Anxiety, Depression, and Cause-Specific Mortality: The HUNT Study

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Objective: To investigate empirically the association between anxiety/depression and cause-specific mortality with particular attention to the underlying mechanisms and causes of death. Depression reportedly increases general mortality. For cause-specific mortality, there is evidence depression has an effect on cardiovascular disease (CVD) mortality and suicide. Less information is known as to other mortality diagnoses. There is scarce and conflicting literature on anxiety in relation to mortality. **Methods:** Employing a historical cohort design, we used a link between an epidemiological cohort study and a comprehensive national mortality database. We gathered baseline information on physical and mental health (Hospital Anxiety and Depression Scale, HADS) from the population-based health study (n = 61,349). Causes of death were registered with International Classification of Diagnoses, 10th edition (ICD-10) during mean follow-up of 4.4 years. **Results:** Case-level depression increased the mortality rate for all major disease-related causes of death, whereas case-level anxiety and comorbid anxiety/depression did not. The effect of depression was similar for cardiac mortality compared with all other causes combined, and confounding effects were also very similar. Symptom load of anxiety was associated negatively with both CVD and other cause mortality in fully adjusted models. Accidents and suicide were associated primarily with comorbid anxiety/depression. **Conclusions:** Depression is a risk factor for all major disease-related causes of death; it is not limited to CVD mortality or suicide. Because the association between depression and cardiac mortality was comparable to the other causes of death combined and confounding and mediating factors were markedly similar, future investigation as to the mechanisms underlying the effect of depression on mortality should not be limited to CVD mortality. **Key words:** anxiety, depression, cause-specific mortality, mortality, suicide, HUNT.

BMI = body mass index; **CAGE** = screening instrument for alcohol problems; **CVD** = cardiovascular disease; **HADS** = Hospital Anxiety and Depression Scale (A or D for subscales); **ICD-8/9/10** = International Classification of Diagnoses, 8th/9th/10th edition; **OR** = odds ratio; **HUNT** = Health Study of Nord-Trøndelag County, Norway.

INTRODUCTION

There is broad evidence that depression is associated with increased overall mortality (1–6) and specifically with cardiovascular disease (CVD) mortality (7–16). In addition to cardiovascular mortality, depression is associated with unnatural deaths (17,18) and suicide (19). The evidence is less strong or consistent for other causes of death (17).

Most of the literature on depression and mortality focuses on links with CVD mortality and the variety of causal mechanisms that may underlie this association (10). This literature generates an impression that depression is a risk factor specific to CVD mortality. However, to the best of our knowledge, no study has sought to compare this particular association for other causes of death.

An important issue is the uncertainty concerning the underlying mechanisms, both relating to lifestyle and biological changes occurring in depression. Various lifestyle factors may be responsible for this association, such as smoking, adverse alcohol consumption, and low physical activity (6,17,19), obesity, hypertension, and dyslipidemia. Furthermore, in people with established physical disorders, depression may increase mortality by influencing help-seeking behavior and/or treatment nonadherence (6,10). Most proposed mechanisms regarding biological changes occurring in depression relate to cardiovascular morbidity; however, there is also no commonly accepted model that describes the underlying mechanisms (8,10). These mechanisms may include increased platelet aggregation, inflammatory processes, lower heart rate variability (reflecting alerted cardiac autonomic tone), and antidepressant cardiotoxicity (10). Depressive disorders have also been found to affect adversely the endocrine and immunological processes, increasing the risk of physical morbidity beyond CVD (6,20). Other pathways linking depression and mortality are suicide (17) and hazardous behavior leading to accidents (6), but these pathways are relatively rare contributors to total mortality. Reactive depression deriving from physical impairment (13) and chronic physical illness (17) offer possible explanations but they should be seen as confounders rather than mechanisms.

Comorbidity between anxiety and depression is strong (21), and the association between comorbid anxiety depression is commonly reported to be more strongly associated with physical morbidity than anxiety or depression alone (22). The literature on the associations between anxiety mortality is scarce and conflicting with reports of both positive (23,24) and negative (25) effects.

Applying a unique record linkage between a large health survey of the general population and the national mortality registry, we aim in this study to address these issues concerning cause-specific mortality in relation to anxiety and depression. Specific objectives were a) to compare the effect of anxiety/depression on mortality across causes of death and b) to compare confounding and mediating factors in these associations between CVD and other causes of mortality.

METHODS

Study Design

Baseline data were obtained from the Health Study of Nord-Trøndelag County (HUNT-2). The county is one of 19 counties in Norway, comprising 3% of the national population. The HUNT-2 study was carried out from

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August 15, 1995 until June 18, 1997. The mortality data were obtained from the National Mortality Registry up until January 1, 2001 by combining the mortality database and the health survey using the national 11-digit personal identity number employed in Norway for health and public affairs purposes, for example. The mean follow-up period was 4.4 (SD = 0.68) years. Information on individuals who emigrated from Norway during the follow-up was not available and was the only source of drop-out.

Based on updated population register lists, all inhabitants (n = 93,138) in Nord-Trøndelag County aged ≥20 years received mailed questionnaires and invitations to participate in a clinical examination. A total of 65,648 (71%) persons participated in parts of the study, and 61,349 (66%) individuals reported valid responses to the variables relevant for this study.

The population of Nord-Trøndelag County is relatively stable with a net migration of 0.3% per year (1996–2000) and is also homogeneous with <3% non-Caucasians. Nineteen percent of the county population holds a university degree versus 24% in Norway. The life expectancy for newborns in the county is 76.5 years, one year higher than for Norway in general.

Exposure: Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a self-report questionnaire comprising 14 four-point Likert-scaled items: 7 points for anxiety (HADS-A) and 7 points for depression (HADS-D) for the past week. No somatic items or items regarding sleeping difficulties are included. The depression subscale covers cognitive features in depression as well as aspects of anhedonia; the items on anxiety covers mainly generalized anxiety and panic attacks (26,27). In accordance with the findings on anxiety disorders and depression in the National Comorbidity Survey (21), we found a 30% shared variance between HADS-A and HADS-D (26). According to a recent literature review covering 31 studies, HADS has shown good case-finding properties for anxiety and depression in inpatient populations in primary care and hospital settings (27). A cut-off score of 8 on both subscales was found to give an optimal balance between sensitivity and specificity, both at about 0.80, for depression and anxiety according to Diagnostic and Statistical Manual of Mental Disorders (third revised version/fourth version) and International Classification of Diagnoses, 8th/10th edition (ICD-8 and 9). By using these cut-off scores, we identified four groups as case-level anxiety only (labeled "anxiety"), case-level depression only (labeled "depression"), and case-level comorbid anxiety and depression (labeled "both" or "comorbid anxiety/depression")—all being compared with a reference group (no disorder) (28). In additional analyses, continuous scores scaled so that 1 unit represents the distance between the 25th and the 75th percentiles were included.

