Type 2 Diabetes and Comorbid Symptoms of Depression and Anxiety: Longitudinal Associations With Mortality Risk

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OBJECTIVE

Depression is strongly linked to increased mortality in individuals with type 2 diabetes. Despite high rates of co-occurring anxiety and depression, the risk of death associated with comorbid anxiety in individuals with type 2 diabetes is poorly understood. This study documented the excess mortality risk associated with symptoms of depression and/or anxiety comorbid with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Using data for 64,177 Norwegian adults from the second wave of the Nord-Trøndelag Health Study (HUNT2), with linkage to the Norwegian Causes of Death Registry, we assessed all-cause mortality from survey participation in 1995 through to 2013. We used Cox proportional hazards models to examine mortality risk over 18 years associated with type 2 diabetes status and the presence of comorbid affective symptoms at baseline.

RESULTS

Three clear patterns emerged from our findings. First, mortality risk in individuals with diabetes increased in the presence of depression or anxiety, or both. Second, mortality risk was lowest for symptoms of anxiety, higher for comorbid depression-anxiety, and highest for depression. Lastly, excess mortality risk associated with depression and anxiety was observed in men with diabetes but not in women. The highest risk of death was observed in men with diabetes and symptoms of depression only (hazard ratio 3.47, 95% CI 1.96, 6.14).

CONCLUSIONS

This study provides evidence that symptoms of anxiety affect mortality risk in individuals with type 2 diabetes independently of symptoms of depression, in addition to attenuating the relationship between depressive symptoms and mortality in these individuals.

Depression and type 2 diabetes are two leading global causes of morbidity and mortality, with type 2 diabetes currently affecting more than 9% and depression affecting 5% of the world's population in any given year (1,2). One of four patients with type 2 diabetes experiences a clinically significant form of depression at a prevalence five-times higher than observed in the general population (3). Major depression is a condition that routinely presents concurrent with symptoms of anxiety—between 50 and 75% of individuals diagnosed with major depression in primary care settings are also diagnosed with a comorbid

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anxiety disorder (4). These disorders share many documented similarities, including hypothalamic-pituitary-adrenal axis dysregulation, activation of inflammatory responses, and effects on functional impairment. Unsurprisingly, depressed patients with comorbid anxiety have a poorer prognosis, with higher severity, greater chronicity, and longer time spent in treatment (5).

Mortality studies of the general population have demonstrated a consistent association between depressive disorders and excess mortality (6). However, evidence for the relationship between anxiety disorders and mortality risk remains inconsistent. Some studies demonstrate a higher observed short-term risk of death, which dissipates over the long-term (7). Other studies find that high levels of anxious symptoms are associated with reduced accidental mortality in early life but higher nonaccidental mortality in later life (8,9). A recent meta-analysis reflects a higher relative risk of mortality associated with depression than anxiety in the general population (10). Additional evidence suggests that the mortality risk associated with depression may differ according to sex (11–13) as well as disorder severity (14). Major depression, for example, increases mortality risk in both men and women, but minor depression is associated with an increased risk only in men (14). Excess mortality was associated with anxiety disorders in men but not women within the same study (15). However, because the presence of comorbid anxiety is rarely considered in depression research studies (or vice versa), the ability to attribute risk to either disorder is obscured.

Individuals with diabetes may be particularly vulnerable to the deleterious effects of affective symptoms. Depression is a known risk factor for noncompliance with medical treatment (16). This can be particularly problematic for a condition like type 2 diabetes, which requires a high degree of patient self-management. Depression is often much less likely to be identified by medical practitioners in male patients (17) and may affect glycemic control more strongly in men than in women (18). Likewise, studies link anxiety disorders to heightened inflammation in men but not women (19). Sex differences in mortality risk associated with affective disorders may therefore be even more pronounced in individuals with type 2 diabetes than in the general population. Relatively little is known about the effect of comorbid anxiety on mortality risk in individuals with diabetes. The purpose of this study was to document the excess mortality risk associated with type 2 diabetes and comorbid symptoms of depression and anxiety in a large general population sample and determine whether men and women are differentially affected by this association.

