)</td>
<td>2,062 (30.4)</td>
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<tr>
<td>Job dissatisfaction</td>
<td>85 (16.6)</td>
<td>86 (10.9)</td>
<td>148 (16.3)</td>
<td>127 (9.3)</td>
<td>128 (16.9)</td>
<td>148 (10.4)</td>
<td>722 (12.6)</td>
</tr>
<tr>
<td>Unemployment</td>
<td>9 (1.7)</td>
<td>76 (9.7)</td>
<td>8 (0.8)</td>
<td>167 (12.8)</td>
<td>27 (2.8)</td>
<td>55 (25.7)</td>
<td>642 (10.8)</td>
</tr>
</tbody>
</table>

* 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 ≥8, Depression subscale (HADS-D) <8
‡ HADS-D ≥8, HADS-A <8
§ HADS-A ≥8, HADS-D ≥8
# Self-report of present or previous angina pectoris, heart infarction or stroke
** Body Mass Index
†† Self-report of ≥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).

<table>
<thead>
<tr>
<th>Cases</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
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<tr>
<td>INCIDENT COHORT§ (N=29,748)</td>
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<tr>
<td>Anxiety disorder¤</td>
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<tr>
<td>College / University</td>
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<tr>
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<tr>
<td>Test for trend</td>
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<td>**</td>
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<tr>
<td>Depression† †</td>
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<tr>
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<tr>
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<td>536</td>
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<tr>
<td>Primary school</td>
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<td>**</td>
</tr>
<tr>
<td>Comorbid disorder‡‡</td>
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<tr>
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<tr>
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<td>**</td>
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<td>PERSISTENT COHORT§§ (N=6,687)</td>
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<td>Primary school</td>
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<tr>
<td>Test for trend</td>
<td>*</td>
<td>*</td>
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<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
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<tr>
<td>Comorbid disorder</td>
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<tr>
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</tr>
</tbody>
</table>

* 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>8‡‡‡, HADS-D§§§ <8.
†† HADS-D>8, HADS-A <8.
‡‡ HADS-A>8, HADS-D >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 ≤ 80th percentile at baseline; Persistence cohort, Individuals with Anxiety Depression Index-12 >80th percentile at baseline; Anxiety disorder, the Hospital Anxiety and Depression Scale, Anxiety subscale (HADS-A) score ≥8, Depression subscale (HADS-D) <8; Depression, HADS-D≥8 and HADS-A <8; Comorbid, HADS-A≥8, HADS-D ≥8.
References


