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Anxiety after coeliac disease diagnosis predicts mucosal healing: a population-based study

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Summary

Background: Coeliac disease has been linked to anxiety and depression. However, their association with mucosal healing is unknown.

Aim: To examine the relationship between anxiety, depression and mucosal healing in coeliac disease.

Methods: Between 1969 and 2008, we collected data on all small intestinal biopsies with villous atrophy from Sweden's 28 pathology departments. We restricted our cohort to individuals with data on follow-up biopsy (either persistent villous atrophy [n = 3317] or mucosal healing [n = 4331]). Through Cox regression, we estimated hazard ratios (HRs) for anxiety or depression.

Results: During follow-up, 123 (2.8/1000 person-years) individuals with mucosal healing had developed anxiety, compared to 94 (2.1/1000 person-years) with persistent villous atrophy. Mucosal healing was hence associated with a higher risk of future anxiety (HR = 1.49; 95% CI = 1.12-1.96). Similarly, 167 (3.8/1000 person-years) individuals with mucosal healing developed depression, compared to 148 (3.3/1000 person-years) with persistent villous atrophy, corresponding to a HR of 1.25 (95% CI = 0.99-1.59). Mucosal healing was more common in individuals with prior diagnoses of anxiety or depression before follow-up biopsy. Anxiety diagnosed between diagnostic and follow-up biopsy for coeliac disease was associated with an almost nine-fold increased chance of mucosal healing (odds ratio = 8.94; 95%CI = 2.03-39.27).

Conclusion: Anxiety and depression are more common in coeliac disease patients with mucosal healing, both before and after follow-up biopsy, an association potentially mediated through more vigilant compliance with a gluten-free diet. This finding raises concern that achieving the goal of mucosal healing may come at a cost of an increased risk of mood disorders.

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1 | INTRODUCTION

Coeliac disease is an immune-mediated disorder triggered by the exposure to gluten in genetically predisposed individuals.[1] While the presence of HLA DQ2/DQ8 is a prerequisite for coeliac disease,[2] other factors likely contribute to disease development.[3]

Coeliac disease has been linked to a range of complications and comorbidities,[4-6] with most[7] but not all[8] studies finding an excess mortality rate compared to the general population. Observations of a link between small intestinal disease (including coeliac disease) and psychiatric disease were made as far back as 1970, by Goldberg[9] This report has since been followed by several studies[10] indicating a link to depression,[11-16] anxiety, eating disorders,[17,18] and even suicide.[19,20] When Smith and Gerdes reviewed the evidence up until 2012 (18 studies on depression and 11 on anxiety), they found a positive association of coeliac disease with depression, but not with anxiety.[21]

The gluten-free diet (GFD) is currently the only available treatment in coeliac disease,[1] the aim being to achieve mucosal healing, but also to decrease symptoms.[22]

In a national cohort of more than 7000 individuals with coeliac disease and follow-up biopsy we have previously shown that mucosal healing may decrease the risk of certain complications such as lymphoproliferative cancer and hip fractures.[23,24] However, as mucosal healing is closely associated with strict GFD adherence, adhering to the diet may in itself influence the quality of life.[25,26] The direction in which mucosal healing in coeliac disease affects the risk of future anxiety and depression is unclear. While we are unaware of any study exploring the association between anxiety and depression and mucosal healing in coeliac disease, Bosch et al have previously shown that mucosal wound healing is delayed in individuals with depressive symptoms.[27] In another gastrointestinal disorder, inflammatory bowel disease (IBD), it has recently been demonstrated that anxiety and depression are tightly linked to IBD activity.[28]

For these reasons, we carried out a population-based study examining the risk of anxiety, depression and their treatment according to follow-up histology among individuals with coeliac disease. As a secondary aim, we examined if the presence of these psychiatric disorders could predict mucosal healing.

2 | METHODS

2.1 | Study sample: patients with coeliac disease undergoing repeated biopsy

In the years 2006-2008, we requested all small intestinal biopsy reports from Sweden's 28 Swedish pathology departments. We obtained information on date of biopsy and personal identity number[29] for biopsies that took place in 1969-2008 (Table 1). The purpose of the data collection was to identify individuals with coeliac disease (here equalled to villous atrophy, Villous atrophy [Marsh III[30]]). Details on the data collection have been published elsewhere,[31] and our initial cohort included 29 096 patients with coeliac disease. The study was approved by the Research Ethics Review Board in Stockholm, Sweden on 14 June 2006. Since this was a strictly register-based study informed consent was waived by the Review Board.[32]

In this study, data were restricted to those with a biopsy within the specified time frame of 0.5-5 years after the first diagnostic biopsy (n = 7648) (in case patients had more than one biopsy, the first in this time span was used). Patients with Marsh III at follow-up biopsy were classified as having persistent villous atrophy, while those with a less severe histopathology were classified as having achieved mucosal healing.