RESEARCH DESIGN AND METHODS

Data Sources and Study Sample

This study used data from the second wave of the Norwegian Nord-Trøndelag Health Study (HUNT2). The HUNT Study is a large population-based survey conducted over three waves, in 1984–1986 (HUNT1), 1995–1997 (HUNT2), and 2006–2008 (HUNT3). The survey was conducted using a simple nonstratified design that included every resident of the Nord-Trøndelag County >20 years old. The study was primarily established to address arterial hypertension, diabetes, tuberculosis screening, and quality of life (20), and the scope has since been expanded to include a wide range of somatic and mental illnesses, lifestyle, and health determinants. The HUNT cohort profile and methodology has been well-described elsewhere (20). For the HUNT2 wave, 92,100 individuals aged 20 to 89 years received an initial questionnaire and a personal invitation to participate. Of these, 65,648 (71%) attended a physical examination, where they also received a second questionnaire. Because our study comparison consisted of individuals with or without type 2 diabetes, individuals with type 1 or other subtypes of diabetes (e.g., gestational or latent autoimmune diabetes of adults) were excluded. All remaining HUNT2 participants were included, consisting of 64,177 individuals.

Primary Outcome

Our primary outcome of interest was all-cause mortality. These data were obtained through linkage to the Norwegian Causes of Death Registry for each year from 1995 through to 2013. This registry is maintained by the Norwegian Institute of Public Health and includes information on cause of death for all deceased persons registered as residents in Norway at the time of death (21).

Exposure Variables

Our primary exposures were type 2 diabetes status, depressive symptom level, and anxious symptom level. Individuals who self-reported type 2 diabetes in The HUNT2 Study questionnaire or who had nonfasting plasma glucose levels $\geq$7 mmol/L received further clinical confirmation of diabetes status, based on results of three repeated laboratory tests (fasting plasma glucose, oral glucose tolerance, and serum HbA_{1c} levels). To receive a final classification of type 2 diabetes, all individuals were additionally confirmed to be anti-GAD and anti–IA-2 negative (to exclude latent autoimmune diabetes of adults cases) and confirmed as having not begun insulin treatment within 1 year of diagnosis.

Symptoms of depression and anxiety were measured in HUNT using the seven-item Cohort Norway Mental Health Index (CONOR-MHI). This tool was derived from widely validated items from the General Health Questionnaire and the Hopkins Symptoms Checklist (HSCL). It was further evaluated against both the HSCL-10 and Hospital Anxiety and Depression Scales (HADS) and found to have excellent accuracy when tested against each of these scales as a gold standard (area under the curve = 0.902 and 0.909, respectively) (22). The internal consistency of the CONOR-MHI was also high (Cronbach $\alpha \geq 0.80$) across multiple Norwegian data sets (22). Individuals were classified as having "high" symptom levels if their mean scores on the depression items or anxiety items were above the recommended cutoff of 2.15 (22). Individuals falling below this score were classified as having "low or no" affective symptoms.

Three variables were generated to compare independent categories of depression, anxiety, and type 2 diabetes status against our referent group of no diabetes and no affective symptoms. The first contained levels of exposure to depressive symptoms and type 2 diabetes status; the second, exposure to anxious symptoms and type 2 diabetes status; and the third, exposure to comorbid depressive-anxious symptoms and type 2 diabetes status. These variables were mutually exclusive (i.e., the depression-only model excluded individuals who had high anxiety scores, and vice versa). Respective models are illustrated in Supplementary Fig. 1.

