Influence of asthma and body mass index on respiratory symptoms, lung function, and work ability: A general population study in Telemark

Dissertation for the degree of PhD

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1 Preface

1.1 Acknowledgements

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1.2 Summary in Norwegian

Bakgrunn

Selv om bade astma og fedme begge er assosiert med negative lungehelseeffekter, er en mulig interaksjon mellom de to tilstandene lite studert. Tidligere studier har klassifisert kombinasjonen av astma og fedme som en egen astma fenotype. Pasienter med denne fenotypen har mindre kontroll på sin astma, en mer alvorlig astma og dårligere lungefunksjon. Fedme og astma har flere felles komorbiditeter. Det er også påvist lavgradig systemisk inflammasjon og endret lungemekanikk hos pasienter med astma og fedme. Sykefravær og selv-evaluert arbeidsevne kan brukes til å beskrive funksjonsnivå hos pasienter med astma og fedme. For pasienter med astma vil funksjonsnivået være avhengig av kontroll av astma, symptombyrde og lungefunksjon. Pasienter med fedme kan også ha redusert arbeidsevne og økt sykefravær på grunn av økt vekt. Så vidt vi vet har ikke arbeidsevne vurdert med bruk av Work ability score (WAS) blitt undersøkt hos pasienter med både astma og fedme. Eksponering for damp, røyk, gass og støv er assosiert med astma og forverring av astma. Flere studier av i hvilken grad astma og forhøyet kroppsmasse indeks (KMI) er uavhengig assosiert med luftveissymptomer, arbeidsevne og lungefunksjon er nødvendig. Det foreligger også få studier av endring i luftveissymptomer på grunn av endring i KMI eller yrkeseksponering for damp, støv, gass og røyk. En bedre forståelse av de kombinerte effektene av astma og fedme kan bidra til å utforme ny og mer persontilpasset behandling og oppfølging av pasienter med både astma og forhøyet KMI.

Mål

Vi undersøkte forekomst av selvrapporterte luftveissymptomer, arbeidsevne og lungefunksjon hos pasienter med astma stratifisert etter KMI. Videre har vi studert i hvilken grad astma og forhøyet KMI er uavhengig assosiert med disse utfallene og hvorvidt det er en interaksjon mellom astma og KMI≥25 kg/m^2 for disse utfallene. I en oppfølgingsstudie har vi vurdert assossiasjonen mellom endring av en respiratorisk byrde skår og endring i KMI og yrkeseksponering for damp, gass, støv og røyk, og hvordan dette varierte med kjønn og astma status.

Material og metode

Avhandlingen er basert på Telemarkstudien, en longitudinell generell populasjonsstudie startet i 2013. 50 000 tilfeldige innbyggere i Telemark fylke i alderen 16 til 50 år fikk tilsendt et spørreskjema (Q_{main}). Spørreskjemaet inneholdt spørsmål om yrkeshistorikk, luftveissymptomer, lege-diagnostisert astma, røykevaner og mulige konfundere. I en nøstet kasus-kontroll studie ble alle deltakere med legediagnostisert astma og et tilsvarende antall data-randomiserte deltakere uten astma invitert til ytterligere medisinske undersøkelser i 2013-2014. Dette innebar å besvare et spørreskjema ($Q_{spesical}$), spirometri med reversibilitetstesting, utfylling av skjemaet asthma control test questionnaire (ACT), måling av fraksjonert ekshalert nitrogenoksid (FeNO) og blodprøver. I 2018 ble alle som svarte i 2013 (n=16 099) invitert til en fem års oppfølging og mottok et nytt spørreskjema i posten (Q_{main}).

Alle deltakere med lege-diagnostisert astma som deltok på ytterligere medisinske undersøkelser i 2013-2014 ble inkludert i en nøstet kasus-kontroll studie (artikkel I). I artikkel II ble deltakerne fra artikkel I supplert med et tilsvarende antall data-randomiserte deltakere

uten astma. Artikkel III er en fem års oppfølgingsstudie der alle som svarte i 2013 ble invitert til å fylle ut spørreskjema på nytt. Deltakere som ikke oppgav høyde og/eller vekt ved begge tidspunkt ble ekskludert i denne artikkelen.

For å vurdere assosiasjonen mellom eksponering og utfallsvariablene ble det brukt justerte lineære eller logistiske regresjonsmodeller. I tillegg er det også brukt andre statistiske analyser som interaksjonsanalyser, Pearson's khikvadrattest test og varians analyse (ANOVA).

Hovedresultater

Ingen spesifikke luftveissymptomer inkludert i vårt spørreskjema var assosiert med forhøyet KMI hos deltakere med astma. Da vi brukte en respiratorisk symptombyrde skår var fedme signifikant assosiert med en odds ratio (OR) på 1.78 (95% KI 1.14 til 2.80) ved en grense på ≥ 6 som var den øverste tertilen av skåren. Fedme hos pasienter med astma var også assosiert med mer nåværende bruk av medisiner for astma med en OR på 1.60 (1.05 til 2.46) og redusert ACT skår (≤19) med en OR på 1.81 (1.03 to 3.18). Vi fant at både pre- og post bronkodilatorisk FVC var negativt assosiert med en KMI ≥30 kg/m^2, med β-koeffisient på henholdsvis -6.5 og -4.5. Den tilsvarende reduksjonen for FEV_1 var ikke like stor, og kun pre-bronkodilatoriske verdier var forskjellig mellom KMI gruppene (β-koeffisient -4.57 [-7.71 to -1.42]). Forhøyet KMI var ikke assosiert med høyere forekomst av sykefravær siste 12 måneder eller redusert arbeidsevne målt med WAS hos deltakere med astma når man sammenlikner med de normalvektige deltakerne.

Astma og forhøyet KMI var uavhengig assosiert med forhøyet respiratorisk symptombyrde skår og redusert lungefunksjon. I de justerte regresjonsmodellene var astma assosiert med redusert WAS (OR 1.9, 95% KI 1.4 til 2.5), sykefravær siste år (OR 1.4, 1.1 til 1.8) og forhøyet

respiratorisk symptombyrde skår (OR 7.3, 5.5 til 9.7). Fedme var assosiert med forhøyet respiratorisk symptombyrde skår (OR 1.7, 1.2 til 2.4) og redusert pre- og postbronkodilatorisk FVC og FEV_1. Fedme var ikke assosiert med mer forekomst av sykefravær eller redusert WAS. Alle luftveissymptomene var sterkt assosiert med astma, mens fedme var assosiert med fem av åtte symptomer. Interaksjonsanalysene viste ingen signifikant additiv eller multiplikativ interaksjon mellom astma og KMI for de undersøkte utfallene, med unntak av pre-bronkodilator FVC med en β-koeffisient på -3.6 (-6.6 til -0.6) hos de med astma og overvekt.

Med endring i respiratorisk symptombyrde skår som utfallsvariabel og endring i KMI som eksponeringsvariabel fant vi en justert β-koeffisient på 0.05 (95 % CI 0.04 til 0.07). Stratifisert for kjønn var β-koeffisienten 0.06 (0.04 to 0.09) for menn og for kvinner var den 0.05 (0.03 til 0.07). Det var ingen signifikant forskjell mellom kjønnene. Stratifisert for astma status var det en signifikant høyere β-koeffisient for deltakere med astma [(0.12, 0.06 til 0.18)] sammenliknet med ikke å ha astma [0.05, (0.03 til 0.06)] (p-verdi 0.011). Med endring i respiratorisk symptombyrde skår som utfallsvariabel og endring i yrkeseksponering for damp, støv, gass og røyk som eksponeringsvariabel fant vi en justert β-koeffisient på 0.15 (95 % KI 0.10 til 0.19). Stratifisert for kjønn var β-koeffisienten 0.18 (0.12 til 0.24) for menn og 0.13 (0.07 til 0.19) for kvinner. Stratifisert for astma status var det en signifikant høyere β-koeffisient for de som ikke hadde astma [(0.15, 0.11 til 0.19)], men den var ikke signifikant for de med astma [0.18, (-0.02 til 0.38)]. Det var ingen forskjell mellom kjønnene eller astma status (p-verdi henholdsvis 0.064 og 0.412).

Konklusjon

Deltakere som hadde både astma og fedme hadde høyere forekomst av nåværende bruk av medisiner for astma, høyere symptom byrde score, dårligere kontrollert astma basert på ACT

og redusert lungefunksjon (FVC and FEV_1) sammenliknet med deltakere med astma og normalvekt. Astma og fedme var uavhengig assosiert med økt respiratorisk symptombyrde skår og lungefunksjon. Redusert WAS og sykefravær var assosiert med astma, men ikke forhøyet KMI. Vi fant en mulig interaksjon mellom astma og overvekt assosiert med pre-bronkodilatorisk FVC, men observerte ingen andre interaksjoner. I oppfølgingsdelen av studien var endring i KMI og yrkeseksponering for damp, støv, gass og røyk assosiert med endring i respiratorisk symptombyrde skår. Endring i KMI påvirket deltakere med astma mer enn de uten, men det var ingen kjønnsforskjeller.

1.3 Summary

Background

Asthma and obesity are associated with adverse respiratory outcomes; however, a possible interaction between the two conditions is less studied. Previous studies have identified the combination of asthma and obesity as a distinct asthma phenotype. Patients with this phenotype have lesser control and greater severity of asthma with more respiratory symptoms and reduced lung function. The frequency of sick leave and self-evaluated work ability can be used to describe the functional level of patients with asthma and obesity. For patients with asthma, this functional level may depend on asthma control, the burden of symptoms, and lung function. Patients with obesity may also have reduced work ability and an increased frequency of sick leave due to difficulties caused by their weight. To our knowledge, work ability assessed by Work Ability Score (WAS) has not been studied in patients with asthma and obesity. Asthma and asthma exacerbations are associated with exposure to vapors, gas, dust, and fumes (VGDF).(1, 2) Obesity and asthma have several common comorbidities; low-grade systemic inflammation and altered lung mechanics have

been demonstrated in both asthma and obesity. However, to which extent asthma and increased BMI are independently associated with respiratory symptoms, lung function, work ability, and sick leave warrants further study. To our knowledge, few studies have focused on the changes in respiratory symptoms due to changes in body mass index (BMI) or occupational exposure to VGDF. A better understanding of the combined effects of asthma and obesity may help establish new and more personalized treatment and follow-up for patients with asthma and obesity.

Aim

We assessed the occurrence of self-reported respiratory symptoms, work ability, and lung function in patients with asthma stratified by BMI. Further, we studied the extent to which asthma and increased BMI are independently associated with these outcomes; and whether there is an interaction between asthma and BMI ≥25 kg/m^2 regarding these outcomes. In a follow-up study, we assessed the association between a respiratory burden score and changes in BMI and occupational VGFD exposure and how it varied with sex and asthma status.

Materials and methods

This thesis is based on the Telemark Study, a longitudinal general population-based study started in 2013. The study was conducted in Telemark County, Norway, and 50 000 random inhabitants between the ages of 16 and 50 years were mailed a questionnaire (Q_{main}). The questionnaire included questions pertaining to occupational history, respiratory symptoms, physician-diagnosed asthma, smoking habits, and possible confounders. In a nested case-control study, all participants with physician-diagnosed asthma and computer-randomized

participants without asthma were invited to undergo a further medical examination in 2013–2014 that included the $Q_{spesical}$ and asthma control test (ACT) questionnaires, spirometry with reversibility testing, measurement of fractional exhaled nitric oxide (FeNO), and blood tests. In 2018, 16 099 responders from 2013 were invited to a 5-year follow-up study and mailed a new postal questionnaire (Q_{main}).

In paper I, all participants with physician-diagnosed asthma attending further medical examination in 2013–2014 were included in a nested case-control study. In paper II, the nested case-control study from paper I was expanded to include computer-randomized participants without asthma. Paper III was a 5-year follow-up study in which all responders of the postal questionnaire in 2013 were invited to complete the questionnaire again. Participants that did not provide data regarding weight and height to calculate BMI in 2013 and 2018 were excluded in paper III.

Adjusted linear or logistic regression models were used to assess the association between exposure and the outcome variables. In addition, other statistical analyses, such as interaction analyses, Pearson's chi-squared test, and one-way analysis of variance (ANOVA), were also used.

Main results

No specific respiratory symptoms included in our questionnaires were associated with increased BMI in participants with asthma. However, when assessing the respiratory symptom score, participants with obesity had a significantly higher score with an odds ratio (OR) of 1.78 (95 % confidence interval (CI): 1.14–2.80) when the cut-off value was set at ≥ 6 (representing the upper tertile of the score). Obesity among the participants with asthma was also associated with the current use of medication for asthma with an OR of 1.60 (1.05–

2.46) and a reduced ACT score of ≤19 with an OR of 1.81 (1.03–3.18). Pre-and post-bronchodilator FVC were significantly negatively associated with a BMI of ≥30 kg/m^2, with β-coefficients of -6.5 and -4.5. The comparable decrements for FEV_1 were not as large, and only pre-bronchodilator values differed significantly between the groups (β-coefficient: -4.57 [-7.71 to -1.42]). Among the participants with asthma, a higher frequency of sick leave in the last 12 months or a reduced work ability measured with WAS were not associated with obesity or overweight compared with normal weight.

Asthma and increased BMI were independently associated with an increased respiratory burden score and reduced lung function. In the adjusted regression models, asthma was associated with a reduced work ability score (OR: 1.9; 1.4–2.5), frequency of sick leave in the last year (OR: 1.4; 1.1–1.8), and an increased symptom score (OR: 7.3; 5.5–9.7). Obesity was associated with an increased symptom score (OR: 1.7; 1.2–2.4) and reduced pre- and post FVC and FEV_1. Obesity was not associated with a higher frequency of sick leave or reduced WAS. On assessing the respiratory symptoms separately, asthma was strongly associated with all eight symptoms, whereas obesity was associated with five. No statistically significant additive or multiplicative interaction was observed between the outcomes assessed and asthma and BMI in the interaction analyses, except for pre-bronchodilator FVC with a β-coefficient of -3.6 (-6.6 to -0.6).

The adjusted β-coefficient was 0.05 (95 % CI: 0.04–0.07) when changes in the respiratory burden score and BMI were used as the outcome and exposure variables, respectively. When stratified by sex, the β-coefficient was 0.06 (0.04–0.09) and 0.05 (0.03–0.07) for males and females, respectively. Statistical testing to assess any difference between the sexes showed no such association. When stratified by asthma status, the β-coefficient for

participants with asthma [0.12, (0.06–0.18)] was significantly higher (p-value: 0.011) than that of those without asthma [0.05, (0.03–0.06)]. The adjusted β-coefficient was 0.15 (95 % CI, 0.10–0.19) when changes in the respiratory burden score and VGDF exposure frequency were used as the outcome and exposure variables. When stratified by sex, the β-coefficient was 0.18 (0.12–0.24) and 0.13 (0.07 to 0.19) for males and females, respectively. When stratified by asthma status, the β-coefficient was significantly higher for participants without asthma [(0.15, 0.11 to 0.19)] than that of those with asthma [0.18, (-0.02 to 0.38)]. Statistical testing to assess any difference between the sexes or asthma status showed no such association (p-values: 0.064 and 0.412, respectively).

Conclusions

Participants with concurrent asthma and obesity used more current medication for asthma, had a higher respiratory burden score, poorly controlled asthma based on ACT, and reduced lung function (FVC and FEV_1) compared with participants with asthma and normal weight. Asthma and obesity were independently associated with an increased respiratory burden score and lung function values. Reduced frequency of sick leave and WAS were associated with asthma but not increased BMI. We observed a possible interaction between prebronchodilator FVC and asthma and overweight; no other significant interactions were observed. In the follow-up part of the study, changes in BMI and occupational exposure were associated with changes in the respiratory burden score. Changes in BMI affected participants with asthma more than participants without asthma; no sex-related difference was observed.