On average, biopsy reports were based on three tissue specimens submitted during the follow-up endoscopy.[33] In the Swedish setting, villous atrophy is rarely due to other causes than coeliac disease, and a patient chart review of 114 individuals with a record of villous atrophy confirmed the coeliac disease diagnosis in 108 (95%) patients. This is actually a higher positive predictive value than for physician-assigned diagnoses of coeliac disease in the Swedish Patient Register.[31,34]

2.2 | Diagnosis of anxiety and depression and retrieval of medications data for prediction and outcome

International classification of disease (ICD) codes was used to define anxiety and depression from the Swedish Patient Register.[35] Psychotropic drugs were defined as having a relevant Anatomic Therapeutic Chemical-code in the Swedish Prescribed Drug Register (Appendix 1).

2.3 | Statistical analyses

We used Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CIs) of subsequent diagnoses of anxiety or depression among individuals with persistent villous atrophy vs individuals with mucosal healing on follow-up biopsy. Follow-up time started from the day of the follow-up biopsy and ended on the date of death, emigration, outcome or 31 December 2009, whichever came first. We performed similar Cox analyses where different medications (described above) were set as the outcomes; these analyses were restricted to individuals diagnosed with coeliac disease from July 2005 and onwards, to align with the start of data collection of the Swedish Prescribed Drug Register.[36] As a sensitivity analysis, we also examined the HR of a first ever (incident or new onset) diagnosis of anxiety or depression according to follow-up biopsy. We used log-minus-log curves to test the proportional hazards assumption. We used conditional logistic regression to evaluate the impact of anxiety and depression at any time before follow-up biopsy and between first (diagnostic) and second (follow-up) biopsies on the probability of mucosal healing. We also examined the impact of psychotropic medications before and in-between biopsies in a similar way.

TABLE 1 Characteristics of patient cohort with coeliac disease and follow-up biopsies

Characteristic	Full cohort			Cohort restricted to the years 2005-2009		
	Mucosal healing, n (%)	Persistent villous atrophy, n (%)	*P*-value (χ^2)	Mucosal healing, n (%)	Persistent villous atrophy, n (%)	*P*-value (χ^2)
Total number	4331	3317		418	155	
Characteristics of included patients						
Age at diagnosis of coeliac disease (y)						
0-19	2130 (49)	1379 (42)	<0.01	154 (37)	26 (17)	<0.01
20-39	868 (20)	499 (15)		111 (27)	26 (17)	
40-59	855 (20)	823 (25)		97 (23)	42 (27)	
≥60	478 (11)	616 (19)		56 (13)	61 (39)	
Male	1548 (36)	1268 (38)	0.03	149 (36)	54 (35)	0.86
Female	2783 (64)	2049 (62)		369 (64)	101 (65)	
Interval between diagnosis and follow-up biopsy						
6 mo-1 y	1006 (23)	1018 (31)	<0.01	170 (41)	84(54)	0.01
>1 to <2 y	2101 (49)	1328 (40)		234 (56)	66 (43)	
2-5 y	1224 (28)	971 (29)		14 (3)	5 (3)	
Calendar period of first biopsy						
≤1989	357 (8)	717 (23)	<0.01	All after 2000		
1990-1999	1637 (38)	1637 (49)				
≥2000	2337 (54)	963 (29)				
Level of education						
Missing data	78 (2)	80 (2)	<0.01	5 (1)	1 (0.7)	<0.01
<2 y of high school	975 (23)	1042 (31)		62 (15)	40 (26)	
2 y of high school	858 (20)	689 (21)		70 (17)	39 (25)	
3 y of high school	919 (21)	695 (21)		94 (22)	31 (20)	
College/University	1501 (35)	811 (24)		187 (45)	44 (28)	
Number of individuals with anxiety and depression diagnoses in different time frames						
Anxiety after follow-up biopsy	123 (3)	94 (3)	0.98	Analyses were not run separately for this group		
Anxiety between diagnostic and follow-up biopsy	22 (0.5)	2 (<0.1)	<0.01			
Anxiety before follow-up biopsy, including time before diagnostic biopsy	41 (1)	14 (0.4)	<0.01			
Depression after follow-up biopsy	167 (4)	148 (4)	0.18			
Depression between diagnostic and follow-up biopsy	30 (0.7)	126 (0.5)	0.24			
Depression before follow-up biopsy, including time before diagnostic biopsy	85 (2)	50 (2)	0.13			
Number of individuals with prescriptions of different types of medications						
Antidepressants after follow-up biopsy	Analyses were not run for the entire cohort due to lack of medication data before 2005			66 (16)	33 (21)	0.12
Antidepressants between diagnostic and follow-up biopsies				47 (11)	25 (16)	0.11
Anxiolytics after follow-up biopsy				39 (9)	25 (16)	0.02
Anxiolytics between diagnostic and follow-up biopsies				21 (5)	8 (5)	0.94
Sleep medications after follow-up biopsy				54 (13)	43 (28)	<0.01
Sleep medications between diagnostic and follow-up biopsies				36 (9)	25 (16)	<0.01

