Severe Gastro-oesophageal Reflux Symptoms in Relation to Anxiety, Depression and Coping in a Population-Based Study

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Summary and Introduction

Summary

Background: The association between psychiatric disorders and gastro-oesophageal reflux symptoms is uncertain, and few population-based studies are available.

Aim: To examine the association between psychiatric and psychological factors and reflux symptoms.

Methods: Population-based, cross-sectional, case-control study based on two health surveys conducted in the Norwegian county Nord-Trondelag in 1984-1986 and 1995-1997. Reflux symptoms were assessed in the second survey, including 65 333 participants (70% of the county's adult population). 3153 subjects reporting severe reflux symptoms were defined as cases and 40 210 subjects without symptoms were defined as controls. Data were collected in questionnaires. Odds ratio with 95% confidence intervals were estimated using unconditional logistic regression, in adjusted models.

Results: Subjects reporting anxiety without depression had a 3.2-fold (95% CI: 2.7-3.8) increased risk of reflux, subjects with depression without anxiety had a 1.7-fold (95% CI: 1.4-2.1) increased risk and subjects with both anxiety and depression had a 2.8-fold (95% CI: 2.4-3.2) increased risk, compared to subjects without anxiety/depression. We observed a weak inverse association between one measure of covert coping and risk of reflux and a weak positive association between another coping measure and risk of reflux.

Conclusions: This population-based study indicates that anxiety and depression are strongly associated with reflux symptoms, while no consistent association regarding coping and reflux was found.

Introduction

Gastro-oesophageal reflux disease (GERD) is a common health problem, affecting about 10-20% of adult populations at least weekly in the Western world.[1-3] GERD is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications,[4] and the cardinal symptoms of GERD are heartburn and acid regurgitation.[5] Frequent or severe reflux symptoms are associated with a substantial risk of morbidity, including oesophageal adenocarcinoma,[6,7] impaired health-related quality of life[8,9] and reduced work productivity.[10,11]

High body mass index (BMI)[2,3,12-14] and tobacco smoking[2,13,15,16] have consistently been associated with an increased prevalence of GERD, but the aetiology of this disease remains incompletely understood.[13] Thus, identifying further modifiable risk factors associated with GERD could be of considerable public health importance.[14]

Anxiety and depression are the most common psychiatric disorders among the adult population in the Western world.[17] These disorders are often found co-existing with chronic medical conditions such as cardiovascular disease and diabetes mellitus, and there is an increasing focus on the interplay between anxiety, depression and medical illness.[18] These psychiatric disorders may negatively influence somatic illness, and many diseases increase the risk of suffering from depression and anxiety.[18] Psychological factors and psychiatric disorders may similarly influence gastrointestinal disorders, such as GERD,[19,20] but the relation between these factors and reflux disease is largely uninvestigated.[21,22] Most previous studies have been performed under laboratory experimental conditions in clinical settings, and did not consider everyday situations or include a comparison group of individuals without GERD.[19] To understand the association between psychiatric disorders and GERD population-based studies are needed, as samples recruited among patients constitute selected groups.[23] Similarly, no population-based studies have examined the association between psychological factors such as coping and GERD. Coping has been suggested as an important factor between stressful events and outcomes such as depression, psychological symptoms and somatic illness[24] and it has been hypothesized that psychosocial factors that arouse anger may cause illness, particularly if a subject is not allowed to show anger or to deal constructively with the factor that provoked it.[25]

The aim of this study was to examine the association between psychiatric and psychological factors and reflux symptoms using a large Norwegian population-based case-control study.

Material and Methods

Study Design

The design of our cross-sectional case-control study has been described in detail elsewhere.[12] Briefly, the Nord-Trondelag Health Study consists of two large population-based health surveys performed in the Norwegian county of Nord-Trondelag in 1984-1986 (Helseundersokelse i Nord-Trondelag, HUNT 1) and in 1995-1997 (HUNT 2).[26] The residents of Nord-Trondelag are essentially representative of the Norwegian population as a whole.[27] HUNT 2 included 65 333 county residents of ages 20 years or older (70% of those 92 808 eligible to participate in the study), and 47 556 subjects participated in both HUNT 1 and HUNT 2. Data were collected in questionnaires and through physical examinations. Informed consent was obtained from each participant. The research was approved by the Regional Committee for Medical Research Ethics, Region IV, Norway. The Norwegian Data Inspectorate approved the establishment of a research register.