Other Variables

Covariates included age, education, waist circumference, physical activity,

smoking, family history of diabetes, antidepressant use, insulin use, and comorbid chronic conditions. Age was included as a continuous variable. Education was classified as having completed any education beyond upper secondary school versus no higher education. Waist circumference was chosen over BMI because of its demonstrated clinical significance in predicting mortality risk beyond BMI (23) and was classified as high if it exceeded 94 cm for men or 79 cm for women. Individuals were classified as physically inactive if they fell below the cutoff of ≥150 min of moderate or ≥60 min of vigorous physical activity per week. Insulin and antidepressant use were reported if taken daily or almost daily within the previous 12 months. Individuals were included in the model as nonsmokers, former smokers, or current smokers, because current and former smoking both have known associations with affective symptoms, diabetes status, and mortality risk (24–26). The presence of any additional chronic condition was included as a binary variable. This included all cancers, cardiac angina, asthma, epilepsy, or any thyroid disease. Alcohol use was not included as a covariate because of its irregular associations with cardiovascular mortality (i.e., it is protective at low levels but acts as a risk factor at high amounts) (27). All exposures and covariates were measured at baseline in 1995–1997.

Statistical Analysis

Cox proportional hazards regression was used to model the risk of dying during the follow-up period associated with each baseline exposure category against the referent unexposed group. Univariate Cox regression was first used to assess the association between exposures and failure time, reported as hazard ratios (HRs). Multivariate Cox regression was then performed using imputation of missing covariate values, under the method of multiple imputation by chained equations. This technique created 30 imputed data sets, from which reported estimates were computed. The amount of data missing was low (1–5%) on almost all covariates.

A test of proportionality indicated no evidence to contradict the proportional hazards assumption in our model variables ($P > 0.05$), and the global fit of the model also indicated a rejection of the null hypothesis ($P = 0.08$) (28). Additional inspection of covariate-adjusted log-log plots for each exposure category indicated no deviations from parallel curves and thus no violation of the proportional hazards assumption. As a result of the simple sampling design of the HUNT survey, analytic weights were not recommended or used. The functional form of the age covariate was specified using restricted cubic splines (according to the Harrell method), to account for the nonlinear relationship between age and mortality (29). All final statistical models were adjusted for or stratified by sex. STATA 14 software was used for all analysis.

RESULTS

The response rate for HUNT2 was 69.5%. Of our 64,177 participants, 1,133 had type 2 diabetes. Differences were observed at baseline between individuals with and without diabetes on most key covariates, specifically age, education, waist circumference, physical activity, smoking, medication use, family history of diabetes, and comorbid chronic conditions (Table 1). The sex distribution was approximately equal in each group.

A total of 13,881 deaths occurred in individuals without diabetes, representing 20.82% of this group. A total of 754 deaths occurred in individuals with diabetes during the 18-year study period, representing more than two-thirds of this group. All key covariates listed above were strong predictors of mortality and were included in the adjusted models. When compared with the "no diabetes/no affective symptom" referent group, the adjusted risk of death was lowest for baseline symptoms of anxiety only, higher for baseline diabetes only, and highest for anxious symptoms comorbid with diabetes (HR 1.20 [95% CI 1.11, 1.30], 1.44 [95% CI 1.26, 1.65], and 1.66 [95% CI 1.25, 2.19], respectively) (Table 2 and Fig. 1). Hazard ratios for the depression exposure followed the same pattern, with slightly larger observed effects (HR 1.27 [95% CI 1.14, 1.41], 1.50 [95% CI 1.32, 1.70], and 2.10 [95% CI 1.41, 3.13], respectively). In the comorbid anxious-depressive exposure, the same pattern was again observed (HR 1.22 [95% CI 1.07, 1.40], 1.44 [95% CI 1.29, 1.60], and 2.01 [95% CI 1.18, 3.00], respectively).

