

The joint associations of anxiety, depression and obesity with incident asthma in adults: the HUNT Study

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Key messages

- Anxiety or depression symptoms may interact with obesity to increase the risk of developing asthma in adults.
- Our study demonstrated that adults with both anxiety or depression symptoms and obesity had a substantially increased risk of asthma than any other group, after the 11-year follow-up.
- This is one of the first studies evaluating the joint associations of anxiety or depression symptoms and obesity with asthma development.

Subject heading: Anxiety, depression and obesity with incident asthma

Abstract

Background: Anxiety or depression symptoms may increase the risk of developing asthma, and their interaction with obesity is not known. We aimed to assess the association of anxiety or depression symptoms and the joint associations of these symptoms and obesity with incident asthma.

Methods: We conducted a prospective cohort study of 23 599 adults who were 19 – 55 years old and free from asthma at baseline in the Norwegian Nord–Trøndelag Health Study. The Hospital Anxiety and Depression Scale was used to measure anxiety or depression symptoms. Obesity was defined as a body mass index $\geq 30.0 \text{ kg/m}^2$. Incident asthma was self-reported new cases of asthma during the 11-year follow-up.

Results: Having anxiety or depression symptoms was associated with incident asthma (odds ratio [OR] 1.39, 95% confidence interval [CI] 1.09 – 1.78). Obese participants with anxiety or depression symptoms had a substantially higher risk of incident asthma (OR 2.93, 95% CI 2.20 – 3.91) than any other group (non-obese participants without anxiety or depression symptoms [reference], non-obese participants with anxiety or depression symptoms [OR 1.20, 95% CI 1.00 – 1.45] and obese participants without anxiety or depression symptoms [OR 1.47, 95% CI 1.19 – 1.82]). The relative excess risk for incident asthma due to interaction between anxiety or depression symptoms and obesity was 1.26 (95% CI 0.39 – 2.12).

Conclusions: This study suggests that having anxiety or depression symptoms contributes to the development of asthma in adults. The risk of asthma may be further increased by the interaction between anxiety or depression symptoms and obesity.

Key words: body mass index, epidemiology, interaction, psychological distress

Introduction

Asthma affects about 300 million people worldwide and represents approximately 1% of the total global disease burden.¹ There are also substantial social and economic burdens from asthma and its care.¹ The prevalence of doctor diagnosed asthma in adults varies greatly between countries (e.g. 0.2% in China versus 21.0% in Australia) and it is globally estimated to be 4.3%.² Asthma is a multifactorial condition and historically mental distress was thought to play a role in asthma pathogenesis. As far back as the 11th century, physicians warned that distress could cause asthma while joyfulness may have a beneficial effect.³ While the influence of emotional distress was seldom investigated in the first half of the 20th century, this historical concept has gained support after recent studies have suggested possible biological mechanisms.⁴

Several studies on the association of anxiety or depression symptoms and asthma have been conducted. Cross-sectional studies have found that anxiety or depression symptoms are more prevalent in asthmatic patients,^{5, 6} while others have observed that asthma patients were no more anxious or depressed than any other participants.⁷ A limited number of prospective studies have investigated this association.^{8, 9} Jonas and Wagener⁸ found a moderate association of anxiety or depression symptoms with incident asthma in non-smoking adults. Scott et al.⁹ found that early-onset anxiety and depression (<21 years of age) had a moderate association with adult-onset asthma. Inflammation, irregular levels of circulating cortisol and glucocorticoid insensitivity may be underlying pathways of this association.⁹⁻¹² Obesity has also been found to be associated with an increased risk of asthma in a number of prospective studies.^{13, 14} One of the potential pathways

for the obesity-asthma association is also via inflammation.¹⁵ If anxiety or depression symptoms and obesity exacerbate a common pathway, we might expect to see a substantially elevated risk of asthma in people with both of these exposures. To our knowledge the joint associations of anxiety or depression symptoms and obesity with incident asthma has not yet been evaluated.

Therefore, we carried out a prospective cohort study of adults using the Nord-Trøndelag Health Study (HUNT) to: 1) investigate the association of anxiety or depression symptoms with incident asthma; and 2) assess the joint associations of anxiety or depression symptoms and obesity with incident asthma.