Definition of Reflux Symptoms, Cases and Controls

In this study, reflux symptoms were defined as severe symptoms of recurrent heartburn or acid regurgitation, and this information was assessed in HUNT 2 only. The participants were asked to report their experience of such symptoms during the past 12 months, and the response alternatives were: (i) no symptoms, (ii) minor symptoms and (iii) severe symptoms. Of the 58 596 subjects (90%) answering this question, the 3153 subjects (5%) reporting

severe reflux symptoms were defined as cases and the 40 210 subjects (69%) reporting no such symptoms were defined as controls.[12] The 15 233 subjects (26%) reporting minor symptoms were excluded from the study, an exclusion based on our validation study described in detail previously,[12] where we found that misclassification of the outcome was high in this group. In the validation study we further found that 95% of the patients with severe reflux symptoms (corresponding to our case group) had experienced reflux symptoms at least once weekly, resulting in a high specificity (99%) for reflux symptoms occurring at least once a week in our case group.[12]

Data on Psychiatric Disorders and Psychological Factors

Data on anxiety and depression were included in both HUNT 2 and HUNT 1, while data on coping were included in HUNT 2 only.

Anxiety and Depression. Anxiety involves feelings of fear, worry and apprehension, while depression is associated with feelings of sadness, sorrow, hopelessness and gloom.[28] The Hospital Anxiety and Depression Scale (HADS) is a widely used self-assessment scale originally designed for detecting depression and anxiety among hospital medical out-patients.[18,28,29] HADS is a validated measure that performs well in screening for the separate dimensions of anxiety and depression, but also as a measure of co-morbid anxiety and depression.[18,28,30] HADS consists of two subscales, the anxiety subscale (HADS-A) and the depression subscale (HADS-D). Each subscale consists of seven items, and each item has a 4-point ordinal scale describing symptom severity, ranging from 0 (not present) to 3 (maximum). These scales are summarized into total scores, and sum score ranges from 0 to 21 on HADS-A and HADS-D, respectively. Possible diagnosis of anxiety and depression is defined by a score of 8 or above on each subscale.[23,28,31]

We examined three exposure groups based on HUNT 2 data; (i) anxiety (HADS-A ≥ 8), (ii) depression (HADS-D ≥ 8) and (iii) combined anxiety and depression (HADS-A ≥ 8 and HADS-D ≥ 8).[32] The HUNT 2 questionnaire included 14 HADS items regarding the participant's feelings during the last week.

First, the total score for each of the two different subscales was dichotomized and analysed separately as:

   a.   (i) no anxiety (score 0-7, reference group) and (ii) anxiety (score ≥8) and

   b.   (i) no depression (score 0-7, reference group) and (ii) depression (score ≥8).

Secondly, the total score for each subscale was categorized into three categories, with the third category set to the 99th percentile of the study population, i.e. anxiety and depression 'high-risk groups'.[33] Thus, these variables were categorized as: (i) no anxiety/no depression (score 0-7, reference group), (ii) anxiety/depression (score 8-12) and (iii) high-risk anxiety/high-risk depression (score 13-21).

Finally, combined anxiety and depression was analysed in one variable and categorized as: (i) no anxiety or depression (reference group), (ii) anxiety without depression, (iii) depression without anxiety and (iv) both anxiety and depression.