Moderate differences were observed between men and women (Table 2). Specifically, compared with our referent group, the mortality risk in men with diabetes increased in the presence of comorbid depression (HR 3.47 [95% CI 1.96, 6.14]) and depression-anxiety (HR 3.42

Table 1—Baseline sociodemographic and health characteristics of HUNT2 participants, by type 2 diabetes status (*N* = 64,177), 1995–1997

	Individuals without diabetes (*n* = 63,044)	Individuals with type 2 diabetes (*n* = 1,133)	*P* value
Age (years)	49.47 (17.0)	68.31 (11.1)	**<0.001**
Female sex	53.28	50.45	0.100
Education (low)	70.00	90.44	**<0.001**
Mental health symptoms (high)	11.56	17.01	**<0.001**
Depression only	2.16	2.04	
Anxiety only	6.19	10.07	
Depression-anxiety	3.21	4.90	
Waist circumference (high)*	45.34	80.16	**<0.001**
Physical activity (inactive)†	52.43	62.07	**<0.001**
Smoking			
Nonsmoker	43.47	44.65	**<0.001**
Former daily smoker	27.18	39.45	
Current daily dmoker	29.35	15.89	
Family history of diabetes (yes)	14.56	44.80	**<0.001**
Chronic conditions (yes)	21.10	46.59	**<0.001**
Baseline antidepressant use (yes)	2.79	4.00	0.01
Baseline insulin use (yes)	—	18.7	—
Died during follow-up	19.87	65.26	**<0.001**

Data are % or mean (SD). Values in boldface type indicate statistical significance. *Defined as waist circumference ≥94 cm for men, ≥80 cm for women. †Defined as ≤150 min of moderate or ≤60 min of vigorous physical activity per week.

Table 2—HRs for mortality risk over 18 years associated with baseline type 2 diabetes status and comorbid symptoms of anxiety and depression by sex (HUNT2 Study, 1995–2013)

	All (*N* = 64,177)				Women (*n* = 34,116)		Men (*n* = 30,061)	
	Unadjusted HR*	95% CI	Adjusted HR†	95% CI	Adjusted HR†	95% CI	Adjusted HR†	95% CI
T2D and DEP								
No T2D, low DEP	(ref)		(ref)		(ref)		(ref)	
No T2D, high DEP	1.37	1.26, 1.50	1.27	1.14, 1.41	1.26	1.08, 1.46	1.26	1.08, 1.47
T2D, low DEP	1.55	1.41, 1.71	1.50	1.32, 1.70	1.86	1.53, 2.26	1.31	1.10, 1.55
T2D, high DEP	2.76	2.00, 3.84	2.10	1.41, 3.13	1.95	1.22, 2.72	3.47	1.96, 6.14
T2D and ANX								
No T2D, low ANX	(ref)		(ref)		(ref)		(ref)	
No T2D, high ANX	1.30	1.21, 1.38	1.20	1.11, 1.30	1.21	1.08, 1.34	1.20	1.06, 1.34
T2D, low ANX	1.52	1.37, 1.69	1.44	1.26, 1.65	1.82	1.48, 2.25	1.26	1.06, 1.51
T2D, high ANX	1.99	1.57, 2.53	1.66	1.25, 2.19	1.38	0.95, 2.01	2.14	1.41, 3.27
T2D and comorbid DEP-ANX								
No T2D, low DEP-ANX	(ref)		(ref)		(ref)		(ref)	
No T2D, high DEP-ANX	1.37	1.23, 1.56	1.22	1.07, 1.40	1.15	1.05, 1.39	1.27	1.04, 1.53
T2D, low DEP-ANX	1.56	1.45, 1.69	1.44	1.29, 1.60	1.65	1.40, 1.95	1.30	1.12, 1.51
T2D, high DEP-ANX	2.56	1.73, 3.79	2.01	1.18, 3.00	1.14	0.57, 2.29	3.42	1.84, 6.38

ANX, anxious symptoms; DEP, depressive symptoms; DEP-ANX, comorbid depressive and anxious symptoms; T2D, type 2 diabetes. *Adjusted for age and sex. †Adjusted for age, sex, education, waist circumference, physical activity, smoking, antidepressant use, insulin use, family history of diabetes, and comorbid chronic conditions.