Methods

Study population

The study area was the county of Nord-Trøndelag (22 463 km²), Norway. The adult population in Nord-Trøndelag (127 000 people in 1995) was invited to participate in three HUNT surveys which have been described elsewhere.¹⁶ The population in Nord-Trøndelag is fairly representative of Norway with respect to age, income, morbidity and mortality.¹⁷ The participants of this study took part in the second (HUNT 2, 1995 – 1997) and third (HUNT 3, 2006 – 2008) surveys of the HUNT, an average 11-years follow-up (n=37 071).^{13, 17, 18} We studied 23 599 participants who were 19 – 55 years of age and free from asthma at baseline. The age limit was set as <65 years in HUNT 3 for two reasons: 1) to reduce misclassification of asthma and chronic obstructive pulmonary disease (COPD).¹⁹ 2) Obesity increases overall mortality.^{20, 21} Senior participants with obesity are more likely to die compared to those without obesity, which can result in an under-estimation of the association of interest. Of the 23 599 participants, we excluded a further 353 (1.5%) with missing information on anxiety, depression or body mass index at baseline and on asthma both at baseline and follow-up, leaving 23 246 participants for the analysis.

Anxiety and depression symptoms

Anxiety and depression symptoms were measured with the Hospital Anxiety and Depression Scale (HADS).²² The HADS consists of 14 questions of which seven measure anxiety symptoms and seven measure depression symptoms, during the past week. Each question is answered on a scale of 0–3 giving one total score for anxiety (HADS-A, range 0–21) and one total score for depression (HADS-D, range 0–21). A total score from 0 to 7 indicates normal state (normal), 8 to

10 indicates borderline anxiety or depression state (borderline), and 11 – 21 indicates caseness of anxiety or depression (caseness).²³ In the analysis stratified by obesity, we combined the last two categories (score 8 – 21) to define presence of symptoms (yes, no). Due to the coexistence of anxiety and depression,²⁴ we defined “anxiety or depression symptoms” by the participants’ highest score on either set of questions. Additional details of HADS are described elsewhere.²² The HADS was used to describe the presence of symptoms and is not a psychiatric diagnosis.

Obesity

Body mass index (BMI) was used as a measure of obesity. Weight was measured to the nearest half-kilogram (kg) and height was measured to the nearest centimeter. BMI was calculated as weight divided by height squared (kg/m^2) and obesity was defined as $\text{BMI} \geq 30$.²⁵

Covariables

Covariables were collected from administrative questionnaires and clinical examinations at baseline. Covariables included age (19–29, 30–39, 40–49, 50–55 years), sex (women, men), current smoking (yes, no, unknown), duration of physical activity (<1, 1–2, ≥ 3 hours/week, unknown), family history of asthma (yes, no, unknown), years of education (<10, 10–12, ≥ 13 years, unknown), receiving social benefit (yes, no, unknown) and economic difficulties (yes, no, unknown). Family history of asthma was defined as any family member (father, mother, brother or sister) with asthma. Social benefit was defined as those that reported receiving sick pay, rehabilitation benefits, retraining benefits, disability pension, old age pension, family income supplement, unemployment benefits, transitional benefits, widow’s pension or any other benefit. Participants with economic difficulties were those who reported difficulties meeting the cost of food, transport, and/or housing.

Asthma diagnosis

Asthma was defined by two approaches.^{13, 18} In the first approach, asthma was defined by the survey question; “Do you have or have you had asthma?”. Participants who reported “no” to this question at baseline, and “yes” at follow-up were classified as having incident asthma. In the second approach, a stricter definition of asthma was used i.e. no wheeze or asthma at baseline and reported asthma and use of asthma medication at follow-up, versus the reference group with no wheeze and no asthma at baseline or follow-up.

Statistical methods

In the analysis cohort of 23 246 participants, we evaluated anxiety or depression symptoms at baseline and cumulative incidence of asthma, in relation to other baseline characteristics. Pearson chi-square tests were used to evaluate differences between categories. To study the association of anxiety or depression symptoms with incident asthma we estimated odds ratios (OR) with 95% confidence intervals (CI) using logistic regression.