1.4 Selected Abbreviations

ACT	Asthma Control Test
BMI	Body Mass Index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume after 1 second
FVC	Forced vital capacity
OR	Odds ratio
RR	Relative risk
VGDF	Vapors, gas, dust, and fumes
WAI	Work Ability Index
WHO	World Health Organization
WAS	Work Ability Score

1.5 List of tables and figures

1.6 List of papers

I. Klepaker G, Svendsen MV, Hertel JK, Holla ØL, Henneberger PK, Kongerud J, Fell AKM. Influence of Obesity on Work Ability, Respiratory Symptoms, and Lung Function in Adults with Asthma. Respiration. 2019;98(6):473-481. doi: 10.1159/000502154.

II. Klepaker G, Henneberger PK, Hertel JK, Holla ØL, Kongerud J, Fell AKM. Influence of asthma and obesity on respiratory symptoms, work ability and lung function: findings from a cross-sectional Norwegian population study. BMJ Open Respir Res. 2021;8(1):e000932. doi: 10.1136/bmjresp-2021-000932.

III. Klepaker G, Henneberger PK, Torén K, Brunborg C, Kongerud J, Fell AKM. Association of respiratory symptoms with body mass index and occupational exposure comparing sexes and subjects with and without asthma: follow-up of a Norwegian population study (the Telemark study). BMJ Open Respir Res. 2022;9(1):e001186. doi: 10.1136/bmjresp-2021-001186.

2 Background

For the last hundred years, the eastern part of the County of Telemark has been a major onshore industrial center of Norway. This region still has a high proportion of industrial workers and craftsmen. Telemark also has a higher frequency of sick leave than any other region in Norway and the highest rate of disability in the country.(3) In addition, the use of medication for obstructive airway diseases is above the national average (87 users per 1000 inhabitants in Telemark County vs. 78 users per 1000 inhabitants in Norway in 2015).(4) The large proportion of industrial workers in this region facilitated assessing the impact of occupational exposure on respiratory health. As a response to these challenges, a population-based study, the Telemark Study, was initiated in 2013 with an overall goal of establishing preventive strategies aimed at improving and maintaining public health. The prevalence of obesity and its co-morbidities is rising, posing a major threat to public health. A close association has been observed between asthma and obesity. This thesis is based on the data collected in the Telemark study conducted in 2013 and 2018 and aims to gain further knowledge regarding the relationship between asthma and increased BMI and their influence on respiratory symptoms, lung function, and work ability.

3 Introduction

3.1 Asthma

Asthma is a heterogeneous respiratory disease characterized by reversible chronic airway inflammation and variable respiratory symptoms, such as wheezing and shortness of breath, with variable expiratory airflow limitation.(5) It is estimated that 334 million individuals worldwide have asthma. The mortality associated with asthma is low; however, 1% of deaths per year worldwide (approximately 250.000) is estimated to be caused by asthma.(6) In

Norway, the prevalence of physician-diagnosed asthma among individuals aged 18–45 years is reported to be 11.05 %.(7) The mean prevalence of asthma worldwide is reported to be 4.27 % (95 % CI: 4.17—4.36), but with large differences between countries and continents.(7) Various conditions, such as chronic rhinosinusitis, obstructive sleep apnea, gastro-esophageal reflux disease, and obesity, are often observed in patients with asthma.(8) These comorbidities may change the asthma phenotype (observable traits of asthma), be a part of the same pathophysiological process, and/or contribute to uncontrolled asthma.(8) Moreover, exposure to airway irritants, allergic agents, dust, and fumes can trigger asthma attacks, and exposure to such agents over time may worsen asthma resulting in more respiratory symptoms, reduced asthma control, and reduced lung function.

Respiratory symptoms, spirometry, and asthma control in participants with asthma

Various respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and/or cough, are a part of the definition of asthma.(5) Asthma is a chronic respiratory disease; however, control and severity may change during the patient's lifetime. A substantial proportion of patients have had asthma since childhood; however, as they move into adulthood, their symptoms may disappear, and medication may not be required. However, the symptoms of asthma or the requirement for medication may relapse later in life. A general population study from Northern Sweden that was standardized for age and sex distribution reported that the prevalence of physician-diagnosed asthma in Northern Sweden was 13.3% in 2016.(9) Current asthma in the same study was defined as any wheezing in the last 12 months, one attack of shortness of breath in the last 12 months, or

current use of asthma medication. The study reported that 10.9% of the participants had current asthma in 2016.

Cross-sectional studies have shown that lung function is lower than predicted in patients with asthma.(10) Spirometry, which is used to measure the forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and FEV1/FVC-ratio, often show normal results in asymptomatic patients.(11) Symptomatic patients typically present with airflow limitation with reduced FEV_1 and FEV_1/FVC-ratio. FVC is usually normal or near-normal; however, it can decrease as a result of air trapping or submaximal inhalation.(11) Asthma may have an impact on the decline in FEV_1, which is larger than that in participants without asthma. However, this is dependent on several factors such as treatment, sex, smoking, severity, and airway responsiveness.(10, 12) Lung function does not strongly correlate with asthma symptoms, but reduced FEV_1 is a predictor of the risk of exacerbations and lung function decline.(5) A persistent bronchodilator reversibility suggests uncontrolled asthma.(5)

It has been customary to assess asthma by describing its severity. However, the current recommendation for assessing asthma is to monitor its control rather than severity. This change has been advised as many physicians regard asthma control to be a better basis for treatment decisions. (13-15) The severity of asthma reflects the intensity of the disease, and when and which treatment to apply, whereas the control of asthma reflects the extent to which the treatment goals are met. Several validated instruments can be used for assessing asthma control. One of the most commonly used instruments is the validated Asthma Control Test (ACT), which consists of five questions (16). All answers are given a score of 1–5, where five corresponds to the best, and the maximum score is 25. A total score of <19

indicates poorly controlled asthma, and intervention and change of treatment may be needed (16). ACT is based only on the respiratory symptoms and use of medication; however, other instruments, such as the Asthma Control Questionnaire (ACQ), also include lung function values. In a large study conducted across five European countries, 53.5% of the participants were reported to have poorly-controlled asthma using the total ACT score.(17) In the same study, well-controlled asthma was associated with lesser health care contacts in the last 6 months, better health-related quality of life, and lesser impact on the Work Productivity Loss and Activity Impairment questionnaires.

Sick leave and work ability in participants with asthma

Sick leave and work ability can be used to describe the functional level of patients with asthma. The frequency of sick leave and work ability may depend on asthma control and severity as well as the burden of symptoms and lung function. It is difficult to compare sick leave estimates between studies as the definition of sick leave varies based on the duration and definition of long-term/short-term and self-reported and register-based sick leave. In addition, cultural and national differences add to the heterogeneity. When assessing sick leave and work ability among participants with asthma, further diversity is added as asthma is a heterogenic disease with several phenotypes. Illmarinen et al. defined the work ability concept as: “How good are workers at present and in the near future and how able are they to do their job with respect to work demands, health and mental resources?”(18). Measuring work ability is complex; therefore, a work ability index (WAI) has been developed and used in epidemiological studies for more than 30 years. WAI is the sum of seven items. It has been validated and is considered a reliable instrument for assessing work ability.(19) Previous studies have shown that a low score predicts later work disability and may help

identify employees requiring support to increase their work ability.(18) WAI is not a static measure and is influenced by age, health status, weight, and level of physical work.(20) It has been reported that patients with asthma receive more welfare and have a higher frequency of sick leave and disability compared with participants without asthma.(21, 22) In a longitudinal study (20-year follow-up), having asthma at the age of 20 years has been shown to affect the work ability measured with the Work Ability Score (WAS), one of the items of the WAI battery.(23)

3.2 Obesity

Obesity can be defined as abnormal or excessive fat accumulation that poses a health risk.(24) It is caused by an energy imbalance between the calories consumed and the calories expended. Body mass index (BMI), calculated as weight in kilograms (kg) divided by the square of height in meters (m^2), is commonly used to classify overweight and obesity. The World Health Organization (WHO) defines overweight as BMI between 25 kg/m^2 and 29.9 kg/m^2, and obesity as BMI of ≥30 kg/m^2.(25) BMI has high specificity (0.90) but low sensitivity (0.50) for assessing obesity and may be a less accurate predictor in some ethnic groups and the elderly. (26) Moreover, it cannot distinguish between muscles and fat and does not describe the fat distribution. However, it is simple and widely accepted, and the cut-off value to define obesity is based on well-established risk factors.(26) Other measurements of obesity, such as the hip-waist ratio, waist circumference, and skinfold thickness, are hampered by the lack of standardized measurement protocols, reference data, and accuracy in individuals with severe obesity (BMI: >35 kg/m^2).(26) It is estimated that 1.9 billion adults worldwide have overweight, and 650 million adults have obesity.(24) In Norway, the average BMI for adult men is 26.5 kg/m^2 (95% CI: 26.3–26.7) and 25.6 kg/m^2 for women (95% CI: 25.4–25.8).(27) The average BMI increases to the highest with 27.6

kg/m^2 for men and 26.3 kg/m^2 for women in the age group of 45–54 years, and then slowly decreases. The proportion of all Norwegians with a BMI over 25 kg/m^2 is 59% for men, and 47% for women. In the 45–54 years age group, 21% of the men and 18% of the women have a BMI over 30 kg/m^2. The proportion of individuals with overweight or obesity in Telemark is 53%, while the average in Norway is 55%.(27) Severe obesity is associated with higher mortality and morbidity. The comorbidities associated with obesity include cardiovascular diseases, cancer, metabolic diseases (e.g., diabetes mellitus), asthma, and gastro-esophageal reflux disease.(28)

Several strategies can be applied to prevent development of overweight and obesity; these strategies should have a life course approach. The prevention measures can be structural measures implemented by the government or society such as educational programs, reduced access to calorie-rich food, promoting transportation such as walking, and taxation of unhealthy products.(29) Individual prevention measures include choosing healthy food products and increasing physical activity. The treatment of overweight and obesity aims to reduce the excess calorie intake or increase the energy expenditure. This can be done with low-calorie diets or increased physical activity. Behavioral modifications and/or lifestyle intervention are an important part of a weight loss program and prevent weight gain after the weight loss.(29) Other treatment options for weight loss include the use of medications such as Orlistat (selective inhibitor of pancreatic lipase that reduces intestinal digestion of fat) and Liraglutide (GLP-1 agonist, which among several effects, reduces hunger).(29) Bariatric surgery may be a treatment option in some cases. Surgical procedures are intended to physically limit the ingestion of food or enhance malabsorption; however, studies have shown that they also alter the metabolic processes, reduce appetite, and give earlier satiety after meals, resulting in weight loss.(29)

Respiratory symptoms in participants with overweight and obesity

Obesity can cause respiratory symptoms even in the absence of lung disease.(30) Obesity and overweight can cause breathlessness regardless of physical fitness and after adjusting for FVC.(31) It has been suggested that this breathlessness is a result of increased workload and respiratory demand.(31) Studies have shown an increase in self-reported dyspnea and wheezing at rest and exertion among participants with obesity compared with that in participants with normal weight.(30, 32). Changes in respiratory symptoms due to weight gain or loss have not been assessed widely. Ekström et al. reported that participants with increased BMI since their 20s reported an increased incidence of breathlessness compared with those with stable weight.(33) Another study has reported that as the participants became obese, males had a greater increase in wheezing without a cold, while females had a greater increase in asthma prevalence.(34)

Spirometry in participants with increased BMI

Several review studies have been published on how obesity affects lung function.(35-37) It has been found that FVC and FEV_1 are consistently mildly decreased in participants with obesity and the FEV_1/FVC ratio remains unchanged. (37) FVC tends to decrease more than FEV_1 in participants with severe obesity, resulting in an increase in the FEV_1/FVC ratio. However, fat distribution may be more important than BMI when determining the effect of obesity on spirometry. Waist-hip ratio, waist circumference, and abdominal height are considered better predictors of FVC and FEV_1 than BMI.(37). Other lung function measurements, such as static lung volumes and gas transfer, are also affected by obesity.(37) The results from a meta-analysis show that the weighted mean difference as the percentage predicted was reduced by -6.9% for FEV1 (95% CI: -11.1 to -2.8), -7.5% (-11.4 to

3.7) for FVC, and -0.9% (-1.9 to 0.1) for FEV1/FVC when comparing adults with overweight/obesity and normal weight.(35) Changes in weight have also been associated with changes in the spirometric values. In studies on patients after bariatric surgery, weight loss was associated with an improvement in the spirometric values.(38, 39) Further, it has been demonstrated that incident or worsening obesity is associated with a more rapid decline in FEV1 and FVC than the age-related decline observed in individuals with normal weight. (40, 41)

Sick leave and work ability in participants with increased BMI

There is clear evidence regarding the association between overweight and obesity and the increased frequency of sick leave. (42-44) This may be a result of the increased number of conditions, such as cardiovascular diseases, in participants with increased BMI. In addition, the increased weight may also cause problems with movement and the physical workload required to perform work tasks. In a review by Neovius et al., obesity was associated with a higher frequency and longer duration of sick leave.(42) They reported that participants with obesity in European studies had ten more sick leave days per person per year compared with their normal-weight counterparts. Moreover, a clear trend for a higher frequency of sick leave with an increasing degree of obesity was indicated. A review using only longitudinal studies came to similar conclusions.(43) The authors concluded that there is strong evidence for a positive relationship between obesity and the frequency of long-term sick leave. The evidence regarding short-term sick leave was considered inconclusive. The relationship between overweight and long-term sick leave was also inconclusive; however, there was a trend for a higher frequency of long-term sick leave. A meta-analysis concluded that being overweight was a risk factor for sick leave with a relative risk (RR) of 1.09 (95% CI: 1.04–1.15)

(44). A RR of 1.30 (95% CI: 1.19–1.42) was found for obesity. Both cross-sectional and longitudinal studies have shown reduced work ability in participants with obesity.(45) Andersen et al. used two items of the WAI questionnaire to assess work ability in different BMI categories.(45) The questions assessed work ability in terms of the physical and mental demands of their work. They reported that the odds ratio (OR) increased for lower work ability with increasing BMI in terms of physical demands. Compared with participants with normal weight, participants who had overweight had an OR of 1.11 (95% CI: 1.01–1.28) for reduced work ability. The OR was 1.17 (95% CI: 1.01– 1.34) for obesity class I (BMI: 30–34.99 kg/m^2). The OR was 1.69 (95% CI: 1.10–2.62) for the highest BMI category, obesity class III (BMI: ≥40 kg/m^2). BMI was not associated with reduced work ability in terms of the mental demands of the work. In a study conducted by Vesikansa et al., the proportion of participants with obesity who rated their current physical working ability as good (53–73 %) was significantly lower than participants with normal weight (90%).(46)

3.3 Obesity and asthma

Asthma is more common among patients with obesity compared with patients with normal weight; however, the respiratory symptoms associated with obesity can mimic asthma.(5) As a consequence, both over- and under-classification of asthma in patients with obesity is reported.(47) Obesity is a common comorbidity in asthma.(5) A recent review concluded that there is sufficient evidence regarding a causal relationship between asthma and increased BMI.(48) Asthma is a heterogeneous respiratory disease, and several phenotypes of asthma have been recognized.(49) However, the number of phenotypes and the definitions of the different phenotypes remains unclear. Nevertheless, several previous studies have consistently classified obese asthma as a distinct phenotype. (49-51) Patients with this asthma phenotype report more respiratory symptoms, reduced lung function, later

onset of asthma, and poorer response to asthma medications compared with patients with asthma without obesity.(50, 51) The potential underlying mechanisms for the link between asthma and obesity are shared genetic components, systemic inflammation, alterations of the gut microbiome, metabolic abnormalities, nutritional factors, and alterations of the lung anatomy and function.(52) Investigating these mechanisms are beyond the scope of this dissertation.