The Hospital Anxiety and Depression Scale was not included in HUNT 1, but four questions concerning symptoms of anxiety and depression, addressing issues of nervousness, calmness, mood and vitality during the last month, were included in both HUNT 1 and HUNT 2. These items could not differentiate sufficiently between anxiety and depression, however. Therefore, in a previous HUNT study, Bjerkeset and colleagues validated a compound index (i.e. anxiety and depression index) based on these four items against HADS in the total HUNT 2 population.[31] Cut-offs of the total index score were set to the 88th percentile of the HUNT 2 study population to match HADS cut-offs. This provided an acceptable indicator whether psychiatric caseness was present in HUNT 1.[31] Thus, we added four items included in HUNT 1 into a total score (sum score range: 0-18) that was dichotomized into: (i) no anxiety or depression (score 0-7, reference group) and (ii) anxiety and depression (score ≥8).

The total anxiety and depression score was further categorized into three categories, with the third category set to the 99th percentile of the study population.[33] Thus, this variable was categorized as: (i) no anxiety or depression (score 0-7, reference group), (ii) anxiety and depression (score 8-10) and (iii) high-risk anxiety and depression (score 11-18).

Subjects not answering all questions that were part of the anxiety and depression indices were excluded from the analyses.

Coping. Two different coping styles in relation to anger control have been defined; open coping, primarily directed towards the aggressor and covert (or passive) coping, directed inwards or towards others.[25]

The HUNT 2 questionnaire contained two items, previously employed and derived from epidemiological studies of hypertension,[25] where the study participant was asked to describe his or her response in relation to two statements. The first statement concerned how the participant expressed his or her anger, and if other people knew whether they were angry. Covert coping was indicated by the response alternatives 'almost never' or 'sometimes', while overt coping was indicated by 'rather often' or 'almost always'. The second statement dealt with whether the participant when boiling with rage, did not show this rage to other people. The response alternatives 'rather often' or 'almost always' indicated covert coping, and 'almost never' or 'sometimes' indicated overt coping. We dichotomized these two variables into: (i) overt coping (reference group) and (ii) covert coping.

Statistical Analyses

We used odds ratios (OR) and 95% confidence intervals (CI), estimated by unconditional logistic regression,[34] to assess the association between anxiety, depression and coping and risk of reflux symptoms. Data were analysed using the PROC GENMOD procedure in SAS.[35] Each psychiatric or psychological factor was evaluated separately in crude models and in models adjusted for variables known *a priori* to be independently associated with risk for reflux symptoms, i.e. age (in 10-year age groups), sex, tobacco smoking [duration in years of daily smoking in three categories: (i) never or <1 year (reference group), (ii) 1-9 years and (iii) ≥10 years], BMI [kg/m^2, in four categories based on the World Health Organization (WHO) classification of overweight and obesity: (i) <25 (reference group), (ii) 25-30 (overweight), (iii) 31-35 (obesity) and (iv) >35 (severe obesity)], and socioeconomic status based on education [in three categories: (i) high education (reference group), (ii) medium education and (iii) low education]. These variables were cross-sectional except for tobacco smoking, where lifetime exposure was assessed. Observations with missing data on any of the covariates included in the

models were excluded from the analyses. Exposures including three categories were evaluated using the Wald test, which considers all categories of the variable and not just pairwise comparisons with the reference category.

Results

Characteristics of the Study Participants

Some characteristics of the 3153 case participants and the 40 210 control participants are presented in Table 1 . There were 30 188 (2378 cases and 27 810 controls) participants in both HUNT 2 and HUNT 1. The case participants were on average slightly older than the control participants, while the distribution of men and women was similar between the groups. Tobacco smoking (≥10 years), obesity (BMI > 30) and a low educational level (≤10 years) were more common among the cases (51%, 27% and 77%, respectively) than among the controls (39%, 12% and 64%, respectively) (Table 1).

Distribution of Psychiatric and Psychological Factors

The number of missing observations for the psychiatric/psychological variables was fairly large, but there were no major differences between the cases and controls; 983 cases (31%) and 10 528 controls (26%) had missing data on the anxiety variables (HUNT 2 data), 738 cases (23%) and 8576 controls (21%) had missing data on the depression variables (HUNT 2 data), 1269 cases (40%) and 17 723 controls (44%) had missing data on the anxiety and depression variables (HUNT 1 data), and 32-35% cases and 29-32% controls had missing data on the coping items.