In model I, we adjusted for age, sex, smoking, physical activity, family history of asthma, education, social benefit and economic history at baseline as potential confounding factors. In model II, we additionally adjusted for BMI as a continuous variable. We found no substantial difference in the associations of anxiety or depression with incident asthma between sexes (data not shown); subsequently we presented data in women and men combined. To test if the associations differed between sexes we used a multiplicative model. The multiplicative model is commonly used to assess heterogeneity of association measures such as relative risks or odds

ratios between subgroups.^{26, 27} To assess the joint associations of anxiety or depression symptoms and obesity with incident asthma, we generated four subgroups, i.e. non-obese participants without anxiety or depression symptoms (reference group), non-obese participants with anxiety or depression symptoms (OR_A), obese participants without anxiety or depression symptoms (OR_B), and obese participants with anxiety or depression symptoms (OR_{AB}). The joint associations of anxiety or depression symptoms and obesity with incident asthma were estimated by using the relative excess risk due to interaction (RERI) with 95% CIs. The RERI was calculated using an additive model: $RERI = OR_{AB} - OR_A - OR_B + 1$.²⁸ The additive model is used to test biological interaction between two or more risk factors that together assert their influence on disease risk.^{27, 29} In brief, $RERI > 0$ and the lower limit of 95% CI > 0 suggests a synergistic effect of anxiety or depression and obesity on incident asthma.²⁸

To test the robustness of the associations we repeated the main analysis using the second approach to define incident asthma (n=20 219). Further to this, we defined anxiety or depression symptoms as above, and additionally included those reporting use of antidepressant medication into the symptom group (n=20 219). Finally, we excluded participants who reported having or ever having had chronic bronchitis, emphysema or COPD in the follow-up questionnaires (n=20 048). We used STATA 12.0 for all statistical analyses (StataCorp LP, College Station, Texas).

Ethics

The project was approved by the Regional Committee for Ethics in Medical Research. All participants signed informed consent for participation and the use of data in research.

Results

At baseline the prevalence of anxiety and depression symptoms (HADS ≥ 8) was 15.0% and 7.8%, respectively (Table 1). The prevalence of anxiety symptoms was higher in women than men, whilst for depression symptoms the pattern was opposite. The prevalence of anxiety and depression symptoms was higher in older participants, obese, smokers, and those with low physical activity, a family history of asthma, social benefit and economic difficulties. The cumulative incidence of asthma during the 11-year follow-up was 3.8%. The cumulative incidence of asthma was higher in women, obese, smokers, and those with less education, a family history of asthma, social benefit and economic difficulties.

We found an association between anxiety or depression symptoms and incident asthma (Table 2). Participants with caseness anxiety or depression symptoms at baseline had a crude OR of 1.83 (95% CI 1.44 – 2.32) for incident asthma, compared to participants without these symptoms. After adjustment for possible confounders (Model I), the OR reduced to 1.39 (95% CI 1.09 – 1.78). Additional adjustment for BMI (Model II) did not change the estimates materially (Table 2). A similar association was found in sex specific analyses (data not shown). The p-value on the multiplicative scale to test heterogeneity between sexes was 0.53.

Table 3 presents the estimates for the joint associations of anxiety or depression symptoms and obesity with incident asthma. Compared to non-obese participants without anxiety or depression symptoms, the OR was 1.20 for non-obese participants with anxiety or depression symptoms and 1.47 for obese participants without anxiety or depression symptoms, while the OR increased to 2.93 (95% CI 2.20 – 3.91) for participants with both obesity and anxiety or depression symptoms (Table 3). We found statistical evidence for a biological interaction beyond additivity for anxiety

or depression symptoms and obesity at baseline and the risk of incident asthma, with RERI of 1.26 (95% CI 0.39 – 2.12). Figure 1 presents unadjusted cumulative incidence of asthma associated with the individual and joint exposures of anxiety or depression symptoms and obesity. We found a similar pattern in sex specific analyses (data not shown).

Using the second approach to define asthma, with a stricter definition, it yielded results similar to our main analyses (Table 4). The OR for the participants with both obesity and anxiety or depression was 3.15 (95% CI 2.16 – 4.58), compared to non-obese participants without anxiety or depression. The relative excess risk for incident asthma due to interaction between anxiety or depression symptoms and obesity was 1.34 (95% CI 0.13 – 2.54). We observed similar associations when we included participants reporting use of antidepressant medication into the anxiety or depression group (Supplementary Table 1), and when we excluded participants reporting chronic bronchitis, emphysema or COPD (Supplementary Table 2).

Discussion

In this large prospective study from the general population, adults reporting symptoms of anxiety or depression at baseline had an increased risk of incident asthma at follow-up. We also found that adults with anxiety or depression symptoms and obesity had a particularly increased risk of developing asthma.