Respiratory symptoms in participants with asthma and increased BMI

As described previously, asthma is defined by variable respiratory symptoms, and obesity may also cause respiratory symptoms. In a study conducted by Kwon et al., 852 patients with asthma were examined, and an OR of 3.2 (p=0.002) was reported for wheezing within the previous 3 months when comparing patients who were overweight with patients with normal weight.(53) The incidence of cough and dyspnea was not related to BMI in their study. Other studies have also reported an association between obese asthma and wheezing.(54, 55) Contrary to these findings, Bildstrup et al. reported that more severe cough and tightness in the chest were associated with increased BMI while wheezing and shortness of breath were not.(56) A possible explanation for the conflicting results may be that each study assessed only a few respiratory symptoms, often as a secondary outcome or finding, emphasizing the need for studies that simultaneously assess several respiratory symptoms.

The burden of respiratory symptoms in adult patients with obesity and asthma is significantly higher than that in patients with normal weight and asthma.(57) They report higher rates of daily symptoms, restricted activity days, missed workdays, and a higher likelihood of severe asthma. In addition, they use more asthma medication.(57) A recent

systematic review and meta-analysis have shown that participants with obesity are more likely to use asthma medication (58). Both asthma and obesity are associated with breathlessness/dyspnea. Previous studies have shown that patients with asthma and obesity report the same symptoms as patients with asthma and normal weight.(57) However, few studies have assessed whether the prevalence of respiratory symptoms among participants with obesity and asthma is different from that of respiratory symptoms in either condition separately. Moreover, to our knowledge, few studies have assessed whether there is an interaction between asthma and obesity regarding respiratory symptoms in these participants. In a study conducted by Nicolacakis et. al., the interaction between asthma and obesity was assessed using different lung function tests. (59) They reported no evidence of a synergistic interaction; however, the study sample was small and not adjusted for important confounders such as smoking habits. A better understanding of whether asthma and increased BMI are dependently associated with more respiratory symptoms and lung function and whether there is an interaction between the outcomes may aid in clinical decision-making and help formulate personalized treatments for patients with asthma and increased BMI.

Studies have demonstrated that patients with asthma and obesity have more severe asthma compared with their normal-weight counterparts. (56, 60) However, few studies have been conducted on asthma control in patients with asthma and obesity. Schatz et al. reported that a higher BMI was an independent predictor of poor asthma control.(61) To our knowledge, only a limited number of studies have assessed asthma control using the asthma control test (ACT) in patients with increased BMI and asthma; other instruments to evaluate asthma control have been used in other studies.(62)

Lung function (Spirometry) in participants with asthma and increased BMI

In previous studies on patients with asthma and obesity, the most frequent outcome studied was lung function. In a meta-analysis by Forno et al., adults with asthma and obesity had a lower % predicted FEV1 and FVC compared with participants with asthma and normal weight; however, no differences were reported for the FEV1/FVC ratio.(35) A case-control study on participants with asthma conducted by Pisi et al. reported that participants who had overweight (BMI between 25 and 30 kg/m^2) had lower FVC (103% vs. 107%), lower FEV_1 (91% vs. 97%), and lower FEV_1/FVC ratio (73% vs. 77 %) compared with participants with normal weight (BMI between 18.5 and 25 kg/m^2). Other studies have reported similar results as these studies, confirming that the lung function measured by spirometry was lower in participants with asthma and obesity than that in participants with asthma and normal weight.(63, 64) The extent of the independent association between lung function and obesity and asthma status and whether there is an interaction between lung function and asthma and increased BMI, is less studied. In the study conducted by Forno et al., the reduction in lung function was more in participants without asthma than that in participants with asthma.(35) However, this study did not assess the separate influence of increased BMI or asthma on lung function in participants with asthma and obesity. Few studies have investigated the possible interaction between lung function and asthma and increased BMI. In the study conducted by Nicolacakis et al., a synergetic interaction between lung function and asthma and obesity was not detected with different lung function tests.(59) However, the study sample was small, and the analyses were not adjusted for smoking status. An interaction between FVC and BMI on breathlessness has been reported by Ekström et al. It was reported that the probability of breathlessness increased more steeply with higher BMI in individuals with lower absolute FVC.(33)

Sick leave and work ability in participants with asthma and increased BMI

As described previously, an increase in BMI is associated with an increase in the frequency of sick leave and reduced work ability. Similar associations have been reported for patients with asthma. However, there is an apparent lack of studies that assessed the frequency of sick leave and work ability of participants with both asthma and increased BMI. In a Swedish study, obesity was more common among participants who were on sick leave because of respiratory problems than that in the general population.(65) This study included only a small sample of 237 patients on sick leave for >2 weeks recruited from a compulsory insurance registry. In a survey from the Telemark Study reported by de Bortoli et al., obesity and asthma were associated with an increased frequency of sick leave [OR: 2.2 (95% CI: 1.5–3.1)] compared with normal weight among participants with asthma.(66) No significant association was reported between increased BMI and reduced work ability in patients with asthma. Few studies on work ability and sick leave have been conducted among patients with asthma and increased BMI. As described previously, there is clear evidence suggesting that both conditions are associated with an increased frequency of sick leave and reduced work ability. However, it is unknown whether participants with asthma and increased BMI have an increased frequency of sick leave or lower work ability compared with participants with normal weight and no asthma; the extent remains unknown. It is also unknown whether there is an interaction between these outcomes and asthma and increased BMI.

4 Hypotheses and objectives

Our main hypotheses were as follows:

- Increased BMI and asthma are independently associated with respiratory symptoms, lung function, and reduced work ability.
- There is an interaction between asthma and increased BMI on respiratory symptoms, lung function, and work ability.
- Changes in BMI or occupational exposure to vapors, gas, dust, and fumes (VGDF) affect respiratory symptoms.

Our objectives were as follows:

- Assess the occurrence of self-reported respiratory symptoms, work ability, and lung function in participants with asthma stratified by BMI (Paper I).
- Study the extent to which asthma and overweight/obese status are independently associated with respiratory symptoms, lung function, work ability, and sick leave; and whether there is an interaction between asthma and a BMI of ≥25 kg/m^2 regarding these outcomes (Paper II).
- Assess the association between a respiratory burden score and changes in BMI and occupational VGFD exposure in a follow-up study and how the burden score varies with sex and asthma status (Paper III).

5 Methods

5.1 Study population, sample, and setting

The Telemark Study is a longitudinal general population-based study that was started in 2013. The study included 50 000 random inhabitants between the age of 16 and 50 years living in Telemark County, Norway, who were mailed a questionnaire (Q_{main}). Participants were considered ineligible if the questionnaire was returned by the postal service because of an unknown address (e.g. had moved), language-related issues, or had other reasons. The questionnaire included questions regarding occupational history, respiratory symptoms, physician-diagnosed asthma, smoking habits, and possible confounders. Among the 50 000 inhabitants to whom the questionnaires were mailed, 16.099 responded by mailing the questionnaire back using the pre-paid envelope provided.

In the second phase, all participants with physician-diagnosed asthma from the survey and computer-randomized participants without asthma (controls) were invited to undergo a further medical examination in 2013-2014, which included completing the $Q_{spesical}$ and ACT questionnaires, spirometry with reversibility testing, measurement of fractional exhaled nitric oxide (FeNO), and blood tests.

In 2018, all 16.099 responders from 2013 were invited to participate in a 5-year follow-up study and were mailed a postal questionnaire (Q_{main}). They could respond by mailing the questionnaire back in the pre-paid envelope or by logging in to a secure website.

5.2 Study design

This dissertation consists of three papers derived from the Telemark study. In paper I, all participants with physician-diagnosed asthma who underwent a further medical examination in 2013-2014 were included in a nested case-control study. A nested case-control study is a variation of a case-control study in which the cases and controls are drawn

from a larger cohort study. In paper II, the nested case-control study from paper I was expanded to also include computer-randomized participants without asthma. Paper III was a 5-year follow-up study in which all responders from the postal questionnaire in 2013 were invited to complete the questionnaire again. Participants who did not provide data regarding their weight and height to calculate BMI in 2013 and 2018 were excluded in paper III. We also excluded participants with an extreme change in BMI (more than ±20 kg/m^2) based on a scatter plot to exclude extreme values and possible errors in recorded weight because of the automatic scanning of the questionnaires.

5.3 Study variables

The study variables were selected as we considered them to be relevant and provide valid answers to the aims and hypotheses within the frame of the data from the Telemark study. The questionnaires are based on validated questionnaires from similar respiratory health studies. Well-known and validated tests of respiratory health, such as spirometry, were performed during further medical examinations. The adjustment variables were selected as they are well-known confounders of respiratory symptoms and diseases. The confounders were also assessed in sensitivity analyses. When building the adjusted regression models, the possible confounders were included separately in the model to assess their influence on the model.

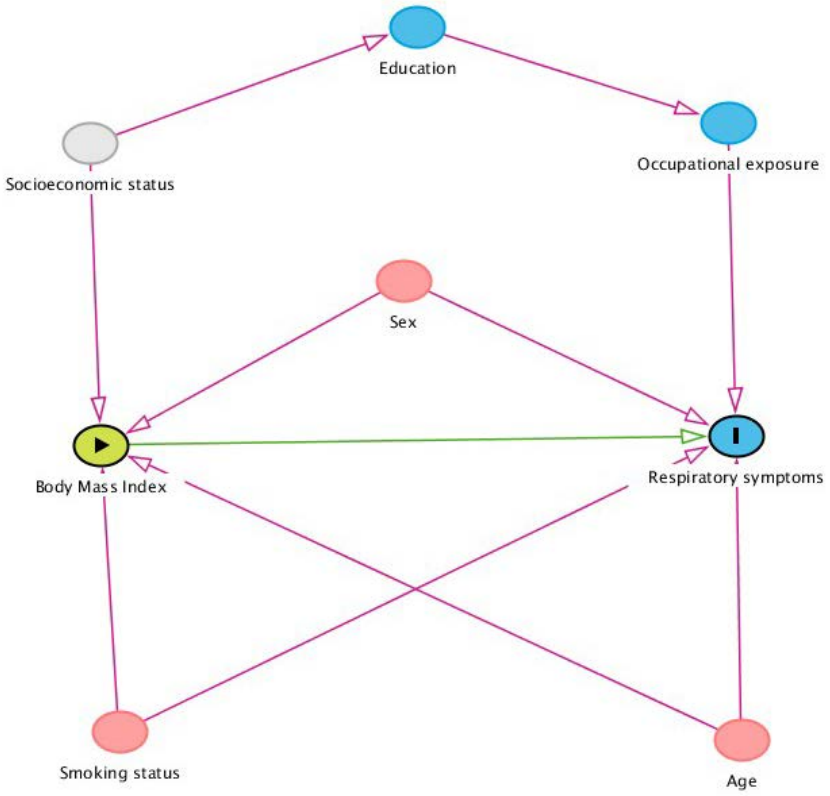


Figure 1. Confounding variables using a directed acyclic graph. Purple paths indicate a biasing pathway. (Figure developed using DAGitty tool by Textor et al. (67))

5.3.1.1 Questionnaires

The questionnaires used in 2013 (Q_{main} and $Q_{spescial}$) and 2018 (Q_{main}) were based on the European Community Respiratory Health Survey questionnaire and a validated survey questionnaire from a similar study conducted in Western Sweden.(68, 69) The Q_{main} questionnaire assessed the respiratory symptoms, occupational history and exposures, frequency of sick leave, allergies, comorbidities, and socioeconomic variables. The $Q_{spescial}$ questionnaire included some questions from the Q_{main} questionnaire in addition to more questions regarding respiratory symptoms, occupational exposures, and other comorbidities. In papers I and II, if the same question was asked in Q_{main} and $Q_{spescial}$, the answer from $Q_{spescial}$ was used in the analyses. All missing data regarding the respiratory

symptoms, physician-diagnosed diseases, and use of medication were recoded as an absence of that symptom/disease or use of medication. Translated unvalidated English versions of the questionnaires are attached in the appendix.

5.3.1.2 Physician-diagnosed asthma

Physician-diagnosed asthma was defined as an affirmative answer to the question in the questionnaires: ”Has a doctor/physician ever diagnosed you with asthma?” The participants were also instructed to specify the age when they first experienced symptoms of asthma and the year they last experienced symptoms of asthma.

5.3.1.3 BMI

In the follow-up part, BMI measured in kg/m^2 was calculated for each participant in 2013 and 2018 using the self-reported weight and height from the questionnaires. BMI was stratified into the following categories recommended by the WHO: normal weight (including underweight), <25.0 kg/m^2; overweight, 25.0–29.9 kg/m^2; and obese, ≥30 kg/m^2.(70) BMI was also used as a continuous variable. The change in BMI was calculated for each participant by subtracting the BMI value in 2013 from that in 2018. In the case-control part of the study, the height and weight were measured by trained study personnel using the same instruments and tools for all participants. The participants were weighed without shoes and heavy garments. Height was rounded to the nearest centimeter and weight to the nearest kilogram. BMI was calculated and stratified into the same categories as in the follow-up part of the study.

5.3.1.4 Respiratory symptoms and burden score.

The questionnaires consisted of questions regarding respiratory symptoms in the last 12 months and the use of medication for asthma, as listed in Table 1. The prevalence of the specific respiratory symptoms and the association with BMI are assessed in papers I and II. A respiratory burden score was constructed; however, the questions included in the score

differed according to aim and study population. Another reason for the difference in the questions was that Q_{main}, in 2013 did not enquire about breathlessness or dyspnea in the last 12 months mistakenly, only such symptoms during the night. The respiratory burden score was calculated for each individual by assigning a value of one to all positive answers and then adding all the positive answers. If dichotomization was appropriate, a cut-off value was set, which was represented by the upper tertile of the scores. In the follow-up part of the study, a change in the respiratory burden score was the outcome variable, and this was calculated by subtracting the burden score in 2013 from that in 2018. A positive number represents more respiratory symptoms in 2018 than in 2013.

Table 1. Questions included in the respiratory burden score in the papers.

Respiratory symptoms analyzed and used in respiratory burden score Question	Questions used in paper (x) Paper I	Paper II	Paper III
Q1: Have you had wheezing or whistling in the chest at some point over the course of the last 12 months?	x	x	x
Q2: Have you ever felt breathless due to wheezing or whistling in your chest?	x	x	x
Q3: Have you had whistling or wheezing in your chest without having a cold?	x	x	x
Q4: Have you experienced shortness of breath when at rest at any time in the last 12 months?	x	x	
Q5: Have you experienced shortness of breath after being exposed to cold at any time in the last 12 months?	x	x	

Q6: Have you experienced shortness of breath after exerting yourself at any time in the last 12 months?	x	x	
Q7: Have you woken up due to coughing attacks during the last 12 months?	x	x	x
Q8: Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?	x	x	x
Q9: Have you been woken up by shortness of breath at any time in the last 12 months?	x	x	x
Q10: Have you experienced an asthma attack in the last 12 months?	x		
Q11: Do you currently use any medication (spray, inhalation powder, or tablets) for asthma?			x
Q12: Have you in the last years had prolonged cough			x
Total maximum score	10	9	8

5.3.1.5 Work ability and sick leave

Data on work ability and sick leave was collected in the questionnaires. Work ability was defined by the self-reported first question of the WAI questionnaire (71). This question is referred to as the Work Ability Score (WAS) (71). Briefly, the participants are asked to grade their work ability on a scale from 0 (I cannot work at all) to 10 (my employability is at its best right now). The WAS was categorized into normal (score ≥8) and reduced (score <8) work ability.(72) Analyses of sick leave were restricted to participants engaged in paid work within the previous 12 months. Sick leave was defined as an affirmative answer to the question: "*Have you been on sick leave over the course of the past 12 month*"". The subjects then selected how many days they had been on sick leave from the following categories: 1–7

days, 8–14 days, 15 days–12 weeks and >12 weeks. A cut-off of 14 days was chosen to differentiate a short-term from a long-term sick leave.