Presence of anxiety and depression was higher among the case participants (27% and 18%, respectively, HUNT 2 data) than among the control participants (12% and 8%, respectively, HUNT 2 data). Presence of combined anxiety and depression was also more common among the cases (11%, HUNT 2 data) than among the controls (4%, HUNT 2 data), with a similar tendency seen regarding HUNT 1 data. The distribution of covert coping was similar between the cases and the controls (Table 2).

Associations Between Psychiatric and Psychological Factors and Reflux Symptoms

The results from the crude and adjusted models are presented in Table 2 . Both anxiety and depression were associated with increased risks of reflux symptoms. We found significant associations between anxiety analysed separately (OR 2.9, 95% CI: 2.6-3.2, adjusted model, HUNT 2 data), and depression analysed separately (OR 2.2, 95% CI: 1.9-2.4, adjusted model, HUNT 2 data) and an increased risk of reflux symptoms. In the analyses including high-risk anxiety and depression groups strong dose-response associations were observed. Subjects in the high-risk anxiety group had a more than fourfold increased risk of reflux symptoms (OR 4.3, 95% CI: 3.5-5.4, adjusted model, HUNT 2 data), while subjects in the high-risk depression group had an almost threefold increased risk of reflux symptoms (OR 2.9, 95% CI: 2.2-4.0, adjusted model, HUNT 2 data; Table 2). Similarly, subjects reporting anxiety without depression had a more than threefold increased risk of reflux symptoms (OR 3.2, 95% CI: 2.7-3.8, adjusted model, HUNT 2 data), subjects with depression without anxiety had a nearly twofold increased risk of reflux symptoms (OR 1.7, 95% CI: 1.4-2.1, adjusted model, HUNT 2 data) and subjects with both anxiety and depression had a nearly threefold increased risk of reflux symptoms (OR 2.8, 95% CI: 2.4-3.2, adjusted model, HUNT 2 data), compared to subjects without reported anxiety or depression (Table 2). A significant association of similar strength was observed between combined anxiety and depression and an increased risk of reflux symptoms also in the model based on HUNT 1 data (OR 2.6, 95% CI: 2.3-2.9, adjusted model), and a dose-response association was observed in the analysis including the high-risk group with an almost fourfold increased risk for reflux symptoms seen among subjects in the high-risk anxiety and depression group (OR 3.8, 95% CI: 3.1-4.7, adjusted model, HUNT 1 data; Table 2).

We observed a weak inverse association between one measure of covert coping and risk of reflux symptoms (OR 0.8, 95% CI: 0.7-0.9, adjusted model), while a weak positive association was observed between the other measure of covert coping and risk of reflux symptoms (OR 1.2, 95% CI: 1.0-1.4, adjusted model; Table 2).

The risk estimates for all studied variables were approximately similar in the crude models and in the models adjusted for age, sex, smoking, BMI and socioeconomic status (Table 2).

Discussion

This study provides evidence of a strong dose-response association between anxiety and depression and an increased risk of reflux symptoms, while no consistent association was observed between covert coping and reflux symptoms.