Our finding that anxiety or depression symptoms are moderately associated with incident asthma is supported by previous prospective studies. Chida et al. reviewed 34 studies of psychosocial factors on atopic disorders (91% were on asthma), and found a robust relationship between psychological factors and atopic disorders.⁴ Further to this, several studies have investigated the association between anxiety or depression and adult asthma,^{8, 9, 30-34} with relative risk estimates ranging from 1.24–2.80. Four of these were prospective studies, which found that anxiety or depression were associated with incident asthma.^{8, 31, 33, 34} Our findings extend previous research by examining this hypothesis in a very large prospective cohort, with a comprehensive range of covariates to adjust for. Furthermore, our study investigated the joint associations of anxiety or depression symptoms and obesity with incident asthma. We found that participants with anxiety or depression symptoms and also obesity had a greater risk of asthma than the sum of their individual risks, as indicated by the RERI.

The association between anxiety or depression symptoms and incident asthma may have biological plausibility. Two main pathways have been suggested, including changes in health behaviors and inflammatory processes.³⁴ Lifestyle related behaviors such as smoking, and less physical exercise due to distress may be mediators leading to the development of asthma. On the other hand, these health behavior variables may also be confounding factors that cause both

psychological distress and asthma. In any case, the attempt of adjustment for these factors (smoking and physical activity) in addition to the other covariates in our models did not substantially alter the association between anxiety or depression symptoms and incident asthma.

Our multivariable analysis suggests that inflammatory processes may be a potential pathway. Several studies have suggested that depression is linked to a state of low grade chronic inflammation,¹¹ and anxiety has been associated with increased production of pro-inflammatory cytokines.³⁵ Furthermore, progression of psychological distress such as anxiety and depression may lead to irregular levels of circulating cortisol, and a glucocorticoid insensitive state.⁹⁻¹² Glucocorticoid receptor resistance has been observed in healthy adults exposed to long-term stressful experiences, parents of children with cancer and spouses of brain-cancer patients.³⁶ Consequently, the down regulation of glucocorticoid receptors may interfere with regulation of inflammation which may increase the risk of inflammatory disorders.³⁶ Miller et al. found that children with asthma and perceived low support from their parents (a proxy for stress) were more resistant to hydrocortisone's anti-inflammatory effects on pro-inflammatory cytokines, which shed some light on how stress affects asthma.³⁷ Therefore, a state of inflammation and glucocorticoid insensitivity due to chronic psychological distress might be the underlying pathophysiology for the association we observed.

Obesity is also a chronic inflammatory condition,³⁸ which will signal cortisol release through normal inflammatory signaling and the hypothalamic-pituitary-adrenal axis.³⁹ High levels of cortisol due to obesity may additionally contribute to cortisol insensitivity.⁴⁰ The further complication of obesity in anxious or depressed participants may worsen a common inflammatory pathway and, at least in part, explain the joint association that we observed. While

a reciprocal link between obesity and psychological distresses such as anxiety and depression has been reported in observational studies,⁴¹⁻⁴³ further research is needed to investigate the underlying mechanism of this interaction. Our observation, that participants with both anxiety or depression and obesity had an excess risk of asthma, suggests that a considerable number of asthma cases may be due to the presence of anxiety or depression and obesity in the same causal mechanism. By identifying people with anxiety or depression symptoms and obesity may make asthma prevention more effective. However, the study findings, and their mechanistic implications, merit further investigation.

Our study has several major strengths. The prospective study design indicates direction of the association. The size and duration of our study was an advantage to increase study power and the possibility to detect associations. Due to the large study size we were able to assess the joint associations of anxiety or depression symptoms and obesity with incident asthma, and also to address potential differences between sexes. The comprehensive data set allowed us to control for a range of potential confounding factors. Height and weight were objectively measured and recorded by nurses in standardized clinical examinations. This would have avoided subjective over-reporting of height and under-reporting of weight. We also used another proxy measure for obesity (abdominal obesity) and found similar results to our original analysis. To strengthen our definition of anxiety or depression symptoms, we used an alternative definition adding those who used antidepressant medication into the symptom group, which minimized misclassification of exposure. The findings from these analyses supported our results.

With regard to potential limitations, we acknowledge that even though we controlled for many confounding factors there may still be residual confounding in our study. Another major

challenge in epidemiological studies of asthma is the definition, since there is no gold standard for the diagnosis of asthma. Although we verified asthma cases by medication use, we cannot rule out possible misclassification bias since, objective airway reversibility or hyper-responsiveness tests, were not performed. Also, misclassification of hyperventilation or shortness of breath as asthma in anxious participants cannot completely be ruled out as an explanation of our finding. However self-reported asthma has been assessed as a reasonably robust method for population studies.^{44, 45} To strengthen our diagnosis of asthma, we used a stricter definition of asthma verified by the use of asthma medication. Further to this, we excluded participants who reported chronic bronchitis, emphysema or COPD in the follow-up questionnaires to reduce possible misclassification of asthma and COPD. The results from all these additional analyses showed similar associations to our main findings.