5.3.1.6 VGDF exposure

Vapors, gas, dust and fumes (VGDF) exposure was defined as an affirmative answer to the question *"Have you ever been exposed to gas, smoke, or dust at work?"* in 2013. All exposed participants in 2013 were then asked to grade their average exposure in the past five years into one of the following categories: "Daily, for large parts of the working day" (exposure=4 points), "Daily, but for short periods" (exposure=3 points), "Weekly" (exposure=2 points) or "Less often" (exposure=1 point), and "never" (no exposure=0 points). In 2018, the participants were asked the same question with the options "No," "Yes," or "Yes, in the last 12 months." In case of an affirmative answer in the last 12 months, the participants were instructed to classify the exposure into the same categories as in 2013. The change in exposure was calculated by subtracting the exposure points in 2013 from those in 2018. Positive and negative values indicates that the exposure frequency had increased and decreased, respectively. The analyses were restricted to participants engaged in paid work in the last 12 months in 2013. Participants who engaged in paid work in the last 12 months in 2013 but not in 2018, were included in the analyses as unexposed in 2018. Further, participants with missing data on VGDF exposure were excluded from analyses using change in VGDF exposure as an independent variable.

5.3.1.7 Variables collected through medical examinations (paper I and paper II)

Spirometry

Spirometry was performed in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (73) using Jaeger Master Screen Pulmonary Function Testing (PFT) (Erich Jaeger GmbH & Co. KG, Würzburg, Germany). FVC, FEV1, and the FEV1/FVC ratio were recorded. Two trained physicians, blinded to the

allocation, manually validated all tests. If a participant had no valid curves, the results were not included. All reference values were calculated using the Global Lung Function Initiative equations (GLI).(74)

Reversibility testing: All participants with at least one acceptable spirometry test (n=1258, 96%) were instructed to inhale 0.4 mg salbutamol, and spirometry was repeated after 10–15 minutes in accordance with the ATS/ERS guidelines.(75) All tests without an acceptable curve were excluded after manual blind validation. In total, 1091 (83%) participants had at least one acceptable test post-bronchodilator. The reasons for not performing the reversibility test included refusal by participants (n=91 [7%]), no valid curves pre-bronchodilator (n=28 [2%]), contraindications (n=14 [1%]), or other reasons (n=15 [1%]).

Fractional exhaled nitric oxide (FeNO)

FeNO was measured for all participants according to the ATS/ERS criteria (76) using the NIOX Vero (Aerocrine AB, Solna, Sweden). The FeNO measurement was performed before the lung function testing. FeNO was used in paper I, and 558 (89%) of the participants managed to produce one acceptable test within three attempts.

Asthma Control Test (ACT)

All participants with physician-diagnosed asthma who had asthma symptoms during the past 12 months completed the ACT questionnaire, and their scores were calculated (16). ACT is a validated test for asthma control that consists of five questions (16). All answers are given a score between 1 and 5, where five corresponds to the best, and the maximum score is 25. A total score of <19 indicates poorly controlled asthma (16). An ACT questionnaire in English is attached in the appendix.

Blood samples

The level of total Immunoglobulin E (IgE) was used in paper I. Total IgE in blood was analyzed using chemiluminescent immunoassay (Immulite2000 XPI, Siemens, Munich, Germany) at the Department of Laboratory Medicine, Telemark Hospital, for 621 (99%) participants.

5.3.1.8 Adjustment variables

Smoking

Smoking habit was classified as daily smoker, occasional smoker, and former smoker at both time-points in case of an affirmative answer to the following questions: *"Do you smoke every day (also applies if you only smoke a few cigarettes, cigars, or light a pipe each day)?," "Do you smoke occasionally (not each day, but weekends, parties, or similar)?,"* and *"Did you used to smoke?,"* respectively. Those who did not answer any of the three questions were classified as missing, and those with three negative responses were classified as never smokers. A variable for the changes in smoking between 2013 and 2018 was constructed, and smoking habits were divided into the following categories: same, increased, and decreased (Paper III).

Education

The highest completed educational levels of the participants were categorized into the following categories: elementary education (≤10 years), upper secondary school and certificate (additional 3–4 years), and university and university college. In addition, we included a category for other education and missing data.

Age and sex

Data regarding the age and sex of the participant were retrieved from the Norwegian Population Register.

5.4 Statistical analyses

All statistical analyses in this thesis were performed using the statistical software IBM SPSS Statistics for Windows (Armonk, New York, USA). Version 23.0 was used in paper I, and version 25.0 was used in papers II and III. The statistical significance level was set at $p< 0.05$, and $0.05 \leq p< 0.10$ was considered borderline statistically significant, and the results were commented in all three papers.

Paper I

In the analyses, the participants were stratified into one of the following categories recommended by the WHO: normal weight, ≤24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; and obese, ≥30 kg/m^2. Normal weight was used as the reference category. To compare the characteristics of the participants between the BMI categories, we used Pearson's chi-squared for categorical data and one-way analysis of variance (ANOVA) for continuous data. Due to the non-normal data distribution, the Kruskal–Wallis test was used to compare the total IgE and FeNO. All dichotomous outcomes were analyzed and adjusted for age, sex, smoking, and education using multiple logistic regression. Continuous outcomes were analyzed using linear regression and adjusted for the same confounders as the categorical outcomes.

Paper II

The study participants were grouped into six categories according to their BMI and asthma status. To analyze the differences between the groups, Pearson's chi-squared and Fisher's exact tests were used for categorical data, and ANOVA was used for continuous data. The association between outcome variables and asthma and BMI was assessed using logistic and linear regression models adjusted for age, sex, smoking status, and level of education. To

assess multiplicative interaction, a separate regression model was fitted for each outcome and included covariates for asthma, BMI categories, asthma × BMI interaction, age, sex, smoking, and level of education. Additive interactions for dichotomous outcomes were assessed via the methods described by Andersson et al. using the Synergy Index (SI), with a null value of 1.0 and a 95% confidence interval.(77)

Paper III

To compare the longitudinal changes in the background variables between 2013 and 2018, a paired *t*-test for continuous variables and a McNemar's test for categorical variables was used. We used linear regression models to assess the associations between the change in burden score as an outcome variable and the changes in BMI or VGDF exposure as exposure variable. In the unadjusted linear regression models, the respiratory burden score was the outcome variable, and the changes in BMI or VGDF exposure or possible confounding variables were the exposure variable. In the adjusted models to estimate the effect of BMI changes or VGDF exposure frequency, we adjusted for age, sex, educational level in 2013 , smoking habit category in 2013, change in smoking habit, BMI category in 2013, physician-diagnosed asthma in 2013, VGDF exposure in 2013, and the burden score in 2013 (full model). The models were then stratified for sex and physician-diagnosed asthma in 2013, and interaction terms were used to assess the differences in the strata-specific effect estimates.

To assess the association between the variables in the respiratory burden score, contingency table analysis with Cramer's V test was used. This is a test of the association between the nominal variables, and is based on Pearson's chi-squared statistics. Internal consistency was assessed using Cronbach's alpha value. In the 2013 survey, we did not enquire about breathlessness or dyspnea in the last 12 months; however, these questions were included in

the 2018 survey. We compared the burden score of the participants in 2018 with a score including questions on dyspnea using intraclass correlation coefficient analyses and a Bland-Altman plot.

Sensitivity analyses

Sensitivity analyses are performed to assess the robustness of the results. Sensitivity analysis is defined as: *"a method to determine the robustness of an assessment by examining the extent to which results are affected by changes in the methods, models, values of unmeasured variables or assumptions."*(78) In papers I and II, the sensitivity analyses included only participants reporting respiratory symptoms in the last 12 months to assess whether the participants with childhood asthma without recent respiratory symptoms, which may lower the frequency of positive responses among the participants, influenced the results. In paper III, only participants with asthma onset before the age of 30 years were analyzed separately. The question regarding physician-diagnosed asthma is susceptible to misclassification of asthma and COPD among older participants. In all studies, participants with a BMI of ≤18.5 kg/m^2 were classified in the normal weight category. In paper III, sensitivity analyses were performed after excluding participants with a BMI of ≤18.5 kg/m^2.

Non-responder analyses

Non-response and low attendance in the medical examinations could affect the results, particularly in papers I and II, as they use a case-control design. The non-responder analysis performed in the Telemark study has been assessed and published in a previous study.(79) In other analyses performed on the Telemark study population,(80) the inverse probability of participation weights was used to minimize selection bias from non-participation. Since this did not substantially change the exposure-outcome associations compared with the use of non-weighted variables in the Telemark study, weights were not used in any of the studies in

the dissertation. For responders and non-responders in the medical examinations in papers I and II, self-reported data from the baseline survey on BMI, age, sex, education, smoking, sick leave, and WAS were used in a conditional logistic regression model to test whether attendance at the medical examination was associated with these variables.

6 Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (REC identification number 2012/1665). All major changes and the follow-up part of the project were notified to the committee and approved. The committee concluded that the purpose of the study and the methods used did not violate any of the generally accepted ethical principles. The follow-up part in 2018 was also approved by the data protection officer at Telemark Hospital; this position did not exist in 2013.

The three main principles of human research ethics are 1) minimizing potential harm, 2) participation should be voluntary and based on informed consent, and 3) participants should have an absolute right to withdraw from the study.(81) All participants received written information describing the purpose of the study, possible benefits and disadvantages, data protection, funding, insurance, and contact information of the project group. The participants were informed about their right to withdraw from the study at any time without any explanation, and that their responses would be deleted in case of withdrawal. Informed consent was assumed if the questionnaire was returned by mail. All participants who underwent the medical examination received written information regarding the examination and a description of the purpose of the study, possible benefits and disadvantages, data protection, funding, insurance, and contact information of the project group. They also signed a consent form and were given the opportunity to ask further questions. All

questionnaires and information were written in Norwegian. All medical procedures were standardized using written instructions after the careful training of the study personnel and performed according to the international guidelines to reduce harm to the participants. If any medical findings requiring further investigations were observed, the participants and their general physicians were informed via mail or telephone if necessary. This was a requirement for approval from the medical committee and separated the role of the researcher and treating physician.

The completed postal questionnaires were returned via mail in 2013. An option to respond using a web-based solution was introduced in 2018 to increase the response rate, particularly among the younger participants. This solution was developed and managed by the government-owned and approved Norwegian Centre for Research Data. The Regional Committee for Medical and Health Research Ethics and the data protection officer at the Telemark Hospital approved this web-based solution. The participants received a unique ID code as part of the invitation to log in to a secure website containing the online version of the questionnaire.

The personal identifiable data obtained from the Norwegian National Population Registry for inviting the participants was replaced by a unique study identification (ID). The list combining the study ID and personal identifiable data had limited access and was kept in a safe. Access to unidentifiable data generated in the project and the completed questionnaires are restricted to select members of the project group. All members of the project group signed a declaration of confidentiality upon employment at the Telemark Hospital or are bound by the Norwegian law as health professionals.

There is an increasing focus worldwide to involve patients and patient organizations in research. The purpose of this involvement is to ensure and guide research that is relevant to the patients, who are the end-users. The involvement of the patients and patients' organization empowers the patients, helps disseminate the results to patients, and provides patient-friendly information during and after the research is conducted. A representative from the Norwegian Asthma and Allergy Association (NAAA) was a member of the study steering committee and contributed to the development of the questionnaires. NAAA representatives were also involved in the planning of the study and the transfer of knowledge to the patient group.

7 Results

7.1 Population characteristics

In 2013, 48 142 participants among the random sample of 50 000 inhabitants who received a postal questionnaire were eligible, implying that the questionnaire was not returned by the postal service because of an unknown address, or because the subject had moved, had language problems, or had other reasons. Among the 48 142 eligible participants, 16 099 returned the questionnaire, giving a response rate of 33%. This part of the survey is described in detail in a previous publication.(80) Table 2 shows the population characteristics for all responders in 2013. Among the responders, there were more women than men, and 42% were in the age group of 41–50 years. Fifty-six percent were never smokers, while 14% were daily smokers. Forty percent had a university/university college degree, and 39% had an upper secondary or certificate as their highest completed education. Work participation was high, and 83% of the participants reported having been employed in the last 12 months. Only 44% of the participants were in the normal weight BMI category. Twenty-eight percent were considered to be in the overweight category, while

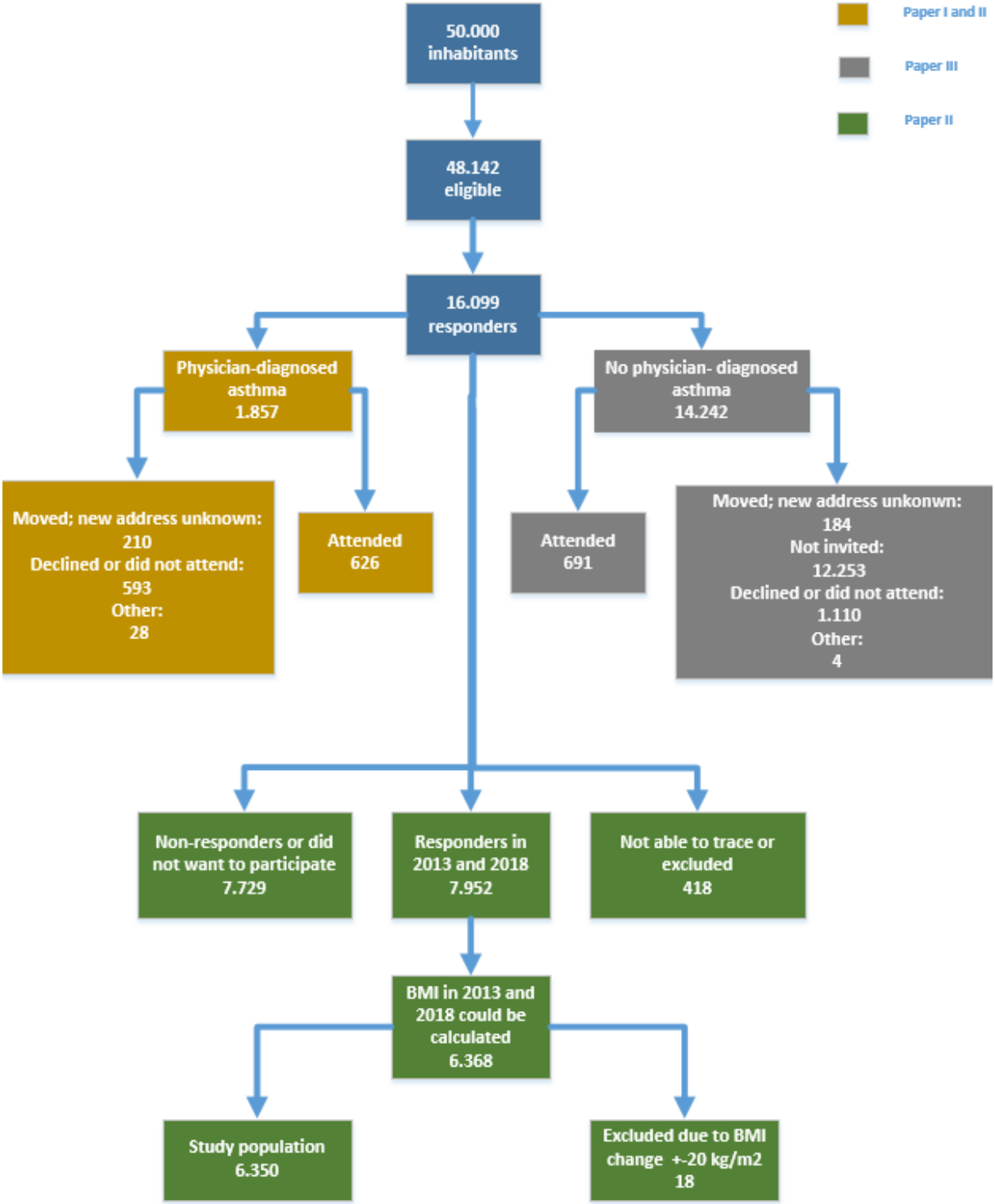
12% obesity. However, 16% did not supply sufficient data to calculate BMI. As reported previously, 11.5% of the participants had physician-diagnosed asthma.(80)