The population-based design and the high participation rates, acting against selection bias, the large sample size and the ability to adjust for many potential confounders are among the strengths of our study. Weaknesses include the cross-sectional study design, as the analyses were based on prevalent, not incident, reflux cases, although the assessment referred to reflux symptoms experienced during the last year. Thus, the temporal, and hence causal, association between the studied psychiatric factors and reflux symptoms is not possible to establish. Yet, the data regarding anxiety and depression were collected at two points in time. The assessment of reflux symptoms was self-reported and misclassification of the outcome might have been introduced. Moreover, as this population-based study did not include endoscopy data, we could not examine separate associations regarding erosive oesophagitis, non-erosive reflux disease or functional heartburn. However, heartburn and acid regurgitation, the symptoms used for case classification, are regarded as the hallmark symptoms of reflux and the use of questionnaires to assess these symptoms is a well-validated measure of the true occurrence of reflux.[5,36,37] Moreover, in our validation study we found a very high specificity for reflux symptoms in the HUNT questionnaire compared to a more extensive questionnaire.[12] Another weakness is the lack of data regarding current antireflux treatment. However, it is unlikely that study participants having severe enough reflux symptoms to be on regular antireflux treatment would report lack of reflux symptoms during an entire 1-year period. This is supported by our validation study and our previous study using a reflux questionnaire, where we found that a majority of individuals who used antireflux medication still reported severe reflux symptoms.[7,12] There might be a risk of biased selection of functional reflux, but our strict definition of case subjects as only those with severe and specific symptoms of heartburn or acid regurgitation should act against such bias. Exposure misclassification is another potential limitation of our study, but the assessment of self-reported anxiety and depression was based on well-validated measures[28] and the assessment of coping has been employed in other studies.[25] However, chronic anxiety and depression could not be measured in this study as only the study participant's feelings during the last week or month were assessed. Possible differential reporting among cases and controls might have been introduced if reflux cases over reported symptoms of anxiety and depression. However, the study participants were unaware of reflux symptoms as a specific outcome in this large health study, and of our hypotheses regarding reflux symptoms and psychiatric factors. Thus, any potential

misclassification is likely to be non-differential, and should not explain our positive findings, but rather dilute the effects as it introduces bias towards the null.[38]

Our finding of positive associations between anxiety and depression and increased risks of reflux symptoms is consistent with some previous cross-sectional population-based studies of smaller sample sizes[2,39,40] and with hospital-based studies.[19,21] Furthermore, in a previous study based on HUNT data where mild and severe reflux symptoms were combined, positive, although weaker, associations between anxiety, depression and reflux symptoms were observed.[23] Our finding of stronger associations is probably due to the strict definition of reflux used in our study. However, in both studies the association between anxiety and reflux symptoms was the strongest.

As the pattern of causality is difficult to assess in this cross-sectional case-control study, there are several potential explanations for a link between psychiatric disorders and reflux symptoms. One explanation is that reflux symptoms may result in anxiety and depression,[19,23,39,40] as a consequence of worry over and being bothered by reflux symptoms over time.[22,23] Furthermore, psychological and psychiatric factors may influence an individual's perception of reflux symptoms,[19] and result in a lower threshold for bodily sensation[21] and alter the way oesophageal stimuli are perceived and reported.[41] Thus, anxiety and depression may exacerbate the sensation of reflux symptoms.[19] Hence, subjects with anxiety and depression may be more likely to report reflux symptoms or seek medical consultation,[23,40] However, in a previous population-based study, the increased prevalence of anxiety and depression was similar between reflux patients who sought medical consultation and those who did not.[40] Finally, psychiatric and psychological factors may truly increase the risk of reflux symptoms.[21,23,40] This is supported by our consistent finding of strong dose-response associations regarding both HUNT 1 and HUNT 2 data, which provides some evidence against reversed causality or co-existing morbidity. Psychologically adverse factors may promote reflux symptoms by decreasing the pressure of the lower oesophageal sphincter,[19] changing the oesophageal motility,[19] increasing the secretion of gastric acid[41] or delaying the clearance of acid from the oesophagus.[41] Moreover, psychiatric disorders may indirectly influence the oesophagus through the effect of different psychiatric medications.[21] A common side-effect of such medications, notably selective serotonin re-uptake inhibitors, is gastrointestinal symptoms[23] and impairment of oesophageal motility.[21] Furthermore, benzodiazepines can lower pain threshold and may alter perception of reflux symptoms. Therefore, a weakness of our study is that no information regarding specific psychiatric medications was available. However, in a previous study, no association between psychiatric medications and reflux symptoms was observed[21] and prior studies indicate that a majority of individuals affected by depression and anxiety do not seek medical care and therefore are untreated.[17] Hence, clinical samples of subjects with depression or anxiety disorders are likely to include more severely ill subjects who use psychiatric medications to a greater extent than subjects with these disorders in population-based samples.[17] Another potential explanation for anxiety and depression increasing the risk of reflux symptoms is a self-abusive lifestyle, as psychiatric disorders may be associated with adverse lifestyle factors such as smoking or obesity.[21] In this study, the associations between anxiety and depression and reflux symptoms were not influenced by such known risk factors for reflux, however. Hence, there seems to be a complex interplay between anxiety and depression and reflux symptoms,[19,40] and the link between psychiatric factors and gastro-oesophageal reflux may be bidirectional.