In the current study, HADS was used as a screening tool to capture symptoms of anxiety or depression. The ability of the HADS to separate clinical diagnoses of anxiety and depression disorders is uncertain,⁴⁶ and the HADS identified cases may not have a close correspondence to clinical anxiety or depression. For example, we observed the lowest prevalence of anxiety or depression in the youngest group, who has been reported to have the highest prevalence of clinical mental disorders by others.^{47, 48} We also observed a high prevalence of depression in men, which is greater than the prevalence from diagnoses based on interviews.^{47, 48} The limitations of the HADS to identify clinical anxiety or depression may limit the generalizability of our results.

In summary, this large prospective cohort study suggests that anxiety or depression symptoms may contribute to the development of asthma and that obesity may interact with anxiety or

depression symptoms to further increase the risk of asthma in adults. Further research is needed to confirm the presence of synergy between these two common risk factors and to explore the underlying mechanisms.

Supplementary data

Supplementary data are available at *IJE* online.

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References

1. Global Initiative for Asthma. *Global strategy for asthma management and prevention*; 2012.
2. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012;**12**: 204.
3. Douwes J, Brooks C, Pearce N. Asthma nervosa: old concept, new insights. *Eur Respir J* 2011;**37**: 986-90.
4. Chida Y, Hamer M, Steptoe A. A bidirectional relationship between psychosocial factors and atopic disorders: A systematic review and meta-analysis. *Psychosomatic Medicine* 2008;**70**: 102-16.
5. Scott KM, Von Korff M, Ormel J, et al. Mental disorders among adults with asthma: results from the World Mental Health Survey. *Gen Hosp Psychiat* 2007;**29**: 123-33.
6. Goodwin RD, Jacobi F, Thefeld W. Mental disorders and asthma in the community. *Arch Gen Psychiatry* 2003;**60**: 1125-30.
7. Janson C, Bjornsson E, Hetta J, Boman G. Anxiety and depression in relation to respiratory symptoms and asthma. *Am J Respir Crit Care Med* 1994;**149**: 930-4.
8. Jonas BS, Wagener DK, Lando JF, Feldman JJ. Symptoms of Anxiety and Depression as Risk Factors for Development of Asthma. *Journal of Applied Biobehavioral Research* 1999;**4**: 91-110.
9. Scott KM, Von Korff M, Alonso J, et al. Childhood adversity, early-onset depressive/anxiety disorders, and adult-onset asthma. *Psychosom Med* 2008;**70**: 1035-43.
10. Priftis KN, Anthracopoulos MB. The causal relationship between stress and asthma. *Allergol Immunopath* 2008;**36**: 343-6.
11. Gouin J-P. Chronic Stress, Immune Dysregulation, and Health. *American Journal of Lifestyle Medicine* 2011;**5**: 476-85.
12. Haczku A, Panettieri RA, Jr. Social stress and asthma: the role of corticosteroid insensitivity. *J Allergy Clin Immunol* 2010;**125**: 550-8.

13. Brumpton B, Langhammer A, Romundstad P, Chen Y, Mai XM. General and abdominal obesity and incident asthma in adults: the HUNT study. *Eur Respir J* 2013;**41**: 323-9.
14. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma - A meta-analysis of prospective epidemiologic studies. *Am J Resp Crit Care* 2007;**175**: 661-6.
15. Beuther DA. Recent insight into obesity and asthma. *Curr Opin Pulm Med* 2010;**16**: 64-70.
16. Krokstad S, Langhammer A, Hveem K, et al. Cohort Profile: The HUNT Study, Norway. *Int J Epidemiol* 2012.
17. Holmen J MK, Krüger Ø, Langhammer A, Holmen TL, Bratberg GH, Vatten L, Lund-Larsen PG. The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation. *Norsk Epidemiologi* 2003;**13**: 19-32.
18. Mai XM, Langhammer A, Chen Y, Camargo CA, Jr. Cod liver oil intake and incidence of asthma in Norwegian adults--the HUNT study. *Thorax* 2013;**68**: 25-30.
19. Tinkelman DG, Price DB, Nordyke RJ, Halbert RJ. Misdiagnosis of COPD and asthma in primary care patients 40 years of age and over. *J Asthma* 2006;**43**: 75-80.
20. Bigaard J, Frederiksen K, Tjønneland A, et al. Waist circumference and body composition in relation to all-cause mortality in middle-aged men and women. *Int J Obes (Lond)* 2005;**29**: 778-84.
21. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008;**359**: 2105-20.
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**: 361-70.
23. 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.
24. Sadock B, Sadock V. *Synopsis of psychiatry: behavioral sciences/clinical psychiatry*. Philadelphia: Lippincott Williams & Wilkins; 2007.

25. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;**894**: 1-253.
26. Lovric M. *International encyclopedia of statistical science*. Berlin ; New York: Springer; 2011.
27. de Mutsert R, Jager KJ, Zoccali C, Dekker FW. The effect of joint exposures: examining the presence of interaction. *Kidney Int* 2009;**75**: 677-81.
28. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. *Eur J Epidemiol* 2005;**20**: 575-9.
29. Rothman KJ. *Epidemiology : an introduction*. 2nd ed. New York, NY: Oxford University Press; 2012.
30. Hasler G, Gergen PJ, Ajdacic V, et al. Asthma and body weight change: a 20-year prospective community study of young adults. *Int J Obes (Lond)* 2006;**30**: 1111-8.
31. Wainwright NW, Surtees PG, Wareham NJ, Harrison BD. Psychosocial factors and incident asthma hospital admissions in the EPIC-Norfolk cohort study. *Allergy* 2007;**62**: 554-60.
32. Scott KM, Von Korff M, Angermeyer MC, et al. Association of childhood adversities and early-onset mental disorders with adult-onset chronic physical conditions. *Arch Gen Psychiatry* 2011;**68**: 838-44.
33. Patten SB, Williams JVA, Lavorato DH, Modgill G, Jette N, Eliasziw M. Major depression as a risk factor for chronic disease incidence: longitudinal analyses in a general population cohort. *Gen Hosp Psychiat* 2008;**30**: 407-13.
34. Loerbroks A, Apfelbacher CJ, Bosch JA, Sturmer T. Depressive symptoms, social support, and risk of adult asthma in a population-based cohort study. *Psychosom Med* 2010;**72**: 309-15.
35. Maes M, Song C, Lin A, et al. The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. *Cytokine* 1998;**10**: 313-8.
36. Cohen S, Janicki-Deverts D, Doyle WJ, et al. Chronic stress, glucocorticoid receptor resistance,

- inflammation, and disease risk. *Proc Natl Acad Sci U S A* 2012;**109**: 5995-9.
37. Miller GE, Gaudin A, Zysk E, Chen E. Parental support and cytokine activity in childhood asthma: the role of glucocorticoid sensitivity. *J Allergy Clin Immunol* 2009;**123**: 824-30.
 38. Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. *Mediators Inflamm* 2010;**2010**.
 39. Bjorntorp P. Endocrine abnormalities of obesity. *Metabolism* 1995;**44**: 21-3.
 40. Sin DD, Sutherland ER. Obesity and the lung: 4. Obesity and asthma. *Thorax* 2008;**63**: 1018-23.
 41. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry* 2010;**67**: 220-9.
 42. Brumpton B, Langhammer A, Romundstad P, Chen Y, Mai XM. The associations of anxiety and depression symptoms with weight change and incident obesity: The HUNT Study. *Int J Obes (Lond)* 2012.
 43. Bjerkeset O, Romundstad P, Evans J, Gunnell D. Association of adult body mass index and height with anxiety, depression, and suicide in the general population: the HUNT study. *Am J Epidemiol* 2008;**167**: 193-202.
 44. Toren K, Brisman J, Jarvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *Chest* 1993;**104**: 600-8.
 45. de Marco R, Cerveri I, Bugiani M, Ferrari M, Verlato G. An undetected burden of asthma in Italy: the relationship between clinical and epidemiological diagnosis of asthma. *Eur Respir J* 1998;**11**: 997-.
 46. Brennan C, Worrall-Davies A, McMillan D, Gilbody S, House A. The Hospital Anxiety and Depression Scale: a diagnostic meta-analysis of case-finding ability. *J Psychosom Res* 2010;**69**: 371-8.
 47. Kringlen E, Torgersen S, Cramer V. Mental illness in a rural area: a Norwegian psychiatric epidemiological study. *Soc Psychiatry Psychiatr Epidemiol* 2006;**41**: 713-9.

48. Kringlen E, Torgersen S, Cramer V. A Norwegian psychiatric epidemiological study. *Am J Psychiatry* 2001;**158**: 1091-8.