End Point: Mortality

Mortality with diagnosis was obtained from the National Mortality Registry. Mortality diagnoses are encoded according to ICD-10 (codes indicated in parentheses) and were categorized into diseases as follows: CVD (I), cancer (C,D), respiratory diseases (J), other diseases (A, B, M, N, Q), diseases relating to the nervous system (G, R54), gastrointestinal diseases (K), metabolic diseases (E), and mental disorders (F). The category for accidents (V01–X59) comprised also murder (Y04) (n = 1) and external causes with unclear intentionality (Y10–Y34 and Y87) (n = 3). Suicide (X60–X84, X87), sudden death of unknown cause (R96), and mortality without medical certificates determining the cause of death (R99) were included as three separate categories.

Mediators and Confounders

Potential mediating and confounding factors were operationalized in accordance with a recent publication based on the HUNT-2 study predicting disability from anxiety and depression (29), and selected a priori. The study is not designed to test formally hypotheses of mediation. To the extent that truly mediating factors are confused to be confounders, we are overadjusting our model, thereby resulting in underestimation of the true effects of anxiety and depression on mortality.

Information on age and gender was obtained from the national population registry, and age was encoded in decades with the group 20 to 29 as reference category.

Physical health was assessed by somatic diagnoses and somatic symptoms, all based on self-report. A sum of somatic diagnoses comprising angina pectoris, asthma, cancer, diabetes, epilepsy, hypotension, infarction, musculoskeletal diseases, respiratory disease, stroke, and thyroidal diseases was computed; each diagnosis was weighted for associated mortality. Weights were based on unstandardized regression coefficients obtained from a logistic regression model including all diagnoses associated with mortality as well as age and gender. Diagnoses negatively associated with mortality (hypothyroid disease, goiter, fibromyalgia, osteoarthritis, and ankylosing spondylitis) were excluded from the index. The index for somatic diagnoses was encoded as a continuous variable in the regression models.

Accordingly, an index for somatic symptoms was computed as the number of organ systems from which symptoms were reported, comprising gastrointestinal symptoms (four questions on nausea, heartburn, diarrhea, and constipation), sensation (two questions on hearing and sight), cardiovascular symptoms (one question on palpitations), and respiratory symptoms (one question on respiratory problems). As for somatic diagnoses, somatic symptoms were weighted for their association with mortality before they were summed up as an index for somatic symptoms. Musculoskeletal symptoms (pain in neck, shoulders, elbow, hands, breast, back (three areas), hips, knees, and ankles) and headaches (two questions on headache and migraine) were adjusted for age, gender, and other somatic symptoms; they were negatively associated with mortality; and consequently, they were not included in the weighting procedure nor in the index.

Self-evaluated physical impairment was computed as an index ranging from 0 to 4, indicating the number of moderate or severe impairments due to somatic disease, musculoskeletal complaint, hearing, and sight.

Three variables concerning health-related behavior were also included. 1) Current smoking was encoded in the categories current, former, and never, in addition to pack years of smoking. 2) Physical activity was encoded according to frequency into three levels from low to high. 3) Problems with alcohol were estimated using CAGE (a screening instrument for alcohol problems) questionnaire scores as a categorical measure ranging from 0 to 3 points. The two latter variables were obtained from a second questionnaire with about 20% lower response rate; the missing responses were encoded as a separate category.

Educational level was encoded according to the highest completed educational level on a 3-point ordinal scale from compulsory school only to university level (28). An index for socioeconomic status according to the Erikson Goldthorpe Portocareros was computed (30) and was condensed from 7 to 4 categories with minimal loss of variance.

A trained nurse obtained measurements of body mass index (BMI), blood pressure, and total cholesterol level during the screening. All these variables were encoded in quartiles.

Statistics

Logistic and Cox regression analyses were used to investigate the associations between anxiety, depression, and mortality and to examine confounding and mediating factors. All associations reported were statistically significant ($p < .05$) using two-tailed tests, except otherwise stated.

The association between anxiety/depression and mortality was not moderated by time elapsed between screening (dichotomy for median time) and mortality ($\chi^2 = 1.33$, $df = 3$, $p = .721$). This and other analyses indicated that the proportional hazards assumption was not violated.

All models were adjusted for age as a categorical variable encoded in decades and gender, and all confounding or mediating variables were entered as continuous variables where appropriate. Results are presented as odds ratios (OR) with 95% confidence intervals. All analyses were performed using SPSS version 12.

First, effects of case-level anxiety, depression, and comorbid anxiety/depression were investigated in relation to CVD mortality and then in relation to all other causes of death combined (Table 1). The analyses were then repeated using continuous scale scores for anxiety and depression (Table 2). Effects were reported with adjustment for age and gender, then with separate adjustment for mediating and confounding factors in addition to a fully adjusted model. Second, case-level anxiety and depression in relation to multiple mortality diagnoses were examined with adjustment for age and

TABLE 1. CVD Mortality and Mortality From All Other Causes as a Function of Case-Level Anxiety and Depression With Adjustment for Potential Confounding and Mediating Factors (Odds Ratios)