Table 2. Study characteristics in 2013 (n=16 099)	
Variable	**N (%)**
Sex	
Men	7159 (44%)
Women	8940 (56%)
Age category	
16–30	5282 (33%)
31–40	4126 (26%)
41–50	6691 (42%)
Highest completed education	
Elementary	2615 (16%)
Upper secondary and certificate	6329 (39%)
University/University college	6477 (40%)
Other and missing	678 (4%)
Smoking status	
Never smoker	8935 (56%)
Former smoker	3291 (20%)
Occasional smoker	1457 (9%)
Daily smoker	2298 (14%)
Missing	118 (1%)
BMI category	
Normal weight (BMI: <24.9 kg/m2)	7008 (44%)
Overweight (BMI: 25–29.9 kg/m2)	4515 (28%)
Obese (BMI: >30 kg/m2)	1957 (12%)
Missing	2610 (16%)
Employed in the last 12 months	
No	2784 (17%)
Yes	13315 (83%)
Physician-diagnosed asthma	
No	14242 (88.5%)
Yes	1857 (11.5%)

All 1857 (11.5 %) participants with asthma and 1989 computer-randomized healthy participants (participants without physician-diagnosed asthma) were invited to undergo further medical examinations in 2014 or 2015. Figure 2 is a flow chart showing the study

participants in the different papers, including those excluded and the reasons for exclusion. In total, 626 participants with asthma and 691 participants without asthma underwent further medical examinations in the case-control part of the study.

Figure 2. Flow chart showing study participants in the paper, including those excluded



In 2018, all 16 099 responders were invited to complete the questionnaire again. Among the 16 099 responders from the 2013 survey, 15 681 were eligible by the same criteria as in 2013. In 2018, 7952 participants responded to the postal questionnaire, resulting in a response rate of 51%. In the follow-up part of the study, the participants who did not provide their height and weight (n=1584), impeding BMI calculation at baseline and follow-up, were excluded from the present study. Moreover, all participants with a BMI change of >±20 points were excluded (n =18) based on a scatter plot to exclude extreme values and errors in recorded weight because of the automatic scanning of the questionnaires. Thus, 6350 subject questionnaires were included for further analyses in the follow-up part of the study.

7.2 Main findings

7.2.1 Paper I

The study population comprised 626 participants with physician-diagnosed asthma attending further medical examination in 2014–2015. The participants who had overweight or obesity were older (42.3 and 42.1 years, respectively) at examination and had a later onset of asthma (16.2 and 16.6 years, respectively) compared with the participants in the normal weight category who, on average, were 36.1 years with the onset of asthma at 13 years of age. Smoking status and level of education were similar across the BMI categories. There were no statistically significant differences between the categories regarding FeNO or total IgE.

Respiratory symptoms

After adjusting for age, sex, level of education, and smoking, none of the specific respiratory symptoms were associated with increased BMI. However, when assessing the respiratory

symptom score, participants with obesity had a significantly higher score with a β-coefficient of 0.68 (95% CI: 0.048–1.31) or OR of 1.78 (1.14–2.80) when using a respiratory symptom score cut-off value of ≥6. Obesity among the participants with asthma was also associated with more current use of medication for asthma with an OR of 1.60 (1.05–2.46) and a reduced ACT score (≤19) with an OR of 1.81 (1.03–3.18).

Lung function

When comparing the BMI categories, the highest mean percentage of the predicted value for FVC pre- and post-bronchodilator was among the participants with normal weight (97.8% and 98.6%, respectively), while participants with obesity had the lowest mean (93.6% and 95.9%, respectively). The pre- and post-bronchodilator FEV_1 had a similar pattern (92.9% and 95.5% compared with 87.8% and 93.2%, respectively). The pre- and post-bronchodilator FEV_1/FVC ratios were similar between the categories. We observed that the pre-and post-bronchodilator FVC were significantly negatively associated with BMI of ≥30 kg/m^2, with β-coefficients of -6.5 and -4.5, respectively. The comparable decrements for FEV_1 were not as large, and only the pre-bronchodilator value differed significantly between the groups (β-coefficient -4.57 [-7.71 to -1.42]). The β-coefficients for the FEV_1/FVC ratios were positive for the overweight and obese categories in both pre- and post-bronchodilator tests, which is consistent with the observation that the decrements were greater for FVC than that for FEV_1.

Work ability and sick leave

In our study, a higher frequency of sick leave in the last 12 months or a reduced work ability measured with WAS were not associated with overweight or obesity status.

7.2.2 Paper II

The study population for this paper comprised 626 participants with physician-diagnosed asthma and 691 participants without asthma. There were more women with obesity among the participants with asthma (66%) compared with the group with obesity alone (49%). Participants in both groups with normal weight had a lower mean age (39.4 and 36.1 years, respectively) compared with the other groups with higher BMI. Among the group with physician-diagnosed asthma, there was a higher frequency of other respiratory diseases, allergies, and mental health issues compared with the groups without asthma. There were no statistically significant differences in the educational level or smoking habits.

Independent associations between asthma and obesity

In this paper, we observed that asthma and increased BMI were independently associated with an increased respiratory burden score and reduced lung function. In the regression models adjusted for age, sex, smoking, and education, we observed that asthma was associated with reduced work ability score (OR: 1.9, 95% CI: 1.4–2.5), reduced frequency of sick leave in the last year (OR: 1.4, 95% CI: 1.1–1.8), and increased symptom score (OR: 7.3, 95 % CI: 5.5–9.7). Asthma was also associated with reduced lung function in all reported pre- and post-bronchodilator values, except for post-bronchodilator FVC. Obesity was associated with an increased symptom score (OR: 1.7, 95% CI: 1.2–2.4) and reduced pre- and post-bronchodilator FVC and FEV_1. When assessing the specific respiratory symptoms, asthma was strongly associated with all symptoms, while obesity was associated with several symptoms. The association between the symptom score and asthma was considerably stronger than that with obesity. When assessing the associations regarding lung function

variables, asthma seems to be associated with a greater reduction in FEV1 than obesity, while obesity is associated strongly with reduced FVC.

Interaction

In the interaction analyses, no statistically significant additive or multiplicative interactions were observed between asthma and BMI and work ability, sick leave, specific respiratory symptoms in the last 12 months, or the respiratory symptom score. When assessing the lung function, we observed an interaction between asthma and overweight in pre-bronchodilator FVC with a β-coefficient of -3.6 (-6.6 to -0.6). No other statistically significant interactions were observed.

7.2.3 Paper III

Among the 7952 participants who responded to the questionnaire in 2013 and 2018, 6368 provided their height and weight on both questionnaires for BMI calculation. All participants (n=18) with a change in BMI of >±20 points were excluded based on a scatter plot to exclude extreme values and errors in the recorded weight because of automatic scanning of the questionnaires. Thus, the study population for further analyses consisted of 6350 participants. We observed that the smoking habits changed significantly in the follow-up period, and fewer participants were daily smokers (from 12% in 2013 to 9% in 2018). We also observed that the frequency of exposure to VGDF was significantly reduced. The smoking habits and occupational exposure in the study population was reduced in the period, and the participants gained weight. The mean BMI for the population significantly increased from 25.55 (SD: 4.38) to 26.10 (SD: 4.44) (p-value: <0.001). Contingency table analysis with Cramer's V test as an effect measure of the association indicated associations among the three wheezing questions; however, the remaining questions in the score had a

low level of association. The burden score had good internal consistency, with a Cronbach's alpha value of 0.83. The Bland-Altman plot indicates that our burden score showed less agreement for high scores.

Change in respiratory burden score as a result of the change in BMI

We obtained an adjusted β-coefficient of 0.05 (95 % CI: 0.04–0.07) when the change in respiratory burden score was set as the outcome variable and the change in BMI was set as the exposure variable. When stratified by sex, the β-coefficient was 0.06 (0.04–0.09) for males and 0.05 (0.03–0.07) for females. Statistical testing to assess whether there was any difference between the sexes showed no such association. Stratified by asthma status, the β-coefficient was a significantly (p-value: 0.011) higher for participants with asthma [(0.12, 0.06–0.18)] compared with participants without asthma [0.05, (0.03–0.06)].

Change in respiratory burden score as a result of the change in VGDF exposure frequency

The adjusted β-coefficient was 0.15 (95 % CI: 0.10–0.19) when the change in respiratory burden score was set as the outcome variable, and the change in VGDF exposure frequency was set as the exposure variable. When stratified by sex, the β-coefficient was 0.18 (0.12–0.24) for males and 0.13 (0.07–0.19) for females. Statistical testing to assess whether there was any difference between the sexes showed no such association (p-value: 0.064). When stratified by asthma status, the β-coefficient was significantly higher for participants with asthma [0.15, (0.11–0.19)] but not for participants without asthma [0.18, (-0.02 to 0.38)], which was a non-positive result with a high estimate close to significance. There was no statistically significant difference (p-value: 0.412) when comparing the asthma status strata.

8 Discussion

8.1 Methodological considerations

8.1.1 Study design

In general, a case-control study includes a group of participants (cases) with the disease of interest who are compared with an unaffected group (controls).(82) Papers I and II are nested case-control studies. In a nested case-control study, the cases and controls are selected from within a larger study or population. In this case, all responders were from the Telemark study in 2013. All participants with asthma (cases) from the 2013 survey and a computer-randomized control group of similar size were invited to undergo further examination. A major strength of this approach was reducing the labor and cost of data collection, such as spirometry, from a large sample (the whole cohort). This was because some of the data had already been collected in the cohort study, and more cases of interest could be examined as they were selected and invited.(83) This enrichment would also enable studying rare conditions; however, this was not a concern in the present study as asthma have a prevalence of approximately 10%.

The nested case-control design also provided an opportunity to address a question or confounder not included in the original cohort. For example, all cases and controls in the nested case-control study underwent the FeNO test and were asked more questions regarding occupational exposure. Moreover, it provides the possibility to validate and improve the outcome and exposure variables through further clinical examinations, questionnaires, or other examinations during a selection of the cohort. For example, we collected spirometry data of the participants in our nested case-control study. A disadvantage of nested case-control studies, such as papers I and II, is the uncertainty in the temporal sequence of time. It is not possible to determine whether the exposure or outcome occurred first. In the present papers, it was not possible to determine whether the

reduced lung function was a result of asthma or whether the reduced lung function caused asthma (reverse causality). This design cannot be applied to investigate the inference of causality; however, it can be used to describe the association between suspected exposures and outcomes. This study design is susceptible to several biases, such as recall bias and responder bias (discussed later), as well as the need for a representative study sample to avoid selection bias. The selection of an appropriate control group is the main difficulty; it should be performed with the exception of the disease/condition in question and be as similar to the disease group as possible. In a nested case-control study, the controls are selected from the same population as the cases, reducing this possible error. Often, the controls are matched for age, sex, and other variables when selected from the cohort to adjust for possible confounding. We did not apply any matching and selected the control participants at random. Misclassification of cases and controls may introduce errors. We used a validated question (ever physician-diagnosed asthma) to reduce the misclassification of asthma.

Non-attendance to the medical examinations may also introduce bias, particularly if there are systematic differences between the cases and controls affecting their ability to attend. One example would be if all controls attending were young, never smokers and the cases were older with more varied smoking status. We performed non-response analyses (discussed later in the selection bias paragraph) to assess non-attendance.

Paper III is a follow-up study in which data on exposure and outcome are collected at two time-points. The inclusion of the element of time makes it possible to make inferences regarding causality in prospective studies. The time dimension also makes it possible to determine the effect of exposure on the outcome and enables the possibility of estimating

the incidence. The ascertainment of exposure and outcome data are set up such that data on exposure is collected before the outcome, making recall bias less of a concern. Prospective cohort studies are assumed to provide more valid and less biased results compared with other study designs.(81) Although there are many advantages to this design, there are some disadvantages to the study design. The data collection takes time and is often costly. Further, if the exposure variable is unstable and shifting, the results of the study will be affected. This can be avoided/reduced by performing repeated assessments of the exposure during the follow-up. A major disadvantage is the loss of participants to follow-up in the study period as they withdraw from the study or do not respond to questionnaires or appointments. This reduces the number of participants providing information and weakens the results and the validity of the study. However, it is of more concern that participants could be lost to follow-up due to reasons related to the outcome studied or the pre-defined risk categories.(82) We did not suspect any particular reason for the loss to follow-up in our study. When assessing the loss to follow-up in paper III, we observed that there were more men, more current smokers, more participants with asthma, fewer participants with a high level of completed education, and fewer participants who were employed in the last 12 months among the participants lost to follow-up. The participants lost to follow-up were also younger and had more respiratory symptoms and current use of asthma medication. More respiratory symptoms and a higher respiratory burden score in 2013 among those lost to follow-up (1.30 in the lost to follow-up group vs. 1.14 in the study population) may have led to an underestimation of the effect of BMI if increased BMI favors loss to follow-up. However, the mean BMI was not statistically different between the study population and the participants lost to follow-up. It is described in the literature that the male sex, younger age, lower education, and participants with more health issues are more often lost to follow-

up.(84-86) This was also observed in our study, and the variables were included as covariates in the regression models accordingly.

8.1.2 Choice of study variables

The study variables selected are commonly used variables for assessing respiratory health and variables that we aimed to investigate. The questions regarding respiratory symptoms, physician-diagnosed asthma, and comorbidities are validated questions used in other large population studies on respiratory health.(68, 69) We calculated the respiratory burden score to better describe the burden of respiratory symptoms, including the use of medication. This score may also better reflect that the continuum in the respiratory symptoms.(87) To measure lung function, we used spirometry with reversibility testing as recommended and in accordance with the guidelines by ATS/ERS.(73) Spirometry is cost-effective, harmless, and the most commonly used investigation to assess lung function.