Table 1. Anxiety or depression symptoms and incident asthma in relation to baseline characteristics in a cohort of the Nord-Trøndelag Health Study, Norway.

	Anxiety symptoms*			Depression symptoms*			Incident asthma†			
	Total	No.	%	P-value‡	No.	%	P-value‡	No.	%	P-value‡
Total	23 246	3 483	15.0		1 807	7.8		890	3.8	
Age (years)				0.001			0.001			0.22
19–29	3 756	500	13.3		153	4.1		164	4.4	
30–39	7 031	1 015	14.4		430	6.1		253	3.6	
40–49	9 099	1 439	15.8		833	9.2		352	3.9	
50–55	3 360	529	15.7		391	11.6		121	3.6	
Sex				0.001			0.02			0.001
Women	12 849	2 162	16.8		951	7.4		560	4.4	
Men	10 397	1 321	12.7		856	8.2		330	3.2	
Body mass index				0.32			0.001			0.001
Obese	2 765	432	15.6		283	10.2		172	6.2	
Non-obese	20 481	3 051	14.9		1 524	7.4		718	3.5	
Smoking §				0.001			0.001			0.001
Yes	6 668	1 275	19.1		685	10.3		344	5.2	
No	15 410	2 042	13.3		1 047	6.8		503	3.3	
Physical activity (hrs/wk) §				0.001			0.001			0.33
<1	5 269	919	17.4		601	11.4		209	4.0	
1–2	8 430	1 200	14.2		607	7.2		326	3.9	
≥3	7 230	1 003	13.9		431	6.0		253	3.5	
Family history of asthma §				0.001			0.01			0.001
Yes	3 410	565	16.6		295	8.7		230	6.7	
No	18 118	2 617	14.4		1 344	7.4		545	3.0	
Education (years) §				0.001			0.001			0.001
≤10	4 598	885	19.3		573	12.5		218	4.7	
10–12	12 382	1 824	14.7		896	7.2		481	3.9	
≥13	6 113	744	12.2		320	5.2		183	3.0	
Social benefit §				0.001			0.001			0.001
Recipient	4 002	921	23.0		502	12.5		239	6.0	
Non-recipient	14 862	1 898	12.8		966	6.5		495	3.3	
Economic difficulties §				0.001			0.001			0.001
Yes	6 406	1 387	21.7		724	11.3		344	5.4	
No	13 516	1 602	11.9		816	6.0		433	3.2	

* Hospital Anxiety and Depression Scale ≥ 8 .

† Participants with asthma at follow-up who were free from asthma at baseline.

‡ P-value between categories.

§ Numbers do not sum up to the total cohort due to missing information.

Table 2. Anxiety or depression symptoms at baseline in association with incident asthma in the Nord-Trøndelag Health Study, Norway (n=23 246).

Symptoms*	Total	Incident asthma	%	Crude OR (95% CI)	Adjusted OR (95% CI) Model I†	Adjusted OR (95% CI) Model II‡
Anxiety						
Normal	19 763	701	3.6	1.00	1.00	1.00
Borderline	2 387	112	4.7	1.34 (1.09 – 1.64)	1.17 (0.95 – 1.44)	1.19 (0.96 – 1.46)
Caseness	1 096	77	7.0	2.05 (1.61 – 2.62)	1.53 (1.19 – 1.96)	1.52 (1.18 – 1.96)
P for trend					0.001	0.001
Depression						
Normal	21 439	783	3.7	1.00	1.00	1.00
Borderline	1 325	80	6.0	1.70 (1.34 – 2.15)	1.46 (1.14 – 1.85)	1.43 (1.12 – 1.82)
Caseness	482	27	5.6	1.57 (1.05 – 2.32)	1.22 (0.81 – 1.83)	1.20 (0.80 – 1.79)
P for trend					0.01	0.02
Anxiety or depression						
Normal	19 079	663	3.5	1.00	1.00	1.00
Borderline	2 840	145	5.1	1.49 (1.24 – 1.80)	1.32 (1.09 – 1.59)	1.32 (1.10 – 1.60)
Caseness	1 327	82	6.2	1.83 (1.44 – 2.32)	1.39 (1.09 – 1.78)	1.38 (1.08 – 1.76)
P for trend					0.001	0.001

Abbreviations: CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; OR, odds ratio.

* Normal HADS<8, borderline HADS 8–10, caseness HADS 11–21.

† Model I adjusted for age, sex, smoking, physical activity, family history of asthma, education, social benefit and economic difficulties at baseline.