TABLE 2 Association of mucosal healing with "subsequent" outcomes of anxiety, depression, antidepressants, psychostimulants, anxiolytics and hypnotics/sedatives

Outcome (group)	Number of events	Adjusted[a] HR (95% CI)	*P* value
Diagnosis of anxiety			
Persistent villous atrophy	94	1.0	<0.01
Mucosal healing	123	1.49 (1.12-1.96)	
Stratified analyses of anxiety			
Diagnosis of anxiety in children			
Persistent villous atrophy	40	1.0	0.02
Mucosal healing	49	1.75 (1.11-2.78)	
Diagnosis of anxiety in adults			
Persistent villous atrophy	54	1.0	0.04
Mucosal healing	74	1.47 (1.02-2.12)	
Diagnosis of anxiety in women			
Persistent villous atrophy	76	1.0	0.02
Mucosal healing	94	1.39 (1.02-1.92)	
Diagnosis of anxiety in men			
Persistent villous atrophy	18	1.0	<0.01
Mucosal healing	29	2.00 (1.06-3.70)	
Diagnosis of depression			
Persistent villous atrophy	148	1.0	0.06
Mucosal healing	167	1.25 (0.99-1.59)	
Stratified analyses of depression			
Diagnosis of depression in children			
Persistent villous atrophy	47	1.0	0.14
Mucosal healing	52	1.39 (0.89-2.13)	
Diagnosis of depression in adults			
Persistent villous atrophy	101	1.0	0.21
Mucosal healing	115	1.19 (0.91-1.59)	
Diagnosis of depression in women			
Persistent villous atrophy	99	1.0	0.02
Mucosal healing	125	1.39 (1.05-1.82)	
Diagnosis of depression in men			
Persistent villous atrophy	49	1.0	0.95
Mucosal healing	42	1.01 (0.65-1.56)	
Prescription of antidepressants			
Persistent villous atrophy	33	1.0	0.50
Mucosal healing	66	1.16 (0.75-1.85)	
Prescription of anxiolytics			
Persistent villous atrophy	25	1.0	0.31
Mucosal healing	39	0.76 (0.44-1.30)	
Prescription of hypnotics/sedatives			
Persistent villous atrophy	43	1.0	0.25
Mucosal healing	54	0.78 (0.51-1.19)	
Prescription of any medication above			
Persistent villous atrophy	63	1.0	0.32
Mucosal healing	103	0.84 (0.61-1.19)	

HR, hazard ratio; villous atrophy, villous atrophy.
[a]Cox regression adjusted for patient age at follow-up biopsy, sex, calendar period of first biopsy, education and duration of coeliac disease at the time of follow-up biopsy.

All models (Cox models and logistic regressions) were adjusted for age at follow-up biopsy, sex, duration of coeliac disease at the time of follow-up biopsy (0.5 to 1, >1 to <2 or 2 to 5 years), calendar period of first biopsy (1990-1999, 2000-2009 vs -1989), and educational attainment (five categories; see Olén et al for more data on education[37]). For children with missing data on education we used the highest educational attainment of either parent.

We used SAS version 9.4 (Cary, NC) for all statistical analyses.

3 | RESULTS

3.1 | Characteristics of included patients

In total, we included 4331 individuals with mucosal healing with a mean follow-up of 10.1 years after follow-up biopsy and 3317 individuals with persistent villous atrophy with a mean follow-up of 13.4 years. Characteristics of the study participants are presented in Table 1. All of the demographic and temporal characteristics described in Table 1 were associated with mucosal healing, and were hence used for adjustment in all analyses.