Adjustments	CVD Mortality (n = 1069 deaths among 60,109 included)			Mortality From All Other Causes (n = 1240 deaths among 60,280 included)		
	Case-Level Anxiety (n = 5769)	Case-Level Depression (n = 2866)	Comorbid Anxiety/ Depression (n = 3523)	Case-Level Anxiety (n = 5797)	Case-Level Depression (n = 2867)	Comorbid Anxiety/ Depression (n = 3567)
Age and gender	1.10	1.67*	1.16	1.25*	1.66*	1.64*
95% CI	0.84–1.43	1.38–2.01	0.90–1.50	1.00–1.56	1.39–1.99	1.34–2.02
Further adjustment entered separately[a]						
Somatic symptoms/diagnoses	0.93	1.52*	0.97	1.10	1.53*	1.38*
95% CI	0.71–1.22	1.26–1.83	0.75–1.26	0.87–1.38	1.28–1.84	1.12–1.71
Physical impairment	1.00	1.52*	1.01	1.14	1.52*	1.43*
95% CI	0.77–1.31	1.26–1.83	0.78–1.31	0.91–1.43	1.27–1.82	1.16–1.76
Health-related behavior[b]	1.07	1.54*	1.03	1.20	1.56*	1.47
95% CI	0.82–1.39	1.27–1.85	0.80–1.34	0.96–1.49	1.31–1.87	1.20–1.81
Educational level and SES	1.08	1.63*	1.13	1.23	1.62*	1.59*
95% CI	0.83–1.41	1.36–1.97	0.87–1.46	0.99–1.54	1.36–1.94	1.29–1.95
Physical measurements[c]	1.11	1.67*	1.17	1.23	1.67*	1.63*
95% CI	0.85–1.44	1.38–2.01	0.91–1.52	0.99–1.54	1.40–2.00	1.33–2.00
Final adjusted model						
All factors above	0.89	1.36*	0.84	1.00	1.39*	1.17
95% CI	0.67–1.16	1.12–1.64	0.64–1.09	0.80–1.26	1.16–1.68	0.94–1.45

CI = Confidence Interval; SES = socioeconomic status.
* $p < .05$.
[a] All models are adjusted for age (categorically in decades) and gender.
[b] Smoking (current, former, never, and pack years of smoking), CAGE (a screening instrument for alcohol problems), and physical activity.
[c] Body mass index, diastolic blood pressure, and total cholesterol level.

gender, further adjustment for somatic symptoms and physical diagnoses, and finally fully adjusted models (Table 3). Again, analyses were repeated with anxiety and depression as continuous scores (Table 4). In prediction of CVD mortality, for example, individuals dying from other causes during follow-up were excluded. To disentangle the effects of pure from mixed symptoms in analyses using continuous scale scores for anxiety and depression (Tables 2 and 4), the effect of anxiety was adjusted for depression, and vice versa. Individuals still alive at the end of follow-up comprised a common reference category across all models.

Ethics

The National Data Inspectorate and the Board of Research Ethics in Health Region IV of Norway approved HUNT. All participants gave their informed consent for participating in the study and for the record linkage.

RESULTS

The participation rate was 66% (61,349 participants of 93,138 individuals eligible for the study). The mean age was 48 years for both genders (SD = 16.7, range 19 to 101 years). Nonparticipants were more often older and institutionalized, and there was a higher mortality rate in nonparticipants than in participants (15% versus 4%). All the following results are based on 2309 deaths among 61,349 participants in the HUNT-2 study.

Case-level anxiety was reported in 5864 (9.6%) individuals, case-level depression in 3032 (4.9%) individuals, and comorbid anxiety and depression in 3640 (5.9%) individuals. All confounding or mediating factors were associated with total mortality in the directions anticipated.

In the first analysis, cause-specific mortality was divided into CVD mortality versus all other causes combined. Adjusted for age and gender, there was no difference in the strength of association between case-level depression and mortality from CVD (n = 1069, OR = 1.67, 95% CI 1.38–2.01) compared with all other causes combined (n = 1240, OR = 1.66, 95% CI 1.39–1.99) (Table 1, row 1). This effect of depression on CVD and other cause mortality is also illustrated as survival plots (Figure 1), by Hazard Ratios based on Cox regression models (Figure 1), and by logistic regression models using continuous scale scores for depression (Table 2, row 1).

Separate adjustments for confounding and mediating factors had markedly similar attenuation of associations for CVD and other mortality (Table 1, rows 2–6). Somatic symptoms and physical conditions, physical impairment, and health-related behavior were the strongest confounding factors, each explaining up to one fifth of the association between depression and either outcome. Adjustment for socioeconomic factors only weakly attenuated associations. BMI, diastolic blood pressure, and total cholesterol level had no relevance for the associations of interest. The fully adjusted models were similar for the associations between depression and both outcomes, and all mediating and confounding variables combined explained up to two fifth of the effect of depression on mortality. Similar effects of confounding and mediating fac-

TABLE 2. CVD Mortality and Mortality From All Other Causes as a Function of Scale Score Anxiety and Depression (Odds Ratios)

	CVD Mortality (n = 1069 deaths among 60,109 included)		All Other Cause Mortality (n = 1240 deaths among 60,280 included)	
	Scale Score Anxiety[a]	Scale Score Depression[a]	Scale Score Anxiety[a]	Scale Score Depression[a]
Age and gender	0.95	1.23*	1.13*	1.28*
95% CI	0.88–1.03	1.15–1.33	1.06–1.21	1.19–1.37
Further adjusted for depression/anxiety[b]	0.79*	1.39*	0.98	1.29*
95% CI	0.72–0.87	1.27–1.51	0.90–1.07	1.19–1.40
Further adjustment entered separately[c]				
Somatic symptoms/diagnoses	0.75*	1.33*	0.93	1.25*
95% CI	0.68–0.82	1.22–1.45	0.86–1.01	1.15–1.36
Physical impairment	0.77*	1.32*	0.95	1.24*
95% CI	0.70–0.85	1.21–1.44	0.87–1.03	1.14–1.35
Health-related behavior[d]	0.81*	1.30*	0.97	1.24*
95% CI	0.74–0.89	1.19–1.42	0.90–1.06	1.14–1.35
Educational level and SES	0.79*	1.37*	0.98	1.27*
95% CI	0.72–0.87	1.26–1.50	0.90–1.06	1.17–1.38
Physical measurements[e]	0.80*	1.39*	0.97	1.30*
95% CI	0.72–0.87	1.27–1.52	0.89–1.05	1.20–1.41
Fully adjusted model				
All factors above included	0.76*	1.23*	0.90*	1.19*
95% CI	0.69–0.83	1.12–1.34	0.83–0.98	1.09–1.29

CI = Confidence Interval; SES = socioeconomic status.