‡ Model II additionally adjusted for BMI as a continuous variable.

Table 3. Adjusted odds ratios for anxiety or depression symptoms and obesity at baseline associated with incident asthma in the Nord-Trøndelag Health Study, Norway (n=23 246).

Symptoms*	Non-obese (BMI <30.0 kg/m ²)			Obese (BMI ≥30.0 kg/m ²)			RERI (95% CI) ‡
	Total	Incident asthma	OR (95% CI) †	Total	Incident asthma	OR (95% CI) †	
Anxiety							
No	17 430	576	1.00	2 333	125	1.57 (1.28 – 1.92) ^{OR_B}	0.94 (0.03 – 1.85)
Yes	3 051	142	1.20 (0.99 – 1.46) ^{OR_A}	432	47	2.71 (1.96 – 3.76) ^{OR_{AB}}	
Depression							
No	18 957	646	1.00	2 482	137	1.57 (1.29 – 1.90) ^{OR_B}	1.38 (0.17 – 2.59)
Yes	1 524	72	1.20 (0.93 – 1.55) ^{OR_A}	283	35	3.15 (2.17 – 4.59) ^{OR_{AB}}	
Anxiety or depression							
No	16 867	553	1.00	2 212	110	1.47 (1.19 – 1.82) ^{OR_B}	1.26 (0.39 – 2.12)
Yes	3 614	165	1.20 (1.00 – 1.45) ^{OR_A}	553	62	2.93 (2.20 – 3.91) ^{OR_{AB}}	

Abbreviations: BMI, body mass index; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; OR, odds ratio; RERI, relative excess risk due to interaction.

* No HADS <8, yes HADS ≥8.

† Adjusted for age, sex, smoking, physical activity, family history of asthma, education, social benefit and economic difficulties at baseline.

‡ The relative excess risk due to interaction (RERI) between anxiety or depression symptoms (A) and obesity (B) was calculated using the formula: $RERI = OR_{AB} - OR_A - OR_B + 1$.

Table 4. Adjusted odds ratios for anxiety or depression symptoms and obesity at baseline associated with incident asthma† in the Nord-Trøndelag Health Study, Norway (n=20 219).

Symptoms*	Non-obese (BMI <30.0 kg/m ²)			Obese (BMI ≥30.0 kg/m ²)			RERI (95% CI) §
	Total	Incident asthma†	OR (95% CI) ‡	Total	Incident asthma†	OR (95% CI) ‡	
Anxiety							
No	15 555	367	1.00	1 946	83	1.74 (1.36 – 2.22) ^{OR_B}	0.75 (-0.51 – 2.00)
Yes	2 425	83	1.26 (0.98 – 1.61) ^{OR_A}	293	24	2.74 (1.76 – 4.26) ^{OR_{AB}}	
Depression							
No	16 782	409	1.00	2 033	87	1.69 (1.33 – 2.15) ^{OR_B}	1.32 (-0.32 – 2.95)
Yes	1 198	41	1.25 (0.90 – 1.74) ^{OR_A}	206	20	3.26 (2.00 – 5.31) ^{OR_{AB}}	
Anxiety or Depression							
No	15 081	355	1.00	1 846	72	1.59 (1.22 – 2.07) ^{OR_B}	1.34 (0.13 – 2.54)
Yes	2 899	95	1.22 (0.97 – 1.54) ^{OR_A}	393	35	3.15 (2.16 – 4.58) ^{OR_{AB}}	

Abbreviations: BMI, body mass index; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; OR, odds ratio; RERI, relative excess risk due to interaction.

* No HADS < 8, yes HADS ≥ 8.

† Incident asthma: no wheeze or asthma at baseline, reported asthma and asthma medication use at follow-up vs. no wheeze or asthma at baseline or follow-up.

‡ Adjusted for age, sex, smoking, physical activity, family history of asthma, education, social benefit and economic difficulties at baseline.

§ The relative excess risk due to interaction (RERI) between anxiety or depression symptoms (A) and obesity (B) was calculated using the formula: $RERI = OR_{AB} - OR_A - OR_B + 1$.

Figure 1. Unadjusted cumulative incidence of asthma associated with the individual and joint exposures of anxiety or depression symptoms* and obesity† (n=23 246).

* Hospital Anxiety and Depression Scale ≥ 8 for anxiety or depression symptoms.

† Non-obese (body mass index [BMI] <30.0 kg/m²), obese (BMI ≥ 30.0 kg/m²).