3.2 | Risk of being diagnosed with "anxiety" after follow-up biopsy

During follow-up, 123 (2.8 per 1000 person-years of follow-up) coeliac individuals with mucosal healing developed anxiety, compared to 94 (2.1 per 1000 person-years) with persistent villous atrophy (Table 1). In the multivariable analysis, mucosal healing was associated with a higher risk of future anxiety (HR = 1.49; 95% CI = 1.12-1.96) (Table 2). This association was also statistically significant in all stratified analyses by age and sex (Table 2). The HR for being diagnosed with a first ever (incident) diagnosis of anxiety after follow-up biopsy showing mucosal healing was 1.23 (95% CI = 0.93-1.64) compared to individuals with persistent villous atrophy.

3.3 | Risk of being diagnosed with "depression" after follow-up biopsy

Depression was seen in 167 (3.8 per 1000 person-years) coeliac individuals with mucosal healing vs 148 (3.3 per 1000 person-years) of those with persistent villous atrophy. This corresponded to an adjusted HR of 1.25 (95% CI = 0.99-1.59). The association was statistically significant in women (HR = 1.39; 95% CI = 1.05-1.82), that is, women with mucosal healing were more likely to have a future

diagnosis of depression than women with persistent villous atrophy, whereas in all other stratified analyses (children, adults and men) there were no significant differences (Table 2). The HR for being diagnosed with a first ever (incident) diagnosis of depression after follow-up biopsy with mucosal healing was 1.12 (95% CI = 0.87-1.45) compared to individuals with persistent villous atrophy.

3.4 | Risk of being prescribed "psychotropic medications" after follow-up biopsy

Restricting our sample to the 573 individuals with coeliac disease diagnosed after 2005 and with a follow-up biopsy, we found no association with later prescriptions of psychotropic medications in the multivariable Cox regression even though the percentage (Table 1) of some of the prescriptions was higher in the persistent villous atrophy group. The HRs were slightly above 1 for anxiolytics and sedatives and below 1 for antidepressants (Table 2).

3.5 | Anxiety, depression and "psychotropic prescriptions" preceding follow-up biopsy

Prior psychiatric disease was associated with mucosal healing. The association was particularly strong for individuals with an anxiety diagnosis between diagnostic and follow-up biopsy (odds ratio, OR = 8.94; 95% CI = 2.03-39.27), but was significant also for anxiety any time prior to the follow-up biopsy as well as having a diagnosis of depression any time before follow-up biopsy (Table 3). We also performed a regression including previous depression, anxiety and prescriptions between first and follow-up biopsy and found that having an anxiety diagnosis was still significantly associated with later mucosal healing OR = 9.02 (95% = 2.07-39.35), that is, an anxiety diagnosis was positively associated with future mucosal healing also when adjusting for depression and all of the psychotropic medications.

TABLE 3 Association of mucosal healing with *prior* anxiety, depression, antidepressants, psychostimulants, anxiolytics and hypnotics/sedatives

Exposure (group)	Number of exposed	Adjusted[a] OR (95% CI) for mucosal healing at second biopsy	*P* value
Anxiety ever before follow-up biopsy			
No	7593	1.0	0.01
Yes	55	2.51 (1.33-4.74)	
Anxiety between diagnostic and follow-up biopsies			
No	7624	1.0	<0.01
Yes	24	8.94 (2.03-39.27)	
Depression ever before follow-up biopsy			
No	7513	1.0	0.04
Yes	135	1.47 (1.01-2.15)	
Depression between diagnostic and follow-up biopsies			
No	7602	1.0	0.42
Yes	46	1.30 (0.69-2.48)	
Prescription of antidepressants between diagnostic and follow-up biopsies			
No	501	1.0	0.65
Yes	72	0.87 (0.49-1.56)	
Prescription of anxiolytics between diagnostic and follow-up biopsies			
No	544	1.0	0.39
Yes	29	1.49 (0.60-3.67)	
Prescription of hypnotics/sedatives between diagnostic and follow-up biopsies			
No	512	1.0	0.45
Yes	61	0.79 (0.43-1.45)	
Prescription of any medication above between diagnostic and follow-up biopsies			
No	458	1.0	0.91
Yes	115	1.03 (0.63-1.68)	

OR, odds ratio; villous atrophy, villous atrophy.
[a]Adjusted for patient age at follow-up biopsy, sex, calendar period of first biopsy, education and duration of coeliac disease at the time of follow-up biopsy.