BMI was selected as the measure of overweight and obesity as it is simple, widely accepted, and the cut-off value to define obesity is based on well-established risk factors.(26) It has a high specificity (0.90) but low sensitivity (0.50) for assessing obesity; however, it may be a less accurate predictor in some ethnic groups and the elderly.(26) Moreover, it cannot distinguish between muscles and fat and does not describe the fat distribution. There are other measurements of obesity, such as the hip-waist ratio, waist circumference, and skinfold thickness; however, these methods are hampered by the lack of standardized measurement protocols, reference data, and accuracy in individuals with severe obesity (BMI: >35 kg/m^2).(26)

In this dissertation, we selected WAS to describe work ability (described in section 5.3.1.5). WAS can be categorized into normal (score of ≥8) and reduced (score of <8) work ability (72); however, other categorizations are also used (88). Previous studies have reported a strong association between WAS and the results of the complete WAI questionnaire (20, 72). One advantage of using WAS over WAI is the use of a single question in WAS. There are 10 questions in WAI, and in addition the participants have to report if they have currently have one or more of 14 diseases (WAI). Space availability is also limited in most questionnaires; thus, the use of WAS is beneficial. The use of WAS over WAI also eliminates other disadvantages such as the complexity of some items, high probability of error in calculating the score, absence of disease data, and the relative importance of health rather than work ability in the WAI score.(89)

Sick leave can be measured using multiple ways; however, the frequency (absence episodes due to sickness), length (number of sick leave days), incidence (new sick leaves during the study period), cumulative incidence (proportion of individuals on sick leave during a time period), and duration (mean or median sick leave days during each sick leave episode) are possible measures.(90). Frequency and duration are easy to assess and understand, can be regarded as basic measures, and be used in studies such as papers I and II.(90) Sick leave in our studies was defined as an affirmative answer to the question: *"Have you been on sick leave over the course of the past 12 months?*" The participants then selected the number of days they had been on sick leave from the following categories: 1–7 days, 8–14 days, 15 days–12 weeks, and >12 weeks. A cut-off value of 14 days was selected to differentiate between short-term and long-term sick leave. The cut-off value and categorization were selected to reflect the official Norwegian sick leave system and important follow-up time points. The cut-off value and categories are also in line with a Norwegian study comparing

sick leave in Norway and Sweden.(91) The use of categories instead of the number of days on sick leave in the questionnaire may reduce the selection and recall bias. A major limitation is that our data on sick leave are self-reported. Previous studies have shown good agreement between self-reported and register-based data on sick leave, which is suitable in common epidemiological studies. (92) However, there are studies showing that self-reported sick leave data are subject to non-response, and participants tend to underreport their sick leave.(93) It would be necessary to obtain better data regarding sick leave by using register-based data. These data are more accurate, and we can analyze the number of sick leave periods. The disadvantages associated with register-based data are the cost of procuring these data and the lack of data regarding short-term sick leave (sick leave not registered by a physician, employer, or authorities). The results from paper II indicated that participants with asthma and obesity do not have a higher frequency of long-term sick leave; however, they have a higher frequency of short-term sick leave.

There are many methods to assess occupational exposure.(94) Some methods, such as direct measurement of each participant's work environment, are time-consuming and expensive and are not feasible in larger studies. Possible assessment tools in epidemiological studies are occupational histories; job-exposure matrices (JEM), where job titles are used to infer exposure and exposure levels; expert assessment of exposures; where experts make an assessment based on the participants' reported information; and self-reported exposure. In this paper, we used exposure to VGDF as exposure measurement. It is a crude and self-reported measurement; however, the question regarding VGDF exposure is commonly used in occupational epidemiology. It has been tested against a 16-item battery assessing specific inhalation exposures and a job-exposure matrix and appears to delineate exposure risk as

well as a multiple-item battery. It also has a modest agreement with the job-exposure matrix.(95, 96) This indicated that this single question gives a fair assessment of inhalation exposure, with the benefit of keeping the questionnaires reasonably short. This approach of measuring occupational exposure in our paper has some limitations. We do not have direct measurements of exposure for each participant or the information regarding exposure between 2013 and 2017, which could lead to misclassification. The question refers to the frequency of occupational exposure to VGDF; however, the exposure levels may have reduced following the use of personal protective equipment, change in production methods, and other measures that increase or decrease exposure. We also assumed that an increase at one point will have an equal but opposite effect on the respiratory burden score as a one-point reduction in exposure. This may have resulted in underestimation of exposure reduction in the most exposed participants and overestimation of the effect of reduction in the least exposed participants. Another limitation is that approximately 50% of the participants have never been exposed to VGDF, and 5–7% of the participants have been exposed daily and for most of the day. More exposed participants could have given narrower CIs for estimates of association.

8.1.3 Internal validity

An epidemiologic estimate is the product of the study design, study conduct, and data analysis.(97) It is an overall goal to make this estimate accurate and valid. Accuracy implies that the value of the parameter that is the object of measurement is estimated with little error.(97) These errors can be classified as random or systematic errors.(97) A study with only a few random errors can be described as precise. Systematic errors are commonly referred to as biases, and a study with only a few systematic errors can be described as valid.

The validity of a study is usually separated into two components: internal validity and external validity (generalizability).(97) Internal validity is related to the estimates and conclusions drawn based on the source population, while external validity is related to individuals outside the source population and how the conclusions drawn from the study fit this population. Increasing the study size can reduce random errors, while bias can only be reduced by changing the study design, such as including an adequate control group and using calibrated/validated instruments.(98) Bias can be classified into three general categories: information bias, selection bias and confounding bias.(97, 98) In the following paragraphs, these categories of bias, their effect on the results, and their management in this dissertation are discussed.

8.1.3.1 Information bias

Information bias is a systematic measurement error in the needed information, which may lead to the misclassification of a variable such as exposure. Misclassification is classified into non-differential misclassification and differential misclassification.(97) In non-differential misclassification, the misclassification of the outcome in those with an outcome is similar to that in those without this outcome; in differential misclassification, the misclassification is not the same between the groups.(97) Non-differential misclassification of the exposure results in a bias in the estimate (OR, RR) towards the null for dichotomous variables, and usually towards the null when using three or more categories. Similarly, when there is a non-differential misclassification of a health outcome and health status, the results will be biased towards the null. In differential misclassification of exposure or health outcome, the estimate can be biased towards or away from the null. If the misclassification is a result of fewer cases being considered to have been exposed or fewer exposed cases being

considered to have the health outcome than the true number, the results are biased towards the null.

Recall bias is a form of information bias due to differences in the accuracy of recall between cases and non-cases. A major limitation for all three studies is that most outcomes are self-reported, particularly in paper III. Self-reported exposure and outcomes are susceptible to recall bias which gives rise to misclassification. Retrospective or cross-sectional studies, such as papers I and II, where the participants were asked about previous exposure or events, are susceptible to this bias.(99) Cases in a case-control study are often more likely to recall previous risk factors or exposures than controls, resulting in underreporting of true exposure among healthy controls and over-reporting among the cases.(99) Recall bias is less important in prospective studies such as paper III, where the exposure, in this case, the BMI reported in 2013, is collected before the outcome, which in this paper was the change in the respiratory burden score in 2018. Recall bias results in misclassification that may lead to incorrect associations being observed between the categories and the outcome, depending on whether the misclassification is differential or non-differential. As the Telemark study focuses on respiratory health, it is reasonable to assume that participants with respiratory symptoms and conditions recall exposures and factors affecting their respiratory health to a higher degree compared with those without any such health issues. This might increase the estimates for the health outcomes. Therefore, to reduce information bias, we used validated and standardized questionnaires.(68, 69) However, such bias may still be important or affect the association between symptoms and exposure.

In all the papers in this dissertation, asthma was defined as self-reported physician-diagnosed asthma. We could not verify the diagnosis using our current study design as

asthma is a heterogeneous disease, which can be difficult to diagnose. A Canadian study has shown that a current diagnosis of asthma could not be verified in 33.1% of adults reporting physician-diagnosed asthma diagnosed within the past 5 years who were not using daily asthma medications or had medications weaned (100). The study points to two phenomena that could account for this failure: 1) the spontaneous remission of previously active asthma and 2) misdiagnosis of asthma. Daily use of asthma medication, history of wheezing, lower FEV_1, and confirmation of airflow limitation at the time of the first diagnosis increased the risk of current asthma, indicating that physician-diagnosed asthma is highly susceptible to misclassification. However, validation studies on self-reported physician-diagnosed asthma have found good sensitivity (65%) and high specificity (94%).(101) This question is susceptible to misclassification of asthma and COPD among older participants. Therefore, to assess this point in paper III, we also performed analyses that included only participants whose age at asthma onset was ≤30 years (n=679). The results showed slightly higher estimates for the β-coefficients; however, the results were otherwise comparable with the analyses in which all participants with asthma were included. This indicated that misclassification between asthma and COPD among older participants with physician-diagnosed asthma was limited in our study. The number of participants with COPD in the study population was low. In paper III, from a study population of 6279 participants, only 71 participants (1 %) had physician-diagnosed COPD. The relatively low number of participants with COPD is probably attributed to a relatively young study population with an age below 55 years. The analysis and low prevalence of COPD indicate that the misclassification between asthma and COPD probably was low in the present study. In 2013 and 2018, 4% of participants with asthma were reported to have both asthma and COPD. Using ever physician-diagnosed asthma as the definition of asthma also allows the inclusion of

participants who have had childhood asthma without recent respiratory symptoms. This may lower the frequency of positive responses and dilute the estimate and associations. To assess this issue in papers I and II, we performed additional analyses in which only participants with active asthma were included. Active asthma was defined as having any respiratory symptoms during the previous 12 months in participants reporting physician-diagnosed asthma. The results of these analyses were comparable with the results of the analyses of all participants with ever asthma but with slightly higher estimates. Hence, we concluded that including all participants with physician-diagnosed asthma provided valid results.

In papers I and II, the height and weight were measured by trained health care professionals in the study group, and BMI was subsequently calculated. Some measurement errors are possible; however, the occurrence of systematic measurement errors is negligibly low when the same instruments were used for all participants and there were fewer co-workers taking the measurement. In paper III, the weight and height of the participants were self-reported. This may have caused misclassification. A review reported that participants tend to overestimate their height and underestimate their weight when using self-reported data, resulting in a lower BMI estimate.(102) In that study, the bias was greater in overweight and obese participants. However, the outcome variable in paper III was the change in BMI. There is no reason to believe that bias from the self-reported height and weight were substantially different at the two time-points. The mean increase in BMI in this study (0.11 kg/m^2/year) was in line with the study conducted by Ekström et al. (0.13 kg/m^2/year). (33)

Another limitation and possible information bias is that we did not have direct measurements of occupational exposure for each participant or information regarding

exposure between 2013 and 2017, which could lead to misclassification of exposure in paper III. The question *"Have you ever been exposed to gas, smoke, or dust at work?"* refers to the frequency; however, the exposure levels may have been reduced after implementing better ventilation, use of personal protective equipment, or a change in production methods. Moreover, we assumed equal steps between the exposure frequencies and that a one-point increase in exposure at one point has an equal but opposite effect on the respiratory burden score as a one-point reduction in exposure. Following this approach, we may have underestimated the effect of exposure reduction in the most exposed participants and overestimated the effect of exposure reduction in the least exposed participants. To obtain a better exposure assessment in future epidemiological studies, we recommend the use of updated JEM combined with more questions regarding exposure and exposure duration. However, this must be balanced to avoid non-response due to the use of an extensive questionnaire and smaller and specific exposure groups with a loss of statistical power.

In papers I and II, the participants performed spirometry with reversibility testing. To reduce misclassification and measurement errors, only a few trained operators were used in the study. Spirometry was also performed according to the ERS/ATS guidelines and was manually validated by two trained physicians. There were relatively few spirometry tests that had to be discarded, indicating good quality and a low chance of any systematic differences.

8.1.3.2 Selection bias

Rothman et al. defined selection bias as distortions that results from procedures used to select participants and factors that influence study participation.(97) Papers I and II are nested case-control studies; therefore, they are more susceptible to selection bias. The control group was recruited from the same population, reducing the possibility of systematic

differences between the cases and controls. Both cases and control were also examined by the same well-trained healthcare workers, reducing the possibility of systematic differences between the cases and controls. Selection bias may also be caused by non-response and loss to follow-up. This bias may also affect the generalizability of the study. Non-response in the postal survey in 2013 has been addressed by Abrahamsen et al.(79) They reported that the Telemark study provides valid estimates for physician-diagnosed asthma and several respiratory symptoms. Non-response was associated with younger age, male sex, history of smoking, and living in a rural area. Non-response is also a concern when inviting the responders to undergo a further medical examination. This was addressed in paper I and paper II. We used a logistic regression model to test whether undergoing the medical examination was associated with sex, BMI, age, education, smoking, sick leave, and WAS. In paper I, we observed that attending the medical examination was significantly associated with older age (30–39 years, OR: 2.2 (1.6–3.1); 40–50 years, OR: 3.5 (2.7–4.7) and current smoking (OR: 0.67 (0.50–0.89)). The corresponding estimates in paper II were 30–39 years with an OR of 2.2 (1.8–2.7), 40–50 years with an OR of 3.8 (3.2–4.6) with 18–29 years as the reference, and current smoking with an OR of 0.61 (0.49–0.77). In addition, the male sex was negatively associated with attendance (OR: 0.8 (0.71–0.98). These tests demonstrated that there were some differences between those participating and not participating in the medical examination and that this may alter the prevalence estimates. We considered that this was unlikely to bias the observed associations; however, this could not be ruled out entirely. To further decrease the likelihood of biased results, all analyses were adjusted for age, smoking, and sex in the regression analyses. There was a significant loss to follow-up (49%) in paper III. When comparing responders to non-responders in 2018, there were more men, more current smokers, more participants with asthma, and a lower level of education

among the non-responders in 2018. The analyses were adjusted for these variables. The non-responders were also younger and reported more respiratory symptoms compared with the responders in 2013, while the mean BMI was not significantly different. The loss to follow-up may introduce bias if there are differences in the likelihood for loss to follow-up related to exposure and outcome. High loss to follow-up does not necessarily result in a biased estimate of the association found; however, it raises concerns regarding accuracy. If the losses among the groups are non-differential, the estimate will not be biased by the loss. In this paper, there was a high loss to follow-up (response rate of 51%), and this should be recognized as a major limitation. Among the participants lost to follow-up, there were more men, current smokers, more respiratory symptoms in 2013, and fewer with higher levels of education. We adjusted for these factors to remedy some of the non-response; however, some bias due to loss to follow-up may remain. As there was more loss to follow-up among the participants with more respiratory symptoms, we may have underestimated the effect of the change in BMI or occupational exposure on the respiratory burden score in this study.

Missing data

Almost all questionnaire-based studies struggle with missing data, and there are multiple methods to manage this. One possible way is to exclude all participants with one or more missing data. However, this will result in a major loss of participants, resulting in a significant loss of statistical power. There are several statistical methods to remedy this situation. One possibility is to use imputation methods such as multiple imputation. In multiple imputation, a probable value for the missing value is calculated and modeled based on the predictive distribution in the data set and multiple plausible data sets. The imputed value is a result from combining the results of these sets.(103) However, if the data is not missing at random,

this may create a new bias. There were missing values for respiratory symptoms and the use of medication in our study; therefore, we recoded missing values to not having that symptom or using medication. In the postal survey (Q_{main}), approximately 3% of values were missing for each question regarding respiratory symptoms in the last 12 months. The corresponding number in the medical examination was 4%, indicating that there were few missing answers. There were no differences between the BMI categories in the percentage of missing data for these questions. Other variables were considered missing and excluded from the analyses. This is a conservative approach and may dilute a possible association. We do not suspect that the missing data is "not missing at random." We anticipate that the missing data (respiratory symptoms) is missing at random because these questions are not sensitive. As discussed by Sterne, this approach can be useful if there are only a few missing values for a binary outcome(103), which is considered to be the case in the studies included in this thesis.