* $p < .05$.

[a] Continuous scores scaled so that 1-U represents the distance between the 25th and the 75th percentiles.

[b] Analysis with symptom score anxiety as exposure adjusted for symptom score depression, and vice versa.

[c] All models are adjusted for age (categorically in decades) and gender.

[d] Smoking (current, former, never, and pack years of smoking), CAGE (a screening instrument for alcohol problems), and physical activity.

[e] BMI, diastolic blood pressure, and total cholesterol level.

tors were found in the models applying continuous scale scores for depression (Table 2).

Unlike case-level depression, associations for the other two categorical exposures showed some differences for the two outcomes. Adjusted for age and gender only, case-level anxiety and comorbid anxiety/depression were not associated with CVD mortality but, for the other causes of death, weak associations were found for anxiety alone (OR = 1.25) and for comorbid anxiety/depression (OR = 1.64) (Table 1). Mediating and confounding factors were the same as for depression, but the attenuations of effect were stronger. The effect of case-level anxiety alone was explained entirely in the fully adjusted model (OR = 1.00), whereas comorbid anxiety/depression was weak and fell below significance levels (OR = 1.17).

The finding of different effects of anxiety on CVD versus other cause mortality was confirmed by analyses applying continuous scale scores (Table 2). Adjusted for age and gender alone, anxiety was not associated with CVD mortality (OR = 0.95). However, after adjustment for depression, anxiety symptoms were associated negatively with CVD mortality (OR = 0.79), which was found also in the fully adjusted model (OR = 0.76). The association between depressive symptom load and CVD mortality was increased substantially by adjusting for anxiety (OR increasing from 1.23 to 1.39). These contrasting associations between anxiety and depression scale scores were also found for other cause mortality combined in the fully adjusted model (OR = 0.90 and 1.19 for anxiety and depression, respectively).

In a second analysis, we further subdivided the cause of death into 11 groups in addition to CVD mortality, applying both case-levels (Table 3) and scale scores (Table 4) for anxiety and depression. We performed nested logistic regression analyses for the separate groups of mortality diagnoses comprising eight for diseases, two for external causes, and two for unknown reasons. Case-level depression predicted mortality for all diseases except the groups "other diseases" and "gastrointestinal diseases" (Table 3), although numbers of deaths were small (71 and 47, respectively). Adjusted for age, gender, somatic symptoms, and somatic diagnoses, depression without comorbidity significantly predicted mortality from CVD, cancer, respiratory diseases, diseases in the nervous system, metabolic diseases, and mental disorders.

Although most disease-related mortality was associated with depression only (and not with anxiety or comorbid anxiety/depression), associations were different for the external causes of death: comorbid anxiety/depression predicted suicide, accidents, and mortality without any certificate. However, of 29 individuals who committed suicide, 17 (59%) were noncases of anxiety and depression at baseline. Sudden death with unknown reason was not predicted by anxiety or depression.

TABLE 3. Cause-Specific Mortality in Relationship to Anxiety and Depression, Adjusted for Age and Gender, Somatic Symptoms and Diagnoses, and Total Adjustment

Mortality Diagnosis (ICD-10 code) [*n* Deaths]	Case-Level Anxiety		Case-Level Depression		Comorbid Anxiety/Depression	
	OR	95% CI	OR	95% CI	OR	95% CI
CVD (I) [*n* = 1069]						
Adjusted for age/gender	1.10	0.84–1.43	1.67*	1.38–2.01	1.16	0.90–1.50
+Somatic symptoms/diagnoses	0.93	0.71–1.22	1.52*	1.26–1.83	0.97	0.75–1.26
Fully adjusted	0.89	0.67–1.16	1.36*	1.12–1.64	0.84	0.64–1.09
Cancer (CD) [*n* = 712]						
Adjusted for age/gender	1.18	0.89–1.58	1.50*	1.19–1.89	1.16	0.86–1.56
+Somatic symptoms/diagnoses	1.05	0.78–1.41	1.39*	1.09–1.76	1.00	0.74–1.35
Fully adjusted	0.99	0.74–1.33	1.33*	1.05–1.69	0.90	0.66–1.22
Respiratory (J) [*n* = 119]						
Adjusted for age/gender	1.19	0.54–2.60	2.06*	1.26–3.38	2.69*	1.57–4.61
+Somatic symptoms/diagnoses	0.88	0.40–1.96	1.84*	1.12–3.03	1.97*	1.13–3.44
Fully adjusted	0.83	0.37–1.85	1.53	0.92–2.56	1.52	0.86–2.71
Accidents (VWXY[a]) [*n* = 80]						
Adjusted for age/gender	0.93	0.37–2.33	2.09*	1.07–4.08	2.23*	1.10–4.56
+Somatic symptoms/diagnoses	0.80	0.31–2.02	1.97*	1.01–3.86	1.89	0.91–3.90
Fully adjusted	0.69	0.27–1.76	1.71	0.87–3.36	1.54	0.74–3.24
Other diseases (ABMNQ) [*n* = 71]						
Adjusted for age/gender	2.19*	1.06–4.51	0.98	0.44–2.18	0.92	0.33–2.56
+Somatic symptoms/diagnoses	1.80	0.86–3.76	0.92	0.42–2.06	0.77	0.27–2.15
Fully adjusted	1.76	0.84–3.70	0.86	0.38–1.93	0.64	0.22–1.83
Nervous system (G, R54) [*n* = 53]						
Adjusted for age/gender	1.93	0.74–5.05	4.66*	2.44–8.92	2.54	1.04–6.19
+Somatic symptoms/diagnoses	1.85	0.70–4.87	4.56*	2.38–8.74	2.42	0.98–5.97
Fully adjusted	1.55	0.58–4.13	3.71*	1.92–7.18	1.79	0.72–4.46
Gastrointestinal (K) [*n* = 47]						
Adjusted for age/gender	0.60	0.14–2.49	0.91	0.32–2.58	1.55	0.60–3.97
+Somatic symptoms/diagnoses	0.46	0.11–1.95	0.80	0.28–2.28	1.18	0.45–3.08
Fully adjusted	0.40	0.09–1.72	0.69	0.24–1.97	0.84	0.32–2.22
Metabolism (E) [*n* = 47]						
Adjusted for age/gender	1.66	0.58–4.77	3.03*	1.46–6.28	2.11	0.81–5.49
+Somatic symptoms/diagnoses	1.24	0.42–3.65	2.56*	1.22–5.39	1.56	0.59–4.15
Fully adjusted	1.20	0.40–3.55	2.09	0.98–4.46	1.19	0.44–3.23
No certificate (R99) [*n* = 40]						
Adjusted for age/gender	1.29	0.39–4.30	0.98	0.30–3.26	2.77*	1.14–6.73
+Somatic symptoms/diagnoses	1.09	0.32–3.64	0.90	0.27–3.00	2.27	0.92–5.63
Fully adjusted	1.01	0.30–3.39	0.69	0.20–2.34	1.84	0.73–4.66
Suicide (X60–X84, X87) [*n* = 29]						
Adjusted for age/gender	2.25	0.75–6.73	N		6.83*	2.91–15.99
+Somatic symptoms/diagnoses	2.47	0.82–7.44	N		7.82*	3.27–18.68
Fully adjusted	2.08	0.68–6.32	N		6.13*	2.49–15.09
Sudden death, unknown (R96) [*n* = 25]						
Adjusted for age/gender	0.63	0.08–4.75	0.38	0.05–2.85	1.20	0.28–5.14
+Somatic symptoms/diagnoses	0.70	0.09–5.26	0.40	0.05–3.00	1.34	0.31–5.80
Fully adjusted	0.73	0.10–5.60	0.34	0.04–2.55	1.31	0.29–5.86
Mental disorders[b] (F) [*n* = 17]						
Adjusted for age/gender	1.48	0.18–12.16	6.75*	2.09–21.78	6.77*	1.97–23.31
+Somatic symptoms/diagnoses	1.38	0.17–11.48	6.54*	2.01–21.22	6.20*	1.75–21.91
Fully adjusted	0.97	0.11–8.17	5.14*	1.56–16.94	4.30*	1.16–15.91