4 | DISCUSSION

In this nationwide population-based cohort study we examined the association between mucosal healing at follow-up biopsy and anxiety, depression and prescription for psychotropic medication. We found that anxiety and depression are more common in coeliac disease individuals with mucosal healing than in those with persistent villous atrophy, both before and after follow-up biopsy. One explanation for our findings may be that individuals with anxiety and depression are more careful with the GFD, but our findings may also represent proof of the burden of treatment in coeliac disease.

4.1 | Earlier literature

The literature on coeliac disease and depression and anxiety is abundant,[21] but so far we are unaware of any studies exploring the association with mucosal healing. One prior study of coeliac disease participants in a clinical trial found that antidepressant use was associated with an increased prevalence of persistent villous atrophy, though depressive symptoms were not measured and clinical trial participants may not be representative of the general coeliac population.[38]

Although mucosal healing is not equal to adherence to a GFD, we have compared our findings to studies on GFD and GFD adherence. Earlier studies have often reported that symptoms of anxiety and/or depression decrease with GFD,[39] but that does not mean that adherence per se protects against anxiety or depression. In fact, some of the most adherent patients may achieve gluten avoidance (and likely mucosal healing) via an extreme vigilance that has been shown to be associated with a reduced coeliac disease-related quality of life.[26]

Most studies have used self-reported dietary adherence and it cannot be ruled out that reported adherence per se is related to well-being.[40] In contrast, we used a measure (histopathology) that is

independent of patient perceptions and therefore possibly more reliable.

Gluten-free diet may impact on psychological well-being and ultimately on the risk of psychiatric disease in several ways.[41] Increased costs, lack of available gluten-free foods, difficulties when eating out or travelling abroad, the social restriction of having another diet, but also poor palatability of gluten-free foods can have a negative effect on quality of life in coeliac disease. For those extremely vigilant about their GFD, the distrust of gluten-free menu designations, dislike of having to constantly ask questions and advocate for safe food and dismissive or uninformed wait staff are even more prevalent barriers than reported by their less vigilant counterparts.[24] The burden of treatment of coeliac disease, including the social restrictions of GFD can be so severe[42] that even the well-being of caregivers of individuals with coeliac disease is impacted.[43,44] Interestingly enough, White et al[41] suggest that dietary adherence is superior in individuals with strong emotional support, but our study indicates that other mechanisms may drive dietary adherence: anxiety and depression.

We found an increased risk of both anxiety and depression after follow-up biopsy in individuals with mucosal healing. This contrasts a recent study by Simsek et al,[45] where GFD per se was not linked to depression scores, but those children who managed to adhere to GFD had lower depression scores. While one of the strengths of the Simsek et al paper was their detailed scoring of depression, their study was only based on 25 children (as opposed to our >7000 study participants) and since several of their analyses were negative, the improvement of depression may have been a chance finding. More similar to our study may instead be the study of van Hees et al[40] In that study, there was no association between insufficient adherence and depressive symptoms, however, the authors noted that with longer GFD, depressive symptoms decreased.

Our findings contrast with data from another gastrointestinal disorder, IBD.[28] Gracie et al found a bidirectional positive association between anxiety scores and disease activity. So far the main driver behind inflammation in diagnosed coeliac disease is adherence to treatment, and we speculate that a strong link between anxiety and treatment in coeliac disease (while not present to the same extent in IBD) may explain the different findings.

The recent study by Wolf et al[26] supports the concept that there is a price to pay for the strict adherence to GFD (and supposedly subsequent mucosal healing). They demonstrated that among both teenagers and adults, those with the extreme vigilance and greater knowledge about GFD had a worse quality of life. Among a number of chronic diseases, another study demonstrated the perceived burden of having coeliac disease was second only to chronic renal failure on dialysis.[42] All patients are advised to adhere to GFD for the entire life; however, we do not know if the amount of gluten that is required to cause damage to the intestine varies between individuals. These studies do provide further evidence that patients may well benefit from medications that could be used in assistance to the GFD.[46] This is something that patients do express considerable interest in.[47,48] It may also suggest the potential importance of having a mental health professional as an integral part of the management team for coeliac disease, in addition to a gastroenterologist and a dietitian.