[95% CI 1.84, 6.38]), and to a lesser extent comorbid anxiety (HR 2.14 [95% CI 1.41, 3.27]). Compared with having diabetes alone, mortality risk in women increased in the presence of depression (HR 1.86 [95% CI 1.53, 2.26] vs. HR 2.05 [95% CI 1.22, 2.72]), but was lowered in the presence of symptoms of anxiety (HR 1.38 [95% CI 0.95, 2.01]) and comorbid depression-anxiety (HR 1.14 [95% CI 0.57, 2.29]).

These sex differences were more pronounced in the subsample with diabetes, where the presence of all affective symptom types was associated with statistically significant increases in mortality risk in men (Table 3) but not in women (i.e., all 95% CIs included 1). The same overall pattern was also noted in the subsample with diabetes, with excess mortality risk observed to be highest in the presence of depressive symptoms (HR 1.67 [95% CI 1.18, 2.36]), slightly lower in the presence of comorbid depression-anxiety (HR 1.58 [95% CI 1.16, 2.15]), and nonsignificant in the presence of symptoms of anxiety (HR 1.30 [95% CI 0.99, 1.69]) (Table 3).

CONCLUSIONS

Three clear patterns emerged from this large, population-based study of mortality risk associated with type 2 diabetes and comorbid depression and anxiety. First, mortality risk was lowest for affective symptoms alone, higher for diabetes alone, and highest for both combined. Second, excess mortality among those with diabetes was observed to be lowest for anxiety alone, higher for combined depression and anxiety, and highest for depression alone. Third, the effects of mental health symptoms appeared to be stronger in men with diabetes than in women. Overall, the highest risk of death was observed in men with diabetes and concurrent symptoms of depression alone.

The first pattern above illustrates the well-documented effect of mental health comorbidities on chronic disease outcomes. Findings from the World Health Organization World Health Surveys, containing data from more than 60 countries, conclude that the presence of comorbid depression incrementally worsens health more than any other combination of chronic diseases (30). Individuals suffering from chronic medical illness and also comorbid depression or anxiety have significantly higher health-care utilization, functional disability, and work absence than those without (31). Comorbid affective symptoms may magnify the effect of chronic illness through both biological and behavioral mechanisms, including innate immunity and inflammatory processes (e.g., proinflammatory cytokines and C-reactive protein), as well as physical inactivity or social adversity (32). The cognitive burden of diabetes is also suggested to increase low mood and negative thoughts, leading to worse diabetes self-care (33).

The second finding demonstrates different patterns of risk for symptoms of depression and anxiety. Overall, individuals with diabetes and depression had a 110% increased risk of death, compared with a 66% increased risk of death associated with symptoms of anxiety. It is worth noting that symptoms of anxiety alone were associated with increased mortality risk over the long-term, regardless of diabetes status. Despite this, comorbid symptoms of depression-anxiety were not demonstrably more predictive of mortality than depression overall. This finding is supported by literature demonstrating a potentially protective effect of anxiety on mortality risk in the general population (34) and evidence that anxiety can be an independent predictor of health-seeking behaviors (35). The effects of comorbid anxiety on mortality risk may also explain why other research, such as three recent meta-analyses of prospective studies on depression as a risk factor for mortality in diabetes, report lower effect sizes for depression than those observed here (i.e., adjusted HRs of 1.49, 1.50, and 1.76, respectively) (36–38). Few studies account for potentially confounding symptoms of anxiety when quantifying the effect of depression on health outcomes, which may frequently bias these observed effects downward.