OR = odds ratios; CI = Confidence Interval; N, no observations.

* $p < .05$.

[a] Accidents V01–X59 (*n* = 78); murder Y04 (*n* = 1); external cause, unclear intentionality Y10–Y34 and Y87 (*n* = 3).

[b] Mental disorders comprised ICD-10 diagnoses: F01 (*n* = 2), F03 (*n* = 6), F10 (*n* = 5), F22 (*n* = 1), F32 (*n* = 1), and F39 (*n* = 1).

Case-level anxiety without depression did not predict any cause-specific mortality when adjusted for age, gender, somatic symptoms, and somatic diagnoses (Table 3).

Depression was found to be a robust predictor of disease mortality across causes of death also when measured as a continuous variable (Table 4). However, nondisease mortality

TABLE 4. Cause Specific Mortality in Relationship to Anxiety and Depression, Adjusted for Age and Gender, Somatic Symptoms and Diagnoses, and Total Adjustment

Mortality diagnosis (ICD-10 code) [#deaths]	Scale Score Anxiety[a]		Scale Score Depression[a]	
	OR	95% CI	OR	95% CI
CVD (I) [n = 1069]				
Adjusted for age/gender	0.95	0.88–1.03	1.23*	1.15–1.33
+Depression/anxiety[b]	0.79*	0.72–0.87	1.39*	1.27–1.51
+Somatic symptoms/diagnoses	0.75*	0.68–0.82	1.33*	1.22–1.45
Fully adjusted	0.76*	0.69–0.83	1.23*	1.12–1.34
Cancer (CD) [n = 712]				
Adjusted for age/gender	1.04	0.95–1.14	1.13*	1.03–1.23
+Depression/anxiety[b]	0.96	0.86–1.07	1.16*	1.04–1.29
+Somatic symptoms/diagnoses	0.92	0.82–1.03	1.12*	1.00–1.25
Fully adjusted	0.89*	0.80–1.00	1.09	0.98–1.22
Respiratory (J) [n = 119]				
Adjusted for age/gender	1.29*	1.06–1.58	1.69*	1.40–2.05
+Depression/anxiety[b]	0.93	0.73–1.19	1.76*	1.40–2.21
+Somatic symptoms/diagnoses	0.82	0.64–1.05	1.70*	1.35–2.13
Fully adjusted	0.82	0.64–1.04	1.54*	1.22–1.93
Accidents (VWXY[c]) [n = 80]				
Adjusted for age/gender	1.21	0.94–1.55	1.40*	1.09–1.79
+Depression/anxiety[b]	1.00	0.73–1.37	1.40*	1.02–1.90
+Somatic symptoms/diagnoses	0.94	0.69–1.29	1.36*	1.00–1.85
Fully adjusted	0.90	0.66–1.23	1.26	0.92–1.72
Other diseases (ABMNQ) [n = 71]				
Adjusted for age/gender	0.98	0.73–1.32	1.04	0.78–1.38
+Depression/anxiety[b]	0.95	0.67–1.34	1.07	0.77–1.49
+Somatic symptoms/diagnoses	0.87	0.61–1.23	1.05	0.75–1.46
Fully adjusted	0.86	0.61–1.22	0.99	0.71–1.39
Nervous system (G, R54) [n = 53]				
Adjusted for age/gender	1.37*	1.03–1.83	1.85*	1.41–2.43
+Depression/anxiety[b]	0.94	0.66–1.34	1.91*	1.37–2.67
+Somatic symptoms/diagnoses	0.92	0.65–1.32	1.90*	1.36–2.65
Fully adjusted	0.88	0.62–1.26	1.69*	1.21–2.37
Gastrointestinal (K) [n = 47]				
Adjusted for age/gender	0.89	0.61–1.28	1.01	0.71–1.43
+Depression/anxiety[b]	0.84	0.54–1.29	1.11	0.73–1.68
+Somatic symptoms/diagnoses	0.76	0.49–1.16	1.04	0.69–1.58
Fully adjusted	0.73	0.47–1.12	0.92	0.60–1.40
Metabolism (E) [n = 47]				
Adjusted for age/gender	1.23	0.89–1.70	1.79*	1.34–2.40
+Depression/anxiety[b]	0.81	0.55–1.20	2.01*	1.41–2.86
+Somatic symptoms/diagnoses	0.75	0.51–1.12	1.85*	1.30–2.65
Fully adjusted	0.75	0.50–1.12	1.66*	1.15–2.39
No certificate (R99) [n = 40]				
Adjusted for age/gender	1.32	0.93–1.86	1.31	0.92–1.86
+Depression/anxiety[b]	1.20	0.78–1.85	1.17	0.75–1.82
+Somatic symptoms/diagnoses	1.11	0.72–1.72	1.14	0.73–1.77
Fully adjusted	1.08	0.70–1.67	1.04	0.67–1.62
Suicide (X60–X84, X87) [n = 29]				
Adjusted for age/gender	1.99*	1.43–2.78	2.06*	1.44–2.95
+Depression/anxiety[b]	1.54	0.97–2.45	1.51	0.92–2.49
+Somatic symptoms/diagnoses	1.63*	1.02–2.61	1.54	0.93–2.53
Fully adjusted	1.51	0.94–2.44	1.48	0.89–2.46
Sudden death, unknown (R96) [n = 25]				
Adjusted for age/gender	1.00	0.61–1.65	1.06	0.66–1.70
+Depression/anxiety[b]	0.96	0.53–1.74	1.08	0.61–1.92
+Somatic symptoms/diagnoses	0.99	0.54–1.82	1.11	0.62–1.96
Fully adjusted	1.09	0.60–1.97	1.01	0.57–1.81
Mental disorders[d] (F) [n = 17]				
Adjusted for age/gender	2.06*	1.34–3.18	2.21*	1.41–3.48
+Depression/anxiety[b]	1.50	0.85–2.65	1.71	0.94–3.09
+Somatic symptoms/diagnoses	1.45	0.81–2.60	1.71	0.94–3.10
Fully adjusted	1.33	0.76–2.33	1.53	0.85–2.74