The findings in our study may be of clinical relevance, as among a subgroup of patients reflux treatment may also improve a subject's psychology.[19] It has been shown that surgical correction for reflux symptoms also improved mental health in reflux patients.[19]

In conclusion, this large population-based study reveals a strong link between anxiety and depression and reflux symptoms, which is not explained by other factors associated with reflux symptoms such as tobacco smoking or obesity.

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Table 1. Characteristics of Study Participants with Reflux Symptoms (Cases) and Without Reflux Symptoms (Controls)

	Cases, *n* (%)	Controls, *n* (%)
Number of participants*	3153	40 210
Age groups (years; HUNT 2)		
19-29	302 (10)	6475 (16)
30-39	526 (17)	7936 (20)
40-49	655 (21)	8828 (22)
50-59	589 (19)	6721 (17)
60-69	536 (17)	4981 (12)
70-79	394 (12)	3939 (10)
80+	151 (5)	1330 (3)
Sex (HUNT 2)		
Male	1555 (49)	18 814 (47)
Female	1598 (51)	21 396 (53)
Tobacco smoking† (years; HUNT 2)		
Never or <1	1072 (34)	18 285 (45)
1-9	282 (9)	3952 (10)

≥10	1594 (51)	15 638 (39)
Missing	205 (6)	2335 (6)
Body mass index‡ (HUNT 2)		
<25	753 (24)	18 356 (46)
25-30 (overweight)	1546 (49)	16 675 (41)
31-35 (obesity)	646 (20)	4194 (10)
35+ (severe obesity)	208 (7)	985 (2)
Education§ (HUNT 2)		
High (>13 years)	353 (11)	9020 (22)
Medium (11-13 years)	199 (6)	4227 (11)
Low (≤10 years)	2437 (77)	25 594 (64)
Missing	164 (5)	1369 (3)

*58 596 of 65 333 participants answered the reflux question in HUNT 2. Missing observations (6737 subjects) for the reflux question and 15 233 subjects reporting minor reflux symptoms were excluded from the study. 3153 subjects reporting severe reflux symptoms represent the case group, 40 210 subjects reporting no symptoms represent the control group;
†Duration of daily smoking in years;
‡BMI calculated as body weight in kilograms divided by the square of body height in meters (kg/m^2). Cut-offs predetermined according to World Health Organization classification;
§1 question: 'What education is the highest you have completed?', 5 response alternatives categorized into high, medium or low education.