8.1.3.3 Confounding

A confounder is a variable that influences the exposure variable and the outcome variable (Figure 3). This results in a distortion that can cause an over- or under-estimation of the association and, if sufficiently large, change the apparent direction of the association.(97) For example, if we want to examine whether COPD (exposure variable) is associated with lung cancer (outcome variable), tobacco smoking would be a confounding variable as it causes both COPD and lung cancer.

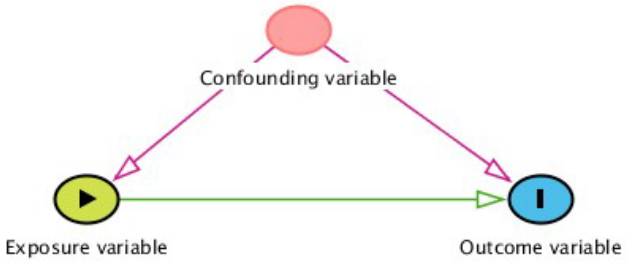


Figure 3. Illustration of the relationship between an exposure variable, outcome variable and a confounding variable. (Figure made with DAGitty tool. (67))

Confounding may be present in any study design. There are two criteria for a confounder: 1) it must be a known risk factor for the outcome and 2) it must be associated with the exposure but not as a result of the exposure. There are several methods to manage confounding.(104) A carefully constructed study design can help manage confounding. One method is to restrict the study population to those unexposed to the confounding variable; for example, exclude all current or past smokers in a study assessing previous asbestos exposure and risk of lung cancer. This may not always be feasible as the study population may become too small for analyses. The Telemark study restricted the age for inclusion to 16–50 years in 2013 to reduce the number of participants with chronic pulmonary disease (COPD) and several other age-related co-morbidities. Another method is to match the confounder variable such that the distribution is similar in the exposed and unexposed groups. It is also possible to randomize the study population; however, this method cannot be used in observational studies as it requires assigning an exposure status to the participants. If there are known confounders, such as age or sex, multivariate analyses, such as regression analyses, can be used, and the confounding variable can be included as a

covariate. We have used this latter approach in all papers in this thesis. A confounding variable can be assessed by stratification. An example of this is shown in paper III, where we stratified the models for sex and asthma status. Unnecessary adjustment of the variables lowers the precision and may introduce bias in the estimate.(105) Moreover, the possibility for measurement errors in the confounders and residual confounding cannot be excluded entirely. There may also be confounding variables that have not been measured or recognized that should have been included in the regression models. In the studies included in this dissertation, the analyses have been adjusted for well-known confounders in respiratory health such as age, sex, smoking, and education. In paper III, we adjusted for education and occupational exposure and are aware that this may pose a problem due to co-linearity. However, when we assessed the models by comparing the results with one or both variables in the regression model, we obtained similar results.

8.1.4 Respiratory burden score

In paper III, the outcome variable was the respiratory burden score; however, a similar burden score was also used in papers I and II. We chose to use the respiratory burden score to better describe the total respiratory symptom burden. A higher score indicates more respiratory symptoms and more burden to the subject. To our knowledge, a well-recognized and validated respiratory burden score for participants without asthma or other respiratory diseases is not available. Similar scores, including some of the questions in our questionnaire, have been used for participants with asthma or other respiratory diseases.(87, 106)

Contingency table analysis with Cramer's V test as an effect measure indicated association among the three wheezing questions; however, the other questions in the score had a low level of association. The burden score had good internal consistency, with a Cronbach's

alpha value of 0.83. The score contained three overlapping questions on wheezing. The score used in paper III was reconstructed using only one question on wheezing: *"Have you had wheezing or whistling in the chest in the last 12 months?"* This score was then compared with our burden score. The analyses showed that the estimates changed slightly as expected, but the associations found were the same. In addition, Cronbach's alpha was decreased to 0.71. From a clinical point of view, wheezing is an important respiratory symptom in asthma. More wheezing symptoms, such as wheezing in the absence of a respiratory tract infection, indicate a more severe effect. We constructed the respiratory burden score with the idea that the higher the number of respiratory symptoms, the more severe effect the exposure had on the participant. Therefore, we included all three questions on wheezing. However, questions on breathlessness and dyspnea were mistakenly not included in the first survey in 2013. Therefore, we compared the burden score of the participants in 2018 with a new score including these questions using the statistical method of intraclass correlation analysis to assess whether the correlation between the two scores was good. This analysis showed a high agreement. The Bland-Altman plot indicated that the burden score showed lesser agreement for high scores, probably because one of the scores included more items (symptoms). This indicates that the absence of the questions used to calculate the score in paper III did not drastically affect the validity of the score used. The reason for this might be that the score in any case has the ability to find participants with a high respiratory burden.

Medication potentially may eliminate respiratory symptoms. However, if the participants are in need of medication, it is from a clinical view thought to be an indication of the severity of the disease. Reanalyzing the data with the respiratory burden score in paper III without the

use of medication showed significant associations, and the estimates were very similar to the original results. Moreover, we noticed that the European Academy of Allergy and Clinical Immunology (EAACI) has recommended the use of combined symptom and medication scores as the primary endpoint for future clinical trials in a position paper on allergy immunotherapy for allergic rhinoconjunctivitis.(107) The use of a score combining symptoms and the use of medication has also been suggested by Caballero et al.(108) In our opinion, these arguments justify the inclusion of the use of medication in our respiratory burden score.

8.1.5 External validity

External validity is determined by the generalizability of the study; in other words, whether the results of the study can be applied to the target population from which the sample was drawn. The external validity of a study is dependent on its internal validity. If the internal validity is poor then the external validity becomes poor. However, it is possible to have excellent internal validity by setting strict restrictions for inclusion and data quality, but the results may not be applicable to a larger population. The ultimate test for external validity is that the results are replicated in other studies using different study populations and designs. If similar results are observed, it will increase the robustness of the findings of this thesis.

The study population is of great importance to the external validity of a study. A strength of the Telemark study is that it is a relatively large general population study with few exclusion criteria other than age, language, and residing outside the Telemark County. This increases the generalizability of the study. Telemark County is a county in south-eastern Norway and consists of 17 municipalities with an area of 15 296 km², including both urban and rural areas stretching from the sea to the high mountains. The county is sometimes referred to as Norway in miniature geographically. It had a population of 173 355 inhabitants in 2019,

among whom 134 266 resided in more urban areas (Grenland).(3) Among the inhabitants, 49.9% were women, and 50.1% were men; 13.7% of the inhabitants between the ages of 18 and 66 years received a disability pension, and 1.5% of the population between the ages of 15 and 74 years were registered as unemployed in 2019. The corresponding numbers for Norway were 49.6% women and 50.4% men, among whom 10.1% received disability pension and 1.5% were registered as unemployed in 2019.(3) Historically, Grenland has been one of the largest industrialized areas in Norway, and the region still has a high proportion of industrial- and craft workers. In general, the population of Telemark is similar to the total population of Norway; however, it has a lower proportion of inhabitants with higher education, a higher proportion of daily smokers, and a lower life expectancy.(109) This may reduce the generalizability to the total Norwegian population.

Sampling bias limits the external validity of a study and occurs when some members of a population are systematically selected into a sample. This may be a result of self-selection, non-response, or health-seeking behavior. It is possible that participants with health-seeking behavior responded and attended the medical examination more frequently, particularly among the controls. Previous studies and data from the analyses of non-responders indicate that participants with more respiratory complaints do not respond to studies. This may reduce the proportion of participants with more uncontrolled and severe asthma resulting in weaker estimates of associations. To reduce sampling bias, all participants were provided the same neutral written information and invitation, and no area in Telemark was excluded when inviting the participants.

A major limitation of the studies are the low response rate and loss to follow-up. In the first survey, the response rate was 33%, and the response rate was 38% in 2018. For participants who also participated in 2013, the response rate was 51%. Non-response analyses have been performed for the Telemark study.(79) These analyses showed that non-response was associated with younger age, male sex, past smoking, and living in rural areas. Despite a low response rate, the Telemark study provided valid estimates for physician-diagnosed asthma and several respiratory symptoms. However, the prevalence of chronic cough and use of asthma medication was slightly overestimated. In other analyses performed in the Telemark study population, the inverse probability of participation weights was used to minimize selection bias from non-participation; however, this did not substantially alter the associations compared with the non-weighted results (80), possibly indicating that non-response had a lesser effect on the associations studied.

A key variable in this dissertation is BMI. In 2020, the proportion of individuals who had overweight or obesity in Telemark was 53%, and the average in Norway was 55%.(27). The proportion varies with age; in paper III, the proportion was approximately 49%. In a survey conducted by the Norwegian National Statics Agency in 2015 using self-reported data, the proportion of inhabitants with obesity in the south-eastern region of Norway (which includes Telemark) was 15 % in the age group of 25–44 years and 18% in the age group of 45–64 years.(3) In paper III, the proportion of patients who are obese was 14%; hence, the proportion of obesity in our paper is comparable with that of Telemark and Norway. In this dissertation, BMI has been categorized into three categories in some analyses. Some studies

used only two categories. The WHO recommends three categories; however, it also recommends the use of six categories (Table 3).

Table 3. BMI categories and nutritional status according to the World Health Organization (WHO)

BMI	Nutritional status
Below 18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Pre-obesity/overweight
30.0–34.9	Obesity class I
35.0–39.9	Obesity class II
Above 40	Obesity class III

Adopted from WHO.(110)

Few participants in this study were underweight and they were placed in the normal weight category (n=228, 2% of all those with BMI data in 2013). There are studies demonstrating that patients who have underweight have poorer health than participants with normal weight.(111) In paper III, 1.3% (n=85) of the participants were underweight. When we performed the analyses without the patients who had underweight, only a minimal effect was observed on the β-coefficients and confidence intervals, apart from the association of change in VGDF in participants with asthma where the confidence interval changed slightly, resulting in a significant association. In a study including only patients who have underweight, variation may be seen; however, no statistically significant effects were detected on excluding these participants from general population studies, such as the Telemark study. In our study, we combined all participants with a BMI over 30 kg/m^2 in one

category. In papers I and II, categorizing the BMI into four or six categories resulted in low statistical power as a result of small categories. This categorization issue could explain why obesity was not associated with an increased frequency of sick leave and reduced work ability, as reported in several other studies.(42-46). This indicates that the results and estimates of this study should not be directly extrapolated among participants with extreme BMI. A different study design may be warranted to assess this in larger studies.

In the Telemark Study, the age of the participants was limited to between 16 and 50 years in 2013, which can be considered to be a relatively young population. Previous studies have shown that respiratory symptoms are more common among the elderly (>75 years) and are a strong predictor of death.(112) However, participants of this age were not included in the Telemark study. Previous studies have also shown that higher age is associated with reduced work ability.(18) However, this could not be assessed in our studies, and the associations reported should not be extrapolated to elderly participants.

8.2 Discussion of main results

8.2.1 Respiratory symptoms

We did not find any specific respiratory symptom to be more prevalent among participants with asthma and obesity compared with participants with asthma and normal weight. However, the results have been somewhat conflicting in previous studies. Several studies have reported that obesity in participants with asthma is associated with more wheezing (53-55), whereas other studies have reported more dyspnea.(56) However, many of these studies assessed only one or two respiratory symptoms, while several symptoms were assessed simultaneously in our studies. A possible explanation for our failure to reproduce an association with respiratory symptoms may be the lack of statistical power because of the

small sample size in the highest BMI categories. The highest BMI category in our study had a wide range; however, the average BMI was close to 30 kg/m^2. Our papers included a limited number of participants with BMI over 35 kg/m^2 and very few above 40 kg/m^2; thus, we were unable to create further categories to assess this. One study reported an increase in specific respiratory symptoms among more number of participants with higher BMI than that in ours and was able to include a category with a BMI of ≥35 kg/m^2.(55) They reported a higher OR for wheezing, shortness of breath, and use of medication in the last 12 months among participants with a BMI of ≥35 kg/m^2 compared with the ORs in the group with BMI of 30–34.9 kg/m^2.

In paper II, we also observed that participants with obesity reported a higher frequency of some respiratory symptoms compared with participants with normal weight. Obesity was associated with more wheezing, dyspnea after exposure to cold, and dyspnea following strenuous activity. These results were in line with the results reported by two other studies.(30, 32) In paper II, we observed that both asthma and obesity were associated with the majority of respiratory symptoms (Supplementary Tables); however, the estimates were stronger for asthma compared with that for increased BMI.

We observed an OR of 1.81 (1.03–3.18) for reduced ACT score among participants with asthma and obesity compared with participants with asthma and normal weight, indicating that participants with asthma and obesity have more uncontrolled asthma. Reduced ACT score among participants with obesity compared with that of participants with normal weight has also been reported in other studies.(61, 113) Compared with participants with asthma and normal weight, we observed an OR of 1.60 (1.05–2.46) for the current use of

asthma medication in participants with obesity and asthma, which may support the finding of more severe asthma among participants with obesity and asthma.

We applied the respiratory burden score in all papers. The respiratory burden score reflects the burden of respiratory symptoms. No specific respiratory symptom was more frequent in participants with asthma and obesity; however, an increased respiratory burden score was observed to be associated with obesity and asthma compared with normal weight and no asthma diagnosis. Compared with lean participants, participants with asthma and obesity had a significantly higher respiratory burden score. In paper I, we observed an OR of 1.78 (1.14–2.80) for a symptom score of ≥6 when comparing participants with asthma and obesity with participants with asthma and normal weight, implying that increased BMI may lead to higher respiratory burden in participants with asthma.

On comparing participants with obesity with participants with normal weight in the adjusted model, we observed an OR of 1.7 (1.2–2.4) for a symptom score of ≥3, supporting the corresponding findings in papers I and II. In paper II, we observed a β-coefficient of 2.4 (2.2–2.7) when we used a slightly different respiratory burden score to compare participants with asthma with participants without asthma. On comparing participants with obesity with participants with normal weight, we observed a β-coefficient of 0.6 (0.3–0.97), indicating that asthma had a stronger effect on the burden score than increased BMI. This was also anticipated as asthma defined by respiratory symptoms. However, assessing this association in participants with extreme BMI is not possible from our data.

In the follow-up part of the study, we observed that an increased BMI was associated with an increased respiratory burden score [β-coefficient: 0.05 (0.04–0.08)] (paper III). This effect

was stronger among participants with asthma (β-coefficient: 0.13 vs. 0.04 in participants with no asthma), and there were no sex differences. These results indicate that an increased BMI is associated with increased respiratory burden and that the effect is stronger among participants with asthma. These results are in line with those of the study conducted by Ekström et al., which found an increased incidence of breathlessness with increasing BMI.(33) The outcomes are different; unfortunately, our study did not include questions regarding activity-related breathlessness. They reported an increased incidence of the respiratory burden increasing as the BMI increased among participants with asthma, confirming the results reported in paper I, where participants with obesity had a higher respiratory burden score. Previous studies have also shown that weight loss in participants with asthma and obesity improves respiratory symptoms and lung function.(39)

Studies have shown that pulmonary diseases affect the sexes differently, their perception of respiratory symptoms, and the symptoms that they report.(114, 115) A previous study demonstrated that as the participants became obese, male participants had a greater increase in wheezing without a cold, while female participants had a greater increase in asthma.(34) Interestingly, we found no sex differences when assessing how the change in BMI affected the respiratory burden score; one explanation could be the use of the symptom score rather than the assessment of a single symptom.