OR = odds ratio; CI = Confidence Interval.

* $p < .05$.

[a] Continuous scores scaled so that 1-U represents the distance between the 25th and the 75th percentiles.

[b] Analysis with symptom score anxiety as exposure adjusted for symptom score depression, and vice versa.

[c] Accidents V01–X59 (n = 78); murder Y04 (n = 1); external cause, unclear intentionality Y10–Y34 and Y87 (n = 3).

[d] Mental disorders comprised ICD-10 diagnoses: F01 (n = 2), F03 (n = 6), F10 (n = 5), F22 (n = 1), F32 (n = 1), and F39 (n = 1).

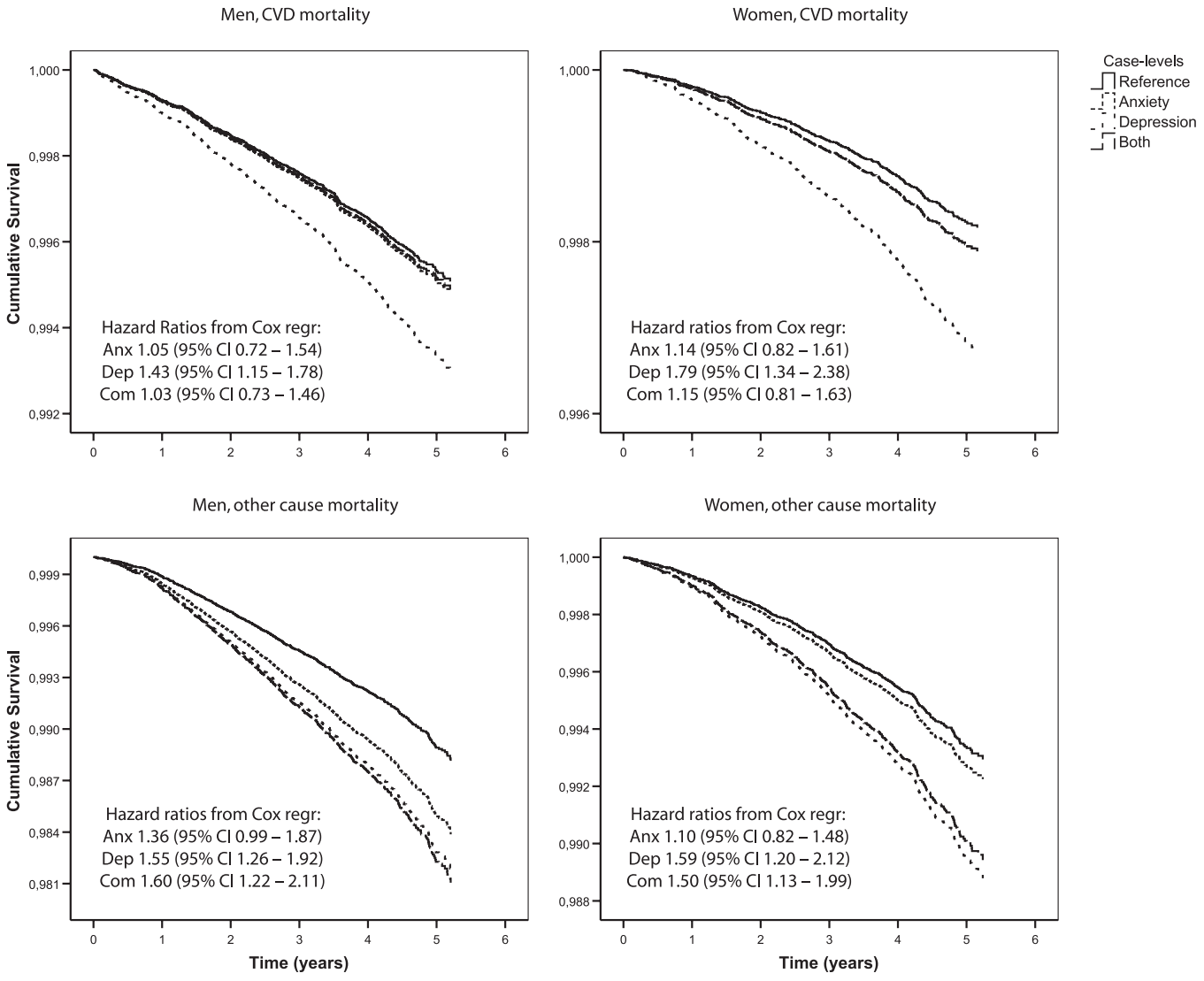

Figure 1. Survival plots: mortality from case-level anxiety, depression and comorbid anxiety/depression, adjusted for age.

generally found to be associated with comorbid anxiety depression in the categorical analysis (Table 3) was not consistently associated with continuous scale scores of neither anxiety nor depression when these were adjusted for each other (Table 4).