Our third finding highlights the differential associations between affective symptoms and mortality in men and

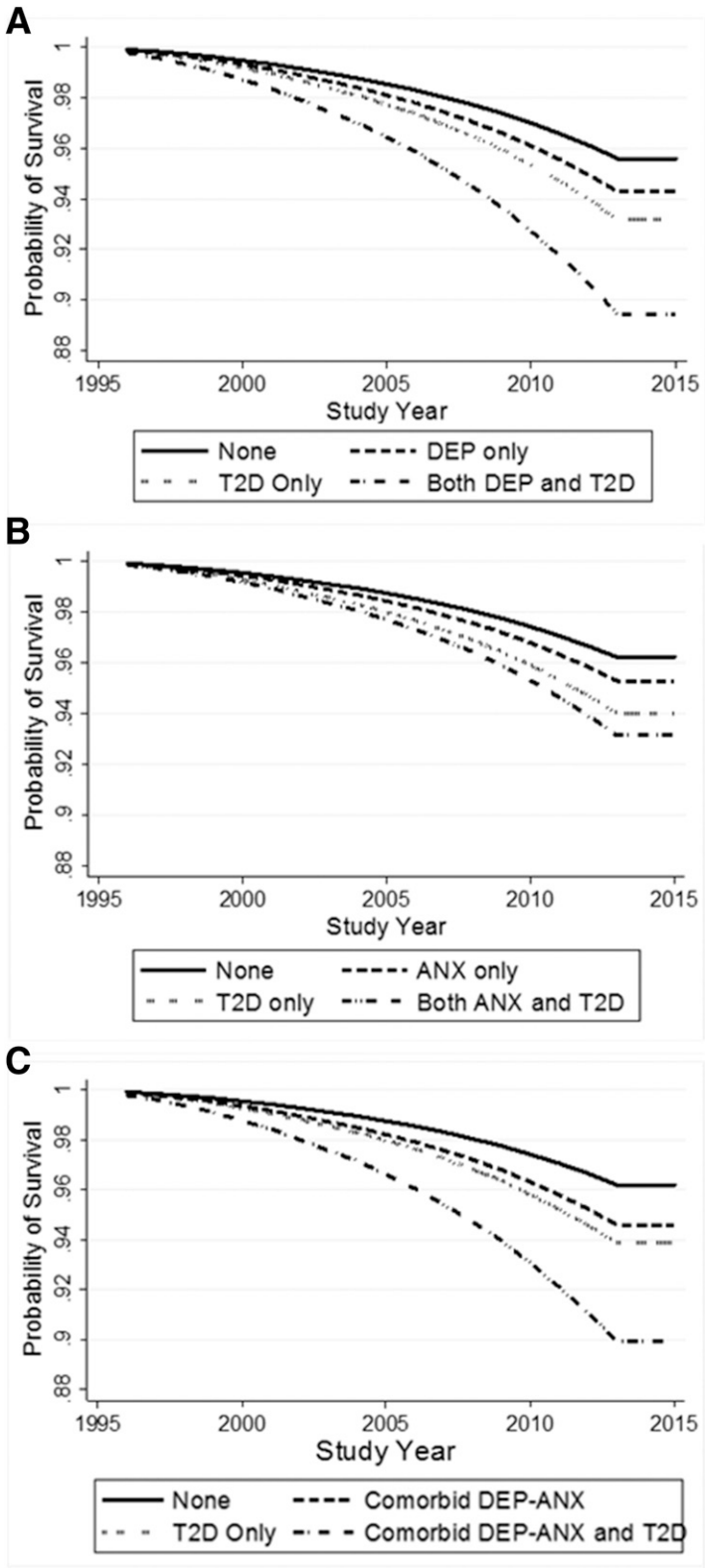

Figure 1—Kaplan-Meier survival curve illustrating adjusted mortality risk over 18 years associated with type 2 diabetes status and baseline symptoms of anxiety and depression (HUNT2 Study, 1995–2013). *A*: Deaths in participants with and without depression (DEP) and type 2 diabetes (T2D). *B*: Deaths in participants with and without anxiety (ANX) and T2D. *C*: Deaths in participants with and without comorbid depression-anxiety (DEP-ANX) and T2D.