4.2 | Strengths and limitations

This study was based on more than 7000 individuals with coeliac disease and follow-up biopsy. The population-based sample is less prone to selection bias and enhances the generalisability of our findings. The large sample ensured adequate statistical power to detect even small excess risks, and allowed us to carry out age- and sex-stratified analyses with adjustment for socioeconomic status. The diagnosis of coeliac disease was based on villous atrophy on a small intestinal biopsy. During the study period in Sweden, some 96% of adult gastroenterologists and 100% of paediatricians performed a small intestinal biopsy in ≥90% of patients with suspected coeliac disease before diagnosis.[31] Although recent paediatric recommendations by ESPGHAN now allow for a nonbiopsy protocol in selected children since 2012,[49] this should not influence our data since they were collected before 2012. An earlier patient chart review found that the positive predictive value for coeliac disease of having villous atrophy is 95%.[31] When two researchers independently reviewed the biopsy reports of more than 1500 individuals with villous atrophy or inflammation, the most common comorbidity was IBD which was seen only in 0.3%[31] of patients with villous atrophy. Although we did not have data on coeliac serology in all individuals with coeliac disease, in a subset of patients with available data, 88% had positive coeliac serology.[31] Another strength was our long follow-up (mean >10 years), and the virtually complete follow-up. In Sweden all individuals receive a unique personal identity number[29] that allows government agencies and Swedish healthcare to follow-up individuals until emigration or death.[50]

Our study also has some limitations. The sample size in our analyses of psychotropic medications was limited (n = 573) and with limited follow-up (up until 4 years). Anxiety (3%) and depression (4%) were rare in the population. We had no information on symptoms. A GFD may be perceived as beneficial in individuals with symptomatic coeliac disease, but not in those with asymptomatic coeliac disease.[51] Our ascertainment of depression and anxiety was based on diagnostic codes and medications, which may have led to misclassification. The codes used do not include primary care and hence may reflect more severe cases of anxiety/depression. On the other hand, medications cover all prescriptions, including also less severe cases. The lower general severity in individuals on medication may partly explain why the associations in this setting were nonsignificant. Another possible explanation for the lack of finding in individuals treated with psychotropic medication is that once the psychiatric condition is treated there is no longer a protective effect. Most importantly, the identified association between mood disorders and healing does not provide directionality. For example, though it is possible that hypervigilance is causing both anxiety and healing, it is also possible that a third factor such as an environmental influence or a fixed personality trait is underlying both mood and histology.

For example, individuals with personalities that may cause them to approach a GFD with more rigidity, control, distrust and/or preoccupation may be more likely to have lower quality of life and develop mood disorders following a coeliac diagnosis. On the other hand, mood disorders themselves may cause individuals with coeliac disease to be more vigilant, controlling, distrusting, etc. about their diet leading to greater vigilance and mucosal healing.

5 | CONCLUSIONS

In conclusion, our study found that anxiety and depression are associated with mucosal healing, and this may be mediated by more vigilant adherence to the GFD in such patients. This finding raises the concern that achieving mucosal healing may increase the risk of mood disorders. Future efforts are warranted to develop strategies to promote mucosal healing while preserving quality of life and mental health.

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AUTHORSHIP

Guarantor of the article: Dr. Emilsson.

Authors contributions: LE, BL, QC, GB, PHRG, JFL: Study concept and design; JFL: Acquisition of data; LE, JFL: Analysis and interpretation of data; LE, JFL: Drafting of the manuscript; LE, BL, QC, GB, RW, PHRG, JFL: Critical revision of the manuscript for important intellectual content; LE: Statistical analysis; JFL: Funding. All authors approve the final manuscript submitted and they approve the authorship list.

ETHICAL APPROVAL

This project (2006/633-31/4) was approved by the Research Ethics Committee of the Karolinska Institute, Sweden on 14 June 2006.

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APPENDIX 1

RELEVANT CODES FOR DEFINING EXPOSURES AND OUTCOMES

INTERNATIONAL CLASSIFICATION OF DISEASE CODES (ICD-CODES). SWEDISH PATIENT REGISTER

Depression: ICD-8: 296.0, 300.4, 311; ICD-9: 296B, 300E; ICD-10: F32, F33

Anxiety: ICD-8: 300.0, 300.2, ICD-9: 300A, 300C; ICD-10: F40, F41

ATC CODES USED FOR THE PRESCRIBED DRUG REGISTER

Antidepressants: ATC-code N06A

Anxiolytics: ATC-code N05B

Hypnotics and sedatives: ATC-code N05C