DISCUSSION

Summary of Results

In this large population-based study with a follow-up period of 3 to 6 years, depression predicted mortality from nearly all major causes of death, and the association between depression and mortality was no stronger for CVD mortality than for other causes combined. Confounding and mediating factors were markedly similar in CVD mortality and other mortality, the most important being previously reported somatic symptoms and diagnoses, followed by physical impairment. Comorbid anxiety and depression were not generally associated with disease mortality but were associated with increased mortality for external causes (suicide and accidents and also mortality without certificates). Anxiety alone at case level was not associated with any cause-specific mortality. Continuous symptom scores for depression showed similar associations to case-levels, and these were generally strengthened by adjustment for anxiety. Symptom scores for anxiety were associated negatively with both CVD and other cause mortality in fully adjusted models, which is consistent with a previous study of general mortality in relation to HADS anxiety and depression (25).

Strengths and Limitations

The present study has several strengths mainly derived from the cohort design. The study sample is large and the participation rate at baseline was high. Both exposure and outcome assessments should have been relatively unbiased. Ascertainment of mortality was obtained from the National Mortality Registry; with the exception of emigration from the country, these data are complete and should not be influenced by exposure status.

There are some limitations to our study. First, anxiety and depression at baseline were established by self-report rather

than clinical diagnosis. Misclassification is likely to have been random, resulting in an underestimation of the true association, but bias cannot be excluded.

Second, screening for psychiatric morbidity was limited to symptoms of anxiety and depression, which in part also will capture, for example, psychoses and substance use. The anxiety subscale in HADS is limited to symptoms of generalized anxiety and panic attacks. We cannot estimate the effects of mental disorders beyond what is covered by the HADS, and we cannot rule out possible confounding of comorbid mental disorders (the exception being alcoholism, which partly is covered by the CAGE questionnaire).

Third, information on somatic diagnoses and symptoms at the baseline are self-reported, and the categories used are not exhaustive. Consequently, the effect of somatic diagnoses and symptoms may be underestimated, and the effects of anxiety and depression, when adjusted for somatic symptoms and diagnoses, may be overestimated. Further, we cannot rule out possible protopathic bias, i.e., symptoms of anxiety and depression being early symptoms of later development of physiological diseases, which may add to further overestimation of the effect of depression on mortality. However, the fact that depression is a risk factor for all major mortality diagnoses reduces the relevance of this bias.

Fourth, nonparticipation was related to increased mortality, suggesting increased pathology among nonparticipants, the most likely consequence—if any—being underestimation of associations between disorders (including mental health factors) and mortality.

Fifth, there is a potentially complex relationship between psychiatric and physical disorders. We attempted to disentangle mental from physical symptoms and disorders by employing the HADS (which includes no somatic symptoms of anxiety or depression) and then by adjusting for somatic symptoms. Using this approach, the model may be overadjusted and may have led to an underestimation of associations of interest. Further, sources of overadjustment reside in the fully adjusted models, where we included variables for health-related behavior (smoking, lack of exercise, alcohol problems) and self-evaluated physical impairment, which may be manifestations of depression. Associations might also have been obscured because of an intervention that formed part of the study and that was aimed at 2% of the population with highest levels of mental health problems. The intervention consisted of an information letter to the participant and his or her primary medical doctor suggesting further screening for mental disorders; general practitioners in the area were also offered a brief course in using a tool for diagnosing mental disorders. However, we believe that this is unlikely to have had a substantial impact on the observations from this analysis.

Sixth, there is also the issue of reliability of mortality diagnoses, in particular in cases of comorbid somatic diagnoses. However, we believe this is most likely to be a nondifferential source of bias and will have obscured rather than exaggerated associations of interest. The demographic characteristics of the population that we studied limits any generalization about the findings.

Interpretation

The present study contributes possible mechanisms involved in the association between depression and mortality. The majority of suggested mechanisms in the literature are specific for CVD mortality. Because depression in our study predicts both CVD and other mortality and because confounding and mediating factors seem identical, we suggest an additional focus on the mechanisms of relevance across mortality diagnoses.

Effect of Depression on Mortality: An Artifact Resulting From Confounding Factors?

It has been suggested that most studies of the effects of depression on mortality have failed to adjust properly for somatic conditions (3). This objection seems relevant for both CVD and other mortality because our adjustment for somatic conditions attenuated the association between depression and mortality by approximately a quarter. This finding indicates that some of the apparent effect of depression on mortality may account for depression that is a reaction to physical conditions (13) and related impairment (17). However, most of the association between depression and mortality from both CVD and other causes remained unexplained in this sample that was adjusted for a large number of potential confounders.

Help-Seeking Behavior and Nonadherence to Treatment Strategies

Depression may interfere with help-seeking behavior, which may in turn increase nonadherence to treatment strategies (6,10) and possibly also help-seeking for somatic symptoms in general. Further, depression without anxiety is reported to be associated with less help-seeking for mental problems than anxiety alone or comorbid anxiety and depression (28). This pattern of low help-seeking in depression without anxiety might explain increased mortality across apparent causes. Our finding of lower mortality in comorbid anxiety depression than depression alone is consistent with this theory because anxiety is known to increase help-seeking for somatic symptoms. Because we know that smoking, alcohol, and physical activity are indicators of poor self-care in general, we found that smoking, alcohol problems, and low physical activity attenuated the effect of depression on mortality whereas BMI, cholesterol, and blood pressures did not.

Biological Changes Occurring in Depression

Our analyses have some relevance for the discussion of biological changes occurring in depression as underlying causal pathways. We were not able to identify any relevance of BMI, blood pressure, and cholesterol level as mediating factors in explaining the association between depression and mortality. Research into biological pathways between depression and mortality has tended to focus on vascular effects (10). Our findings of similar associations for other causes of death suggest that this focus may not be appropriate although it is possible that different specific mechanisms were giving rise to the observed equal effects. For future research, we recom-

mend the development of hypotheses with relevance across all major disease-mortality diagnoses.