Table 2. Anxiety, Depression and Coping in Relation to Reflux Symptoms

	Cases*, *n* (%)	Controls†, *n* (%)	Crude OR (95% CI)	Adjusted OR‡ (95% CI)
Anxiety§ (HUNT 2)				
Absence of anxiety (score 0-7)	1474 (73)	24 513 (88)	1.0 (reference)	1.0 (reference)
Presence of anxiety (score ≥8)	548 (27)	3239 (12)	2.8 (2.5-3.1)	2.9 (2.6-3.2)
Anxiety, 3 categories (HUNT 2)				
Absence of anxiety (score 0-7)	1474 (73)	24 513 (88)	1.0 (reference)	1.0 (reference)
Presence of anxiety (score 8-12)	427 (21)	2789 (10)	2.5 (2.3-2.9)	2.6 (2.3-2.9)
High-risk anxiety (score 13-21)	121 (6)	450 (2)	4.5 (3.6-5.5) *P*-value: <0.0001¶	4.3 (3.5-5.4) *P*-value: <0.0001
Depression** (HUNT 2)				
Absence of depression (score 0-7)	1813 (82)	26 956 (92)	1.0 (reference)	1.0 (reference)
Presence of depression (score ≥8)	401 (18)	2368 (8)	2.5 (2.2-2.8)	2.2 (1.9-2.4)
Depression, 3 categories (HUNT 2)				
Absence of depression (score 0-7)	1813 (82)	26 956 (92)	1.0 (reference)	1.0 (reference)
Presence of depression (score 8-12)	342 (15)	2110 (7)	2.4 (2.1-2.7)	2.1 (1.8-2.3)
High-risk depression (score 13-21)	59 (3)	258 (1)	3.4 (2.6-4.5) *P*-value: <0.0001	2.9 (2.2-4.0) *P*-value: <0.0001
Anxiety and depression†† (HUNT 2)				
Absence of anxiety or depression	1316 (67)	22 891 (85)	1.0 (reference)	1.0 (reference)
Presence of anxiety, not depression	309 (16)	2083 (8)	3.6 (3.1-4.2)	3.2 (2.7-3.8)
Presence of depression, not anxiety	119 (6)	1006 (4)	2.1 (1.7-2.5)	1.7 (1.4-2.1)
Presence of both anxiety and depression	222 (11)	1067 (4)	2.6 (2.3-2.9)	2.8 (2.4-3.2)
Anxiety and depression‡‡ (HUNT 1)				
Absence of anxiety/depression (score 0-7)	1073 (64)	16 836 (83)	1.0 (reference)	1.0 (reference)
Presence of anxiety/depression (score ≥8)	606 (36)	3541 (17)	2.7 (2.4-3.0)	2.6 (2.3-2.9)
Anxiety and depression, 3 categories (HUNT 1)				
Absence of anxiety/depression (score 0-7)	1073 (64)	16 836 (83)	1.0 (reference)	1.0 (reference)
Presence of anxiety/depression (score 8-10)	472 (28)	3022 (15)	2.4 (2.2-2.7)	2.4 (2.1-2.7)

High-risk anxiety/depression (score 11-18)	134 (8)	519 (2)	4.1 (3.3-4.9) *P*-value: <0.0001	3.8 (3.1-4.7) *P*-value: <0.0001
Coping §§ (HUNT 2*)*				
Overt coping (unexposed)	206 (10)	2282 (9)	1.0 (reference)	1.0 (reference)
Covert coping (exposed)	1794 (90)	24 505 (91)	0.8 (0.7-0.9)	0.8 (0.7-0.9)
Coping ¶¶ (HUNT 2)				
Overt coping (unexposed)	1647 (86)	21 872 (85)	1.0 (reference)	1.0 (reference)
overt coping (exposed)	278 (14)	3765 (15)	1.0 (0.9-1.1)	1.2 (1.0-1.4)

HADS, Hospital Anxiety and Depression Scale.
*Cases defined as subjects with severe reflux symptoms;
†Controls defined as subjects without reflux symptoms.;
‡ORs adjusted for age, sex, smoking, BMI and education;
§Anxiety, HADS-scale, seven items. 983 cases (31%) and 10 528 controls (26%) had missing data on the anxiety variable;
¶Wald test of overall effect across all exposure strata; ** Depression, HADS-scale, seven items. 738 cases (23%) and 8576 controls (21%) had missing data on the depression variable;
††Anxiety and depression, HADS-scale, 14 items. 1049 cases (33%) and 11 338 controls (28%) had missing data on this variable;
‡‡Anxiety and depression, four items. 1269 cases (40%) and 17 723 controls (44%) had missing data on this variable. Anxiety and depression, four items. 1269 cases (40%) and 17 723 controls (44%) had missing data on this variable;
§§1 item: 'I express my anger, and other people know that I am angry', 4 response alternatives categorized into overt and covert coping. 1014 cases (32%) and 11 702 controls (29%) had missing data on this variable;
¶¶1 item: 'I am boiling with rage, but I do not show it to other people', 4 response alternatives categorized into overt and covert coping. 1092 cases (35%) and 12 887 controls (32%) had missing data on this variable.

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