women. Notably, although mood disorders are more common in women, affective symptoms in conjunction with diabetes yielded a significant increase in mortality risk only men. These findings are particularly illuminating given the lack of sex-specific results in most studies on mortality and diabetes. A range of patient and health care provider characteristics may affect these outcomes. As mentioned previously, men are less likely to be diagnosed or treated for depression (17) and may also experience greater increases in inflammatory agents in the presence of an anxiety disorder (e.g., C-reactive protein [19]). Another explanation could be that men experience anxiety phenotypes associated with higher functional impairment than women. Sex differences in the prevalence of affective disorders are well documented, but few studies to date have examined sex differences in the clinical features of anxiety or depression.

Despite the large body of evidence supporting links between depression and both mortality and diabetes, drawing a causal conclusion from these findings is not possible for several reasons. Many of the risk factors for type 2 diabetes and affective disorders have complex (i.e., mediating or moderating) relationships with one another. In addition, affective disorders themselves can present as chronic or episodic conditions. Their relationship may alternately be conceptualized as an accumulation of risk over an individual's lifetime through trajectories or chains of risk precipitated by psychiatric symptoms (39). A clearer understanding of anxious symptomatology and its correlates would help to explain the differences observed here as well as to clarify the inconsistent findings around anxiety and mortality that persist in the literature.

Strengths and Limitations

Research based on this survey may not easily generalize to other populations, because Nord-Trøndelag is a rural county that demonstrates little ethnic heterogeneity and a lower prevalence of diabetes compared with most developed countries. As with many cohort studies, the current study design is vulnerable to the presence of unmeasured confounders such as baseline metabolic syndrome or prediabetes status. Similarly, although participation was relatively high, nonparticipation in the study may be linked to

Table 3—Adjusted HRs for mortality risk over 18 years associated with baseline symptoms of anxiety and depression in individuals with type 2 diabetes only, by sex (1995–2013)

	Women (n = 575)		Men (n = 558)		All (N = 1,133)	
Affective symptom type	HR*	95% CI	HR*	95% CI	HR*	95% CI
Depression	1.36	0.86, 2.17	**2.47**	**1.47, 4.17**	**1.67**	**1.18, 2.36**
Anxiety	1.10	0.77, 1.57	**1.63**	**1.08, 2.47**	1.30	0.99, 1.69
Comorbid depression-anxiety	1.28	0.85, 1.93	**2.23**	**1.38, 3.59**	**1.58**	**1.16, 2.15**

Values in boldface type indicate statistical significance at the $P < 0.05$ level. *Adjusted for age, sex, education, waist circumference, physical activity, smoking, antidepressant use, insulin use, family history of diabetes, and comorbid chronic conditions.

mortality. The latter two factors are expected to bias our results toward the null, however, rather than overinflate our estimates.

Another possible limitation of the HUNT data is that symptoms of depression and anxiety were measured by self-report rather than by diagnostic interview. "High" symptom levels defined here may represent subthreshold levels for their respective diagnoses; however, minor depression and subthreshold symptoms have both demonstrated associations with excess mortality comparable with major depression (40). This study also does not consider the duration of diabetes or affective symptoms at baseline, which may have the potential to exert moderating effects on the observed relationships.

Despite these limitations, this study had substantial strengths. These included data on a comprehensive range of confounders and a reliable source for mortality data from a relatively large study population. A generous follow-up time allowed us to illustrate that high baseline levels of affective symptoms are associated with increased mortality spanning 18 years, with pronounced effects in individuals with type 2 diabetes. The inclusion of anxious symptoms allowed us to estimate their associations with mortality risk independently of symptoms of depression. These findings point to the potential usefulness of research examining sex-specific differences in the clinical features of anxiety and depression in individuals with type 2 diabetes.

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