Suicide

Our results support the hypothesis that suicide accounts for some of the effect of depression on mortality (17). This effect was found only in the presence of comorbid anxiety, perhaps indicating higher severity of psychopathology. Of the 2309 deceased individuals, 29 (1.3%) committed suicide, but the majority ($n = 17$, 59%) did not have case-level symptoms of anxiety or depression at the time of health screening. Although our results support an association between depression (comorbid with anxiety) and suicide, the potential effect of depression on mortality from the major disease groups accounts for a far higher number of deaths. Screening for depression in the general population and subsequent interventions has been suggested to decrease the suicide rate (31). Our findings suggest that hypothesized effects of interventions targeting depression could be much stronger in reducing disease mortality than suicide. Perhaps there is also a potential in improving the screening tools for suicide.

Finally, our results provide support for associations between mental disorder and suicide-like "accidents" (17). Sudden death from unknown reason ($n = 25$) was not associated with depression or anxiety, but comorbid anxiety depression predicted mortality without certificate ($n = 40$), a pattern similar to that of suicide. A possible effect of depression and comorbid anxiety and depression was also found for accidents ($n = 80$), which might indicate suicide-like "accidents" (17) or hazardous behavior (6).

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REFERENCES

1. Bruce ML. Psychiatric status and 9-year mortality data in the New-Haven epidemiologic catchment-area study. Am J Pychiatry 1994;151:716–21.
2. Pulska T, Pahkala K, Laippala P, Kivela SL. Follow up study of long-standing depression as predictor of mortality in elderly people living in the community. BMJ 1999;318:432–3.
3. Saz P, Dewey ME. Depression, depressive symptoms and mortality in persons aged 65 and over living in the community: a systematic review of the literature. Int J Geriatr Psychiatry 2001;16:622–30.
4. Zheng D, Macera CA, Croft JB, Giles WH, Davis D, Scott WK. Major depression and all-cause mortality among white adults in the United States. Ann Epidemiol 1997;7:213–8.
5. Joukamaa M, Heliovaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V. Mental disorders and cause-specific mortality. Br J Psychiatry 2001; 179:498–502.
6. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. J Affect Disord 2002;72:227–36.
7. Schulz R, Beach SR, Ives DG, Martire LM, Ariyo AA, Kop WJ. Association between depression and mortality in older adults: the cardiovascular health study. Arch Intern Med 2000;160:1761–8.
8. Barth J, Schumacher M, Herrmann C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med 2004;66:802–13.
9. Melle JP. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. Psychosom Med 66:814–22.
10. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. J Psychosom Res 2002;53:897–902.
11. Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, Jones R, Mathew JP, Newman MF. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet 2003;362:604–9.
12. Ammon Cavanaugh S, Furlanetto LM, Creech SD, Powell LH. Medical illness, past depression, and present depression: a predictive triad for in-hospital mortality. Am J Psychiatry 2001;158:43–8.
13. Carney RM, Freedland KE, Jaffe AS. Depression as a risk factor for coronary heart disease mortality. Arch Gen Psychiatry 2001;58:229–30.
14. Carney RM, Sheps DS. Depression is a risk factor for mortality in coronary heart disease. Psychosom Med 2004;66:799–801.
15. Abas M, Hotopf M, Prince M. Depression and mortality in a high-risk population. 11-Year follow-up of the medical research council elderly hypertension trial. Br J Psychiatry 2002;181:123–8.
16. Morris PL, Robinson RG, Andrzejewski P, Samuels J, Price TR. Association of depression with 10-year poststroke mortality. Am J Psychiatry 1993;150:124–9.
17. Wulsin LR, Vaillant GE, Wells VE. A systematic review of the mortality of depression. Psychosom Med 1999;61:6–17.
18. Hiroeh U, Appleby L, Mortensen PB, Dunn G. Death by homicide, suicide, and other unnatural causes in people with mental illness: a population-based study. Lancet 2001;358:2110–2.
19. Allgulander C. Suicide and mortality patterns in anxiety neurosis and depressive neurosis. Arch Gen Psychiatry 1994;51:708–12.
20. Leserman J. Severe stress, depressive symptoms, and changes in lymphocyte subsets in human immunodeficiency virus-infected men. A 2-year follow-up study. Arch Gen Psychiatry 1997;54:279–85.
21. Kessler RC, DuPont RL, Berglund P, Wittchen HU. Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in two national surveys. Am J Psychiatry 1999;156:1915–23.
22. Stordal E, Bjelland I, Dahl AA, Mykletun A. Anxiety and depression in individuals with somatic health problems. The Nord-Trondelag health study (HUNT). Scand J Prim Health Care 2003;21:136–41.
23. Eaker ED. Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillation, and total mortality: The Framingham offspring study. Psychosom Med 2005;67:692–6.
24. Allgulander C, Lavori PW. Excess mortality among 3302 patients with 'pure' anxiety neurosis. Arch Gen Psychiatry 1991;48:599–602.
25. Herrmann C, Brand Driehorst S, Buss U, Ruger U. Effects of anxiety and depression on 5-year mortality in 5,057 patients referred for exercise testing. J Psychosom Res 2000;48:455–62.
26. Mykletun A, Stordal E, Dahl AA. Hospital anxiety and depression (HAD) scale: factor structure, item analyses and internal consistency in a large population. Br J Psychiatry 2001;179:540–4.
27. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. An updated literature review. J Psychosom Res 2002;52:69–77.
28. Roness A, Mykletun A, Dahl AA. Help-seeking behaviour in patients with anxiety disorder and depression. Acta Psychiatr Scand 2005;111: 51–8.
29. Mykletun A, Overland S, Dahl AA, Krokstad S, Bjerkeset O, Glozier N, Aaro LE, Prince M. A population-based cohort study of the effect of common mental disorder on disability pension awards. Am J Psychiatry 2006;163:1412–8.
30. Krokstad S, Westin S. Health inequalities by socioeconomic status among men in the Nord-Trondelag health study, Norway. Scand J Public Health 2002;30:113–24.
31. Jacobs DG. Depression screening as an intervention against suicide. J Clin Psychiatry 1999;60:42–5.