8.2.2 Lung function

Lung function was analyzed in papers I and II. In paper I, participants with asthma and obesity had a lower pre-bronchodilator FVC (β-coefficient: -6.47 [-9.1- to -3.80]) and FEV_1 (β-coefficient: -4.57 (-7.71 to -1.42]) compared with participants with asthma and normal weight. After bronchodilation, FEV1 was no longer significantly different; however, FVC

remained lower among those with asthma and obesity. As the increase in FEV_1 exceeded the relative increase in FVC, the FEV_1/FVC ratio improved. In participants who were overweight and had asthma, only FVC was negatively affected. Previous studies have shown that patients with asthma and increased BMI have reduced lung function compared with participants with asthma and normal weight. (63, 64, 113). This is in line with the results obtained in paper I. Forno et al. reported that adults with obesity and asthma had a lower FEV_1, RV, and TLC compared to those with normal weight and asthma, suggesting that obesity may have a stronger effect on FVC and FEV_1 in participants without asthma than in those with asthma.(35) They also speculated that the effects of obesity are more readily apparent in participants without asthma because of their normal lung function as participants with asthma already have lower lung function; therefore, the effect of obesity is not as prominent.

In paper II, asthma had a significantly negative effect on all measured lung function values, while obesity was negatively associated with FVC and FEV_1 both pre- and post-bronchodilator. The estimate was greater for the measurements of FVC compared with that for FEV_1, indicating a restrictive pattern in participants with increased BMI. The effect of obesity on lung function is also well documented, and the previously reported effects on FVC and FEV_1 are in line with our studies.(35, 36, 116, 117) In a review by Dixon and Peters, it was concluded that FVC and FEV_1 were slightly reduced in participants with obesity and that the FEV_1/FVC-ratio was often unaffected unless the BMI was over 60 kg/m^2.(36) This does not imply that increased weight does not affect lung function, as they found body fat distribution to be more strongly associated with lung function than BMI. Other studies have also reported that FVC and FEV_1 can be affected by obesity; however, since the FEV_1/FVC-ratio often is relatively well-preserved, spirometry demonstrates a restrictive pattern in

patients with obesity.(118) In a meta-analysis by Forno et al., adult participants with obesity had lower FEV_1, FVC, total lung capacity (TLC), and residual volume (RV) compared with the participants with normal weight. Compared with participants who were overweight, participants with obesity had a larger reduction in these lung function values. This corresponds well with the results from our papers, which showed that FVC decreased more than FEV_1 in participants with obesity.

8.2.3 Work ability and sick leave

Work ability was assessed using WAS in papers I and II. In paper I, we observed no evidence for a reduced work ability among patients with asthma who had overweight or obesity compared with participants with normal weight and asthma. In paper II, participants with asthma had a reduced WAS compared with participants without asthma [OR: 1.9 (1.4–2.5)]. However, elevated BMI was not associated with reduced WAS.

Sick leave in the last 12 months was also assessed in papers I and II. In paper I, no significant increase in the frequency of sick leave in the last 12 months was observed in the groups with higher BMI compared with participants with normal weight. In paper II, asthma was associated with an increased frequency of sick leave in the last 12 months [OR: 1.4 (1.1–1.8)], while increased BMI was not. We did not observe an association between sick leave of >14 days in participants with asthma or increased BMI.

To our knowledge, the work ability measured using WAS in patients with asthma and obesity has not been studied previously at the time that papers I and II were published. In a recent 10-year follow-up study on middle-aged patients with asthma, it was demonstrated that WAS was stable in the follow-up period in most patients with asthma.(119) Loss of work ability was associated with increased BMI, physically strenuous work, and the number of comorbidities in that study. Work ability among participants with increased BMI was

assessed in a previous cross-sectional study conducted by Andersen et al.(45), who demonstrated reduced work ability with increasing BMI, with an OR of 1.69 (95% CI: 1.10–2.62) for lower work ability among working participants with grade III obesity (BMI: ≥40 kg/m^2) compared with that of those with normal weight. For BMI ranging between 30 and <35 kg/m^2, the OR was 1.11 (95% CI: 1.01–1.22). However, the researchers used a different instrument to evaluate work ability that focused on physical demands, which may explain the results differing from that of our study, where WAS was used to measure total work ability.

In a longitudinal study (20-year follow-up) that did not consider obesity, asthma was shown to reduce the WAI score of participants, and the effect was increased by the severity of asthma.(23) Previous studies have also shown an effect of BMI on sick leave regardless of concurrent asthma. In a review by Neovius et al.(42), obesity was associated with a higher frequency and longer duration of sick leave. The associations with overweight were less clear. Another review that included only longitudinal studies came to similar conclusions.(43) Several studies have reported an increased frequency of sick leave among patients with asthma, regardless of their weight, than that in healthy controls.(21, 22) Hansen et al. showed that patients with asthma receive more welfare, sick leave, and disability compared with participants without asthma.(21) In paper II, we found an increased frequency of sick leave within the past 12 months among participants with asthma; however, there was no indication of an increased incidence of sick leave longer than 14 days. This finding may suggest that participants with asthma are more frequently on sick leave; however, the duration is relatively short. A limitation of this paper is that we could not collect data on the cause of sick leave or register-based data. To our knowledge, only one study has reported a higher frequency of sick leave among patients with asthma and obesity (65). This Swedish

study reported that obesity was more common among participants who were on sick leave because of respiratory problems than that in the general population. However, the study included only a relatively small sample (n = 237) of patients on sick leave for >2 weeks who were recruited from a compulsory insurance registry.

There are several possible explanations for the conflicting results regarding self-reported work ability and sick leave.(42, 43) This study had few participants with BMI >40 kg/m^2. In paper I, the analyses were also performed using four BMI categories that included a category containing those with a BMI of ≥35 kg/m^2 (data not shown). This category had an OR of 2.9 (95% CI: 0.99–4.0) for reduced WAS and OR of 1.2 (0.56–2.54) for sick leave in the last 12 months compared with that of the normal weight category. However, using four BMI categories for the small number of participants in the two strata resulted in low statistical power. Neovius et al. reported an OR of 1.3–2.1 for the frequency of sick leave in studies comparing participants with obesity with those with normal weight and found that participants with obesity had approximately ten additional days of sick leave per person per year compared with those with normal weight.(42) In the Telemark study, the participants were relatively young (the oldest participants were 52 years old); thus, the frequency of sick leave was lesser compared with that of an older population. In addition, we included only participants who had been employed in the last 12 months in the analyses of sick leave data. This may have introduced a healthy worker effect bias as participants with more severe asthma or other conditions may have been receiving disability pensions or were not currently employed. The relatively young study population may also influence the assessment of work ability. Moreover, in Norway, the awareness regarding reducing sick leave is high, and employers will make great efforts to adjust work tasks and provide alternative jobs to ensure the workers can stay at work.

8.2.4 Interaction between increased BMI and asthma

We found no indication of an interaction between asthma and increased BMI on any symptoms, respiratory burden score, sick leave, or work ability. To the best of our knowledge, this has not been assessed in previous studies. However, we found a possible interaction between FVC and asthma and overweight. Nicolacakis et al. reported no synergistic interaction between asthma and obesity and concluded that the effects on lung function were a result of the combined effects.(59) However, this study was small (n=210, divided into four groups), and the results were not adjusted for important confounders. The lack of interaction was attributed to the existence of different pathways: obesity reduces lung volumes and influences the thoracic wall movement, while asthma affects the smooth muscle tone, leading to airway obstruction. Contrary to these results and in line with our results, Ekström et al. found evidence for an interaction between breathlessness and BMI and FVC.(33) The increase in breathlessness with increasing BMI was steeper among individuals with smaller lung volumes, and the difference between the sexes was related to the smaller lung volumes in women. However, they assessed the interaction between FVC and BMI for a single respiratory symptom. Nevertheless, this may indicate that there may be an interaction also between BMI and FVC. We observed no interaction for the remaining spirometric values.

8.2.5 Change in VGDF-exposure affecting respiratory burden score

We observed that changes in the respiratory burden score were associated with changes in the VGDF exposure score with a β-coefficient of 0.15 (0.10–0.19) in the adjusted models, indicating that increased VGDF exposure was associated with increased respiratory burden, and a reduced exposure was associated with a reduced respiratory burden score. Exposure to VGDF has been associated with respiratory symptoms in several previous studies.(120) To our knowledge, only a few prospective studies have assessed the effects of changes in

occupational exposure on respiratory symptoms. There are some studies whose results support our results. In a Polish follow-up study comparing participants exposed to dust with those who were not exposed to dust, a lower OR was reported for a chronic cough on removing exposure compared with continued exposure. In a follow-up study (over 11 years), occupational airborne exposure to dust, fumes, and gas was weakly related to the incidence of respiratory symptoms.(121) Exposure to dust or fumes has been shown to increase the risk for developing respiratory symptoms and asthma, independent of sex, age, educational level, and smoking in a general population follow-up study.(122) However, none of these studies described how the changes in exposures affect the incidence or prevalence of respiratory symptoms.

We found no difference between the sexes in the extent of the changes in VGDF exposure affecting the respiratory burden score. In other studies, the health response to air pollution has been shown to differ between male and female participants.(123) These studies indicated a stronger effect among women; however, the effect may vary according to the stage of life, hormonal status, and co-exposures. Sex differences in respiratory signs and symptoms in occupational settings have been described in a narrative review.(124) Potential factors that influence sex differences in an occupational setting are differences in work tasks; effectiveness of protective measures, such as respiratory masks; effectiveness of internal mechanisms, such as mucus composition; lung mechanics; and pre-existing susceptibility to inhaled agents, such as stress and inflammatory response. When assessing the respiratory sign and symptoms, there is little evidence regarding a clear pattern of susceptibility, and the results are not consistent between studies.(124) A previous meta-analysis demonstrated that the effects of occupational exposure to dust are different among

men and women.(125) Men were more affected by organic dust, while women were more affected by inorganic dust. More consistent sex differences have been reported in population-based studies; however, whether occupational exposure aggravates sex differences in respiratory symptoms warrants further research. Skorge et al. reported that exposure to dust, fumes, and gas was significantly associated with an increased incidence of respiratory symptoms in women than that in men.(121) The estimates in our study may indicate that males are slightly more affected than females (β-coefficient: 0.18 vs. 0.13); however, this finding was not statistically significant (p= 0.064). Thus, this result should be interpreted with caution as the groups including exposed women were small and may have resulted in insufficient statistical power to replicate previous findings. The result may also be influenced by the lack of more accurate exposure data and the differences in occupations and exposures among men and women.

High occupational exposure to VGDF has been associated with severe asthma exacerbation with a RR estimate of 3.1 (95% CI: 1.9–5.1).(126) A Cochrane review showed that continued exposure reduction or removal of exposure was associated with improvement in the symptoms in patients with occupational asthma.(127) Reduction and removal of exposure increased the likelihood of reporting the *absence* of symptoms. This review did not include any studies on the *improvement* of asthma symptoms after a reduction in exposure, while for the removal of exposure, RR was 2.47 (1.26—4.84). Reduced exposure to VGDF was not associated with a statistically significant improvement in the burden score among participants with asthma in paper III. A possible explanation for this could be that all participants with asthma were included, not just those with occupational or work-related

asthma; thus, we expected to find a significant effect of reduction or removal of the harmful exposure.

8.2.6 Sensitivity analyses

Excluding participants with BMI≤ 18.5 kg/m^2 (1.3% of the study population) in paper III did not change the estimates significantly. Similarly, the restriction of participants with asthma onset to those aged ≤ 30 years did not have a substantial effect on the results compared with those obtained when we included all participants with asthma. The logistical regression models used to test whether attendance at medical examination was associated with BMI, age, sex, education, smoking status, sick leave, and WAS showed that the older age groups, women, and non-smokers had a higher odds of attendance (papers I and II). This may have altered the prevalence estimates, although we considered that it was unlikely that the associations were affected. However, such bias cannot be ruled out entirely. To decrease the likelihood of biased results, all analyses were adjusted for age, smoking, sex, and level of education.

9 Implications

Our studies showed that increased BMI was associated with more respiratory symptoms. Patients with concurrent asthma and obesity had the same respiratory symptoms but had a higher respiratory burden, reduced lung function, and lesser control over their asthma compared with patients with asthma and normal weight. Our study indicated that asthma and obesity were independently associated with these outcomes; hence, both conditions should be treated. Increased BMI was associated with a higher respiratory symptom burden, and the effect was stronger among participants with asthma. This adds to the evidence that promoting weight loss is an important treatment for some patients with asthma. Our results also showed that despite an increased BMI, the participants do not report significantly

reduced work ability or more sick leave. This may help reject the myth that individuals with moderately increased BMI should not be employed as they have an increased frequency of sick-leave and reduced work ability, although more studies are needed. Another myth, although scientific evidence refutes this, is that a large proportion of participants with asthma have few symptoms and little implications on daily life and quality of life. In our studies, patients with asthma had reduced lung function, increased frequency of sick leave in the last 12 months, and reported reduced work ability, which in our opinion may indicate that more patients with asthma need support and measures to increase work ability. The measures can be personal, such as weight loss if appropriate, or optimization of medication, or on a structural level, such as reduction of the triggers of asthma or adjustments of work tasks to retain employment. Moreover, it is important to keep reducing the occupational exposure to VGDF as this is associated with a reduction in respiratory symptom burden, and previous studies have shown the association of such exposure with the risk of other respiratory diseases such as COPD.(128)

10 Conclusion

We showed an association between a higher respiratory symptom burden, higher consumption of asthma medication, and reduced asthma control in participants with asthma and a BMI of ≥30 kg/m^2. There was no clear evidence that any specific respiratory symptom was related to obesity in participants with asthma.

The participants with asthma and obesity used more current medication for asthma (OR: 1.60), had a higher respiratory burden score (OR: 1.78), more poorly controlled asthma (OR: 1.81), and reduced lung function (FVC and FEV_1) compared with participants with asthma and normal weight; however, they seemed to have similar work ability and frequency of sick leave.

Both asthma and obesity were independently associated with an increased respiratory burden score and lung function values, while reduced WAS and sick leave were associated with asthma, but not increased BMI.

We found a possible interaction between pre-bronchodilator FVC and asthma and overweight; however, no other significant interactions for the other lung function values were observed.

In the follow-up part of the study, changes in BMI and occupational exposure were associated with changes in the respiratory burden score. Changes in BMI affected participants with asthma more than participants without asthma; however, no sex difference was observed.

Due to the relatively small number of participants with a BMI of ≥35 kg/m^2, the results should not be extrapolated to participants with higher BMI, and we recommend further studies on this subpopulation.

11 Future research and recommendations

Future studies should be performed on participants with a BMI of >35kg/m^2 (WHO obesity class II) as our study did not have the statistical power to categorize BMI into more categories. These studies should be performed on participants with and without asthma as the effect on respiratory symptoms, lung function, and work ability might be stronger in patients with BMI of >35 kg/m^2. A follow-up study on the results of papers I and II may discover whether there is a causal relationship between asthma, increased BMI, and the assessed outcomes. A causal inference cannot be concluded in a cross-sectional study as the results only describe an association. We could not resolve whether increased BMI caused the respiratory symptoms or the respiratory symptoms were caused by increased BMI as we lacked the time-based aspect in papers I and II.

Studies on changes in BMI should also include other objective outcomes and anthropological measurements of the participants. Objective outcomes could be lung function and changes in inflammatory or other biomarkers. However, researchers should not discard the use of respiratory symptoms for other objective outcomes but assess them simultaneously. In this dissertation, we used the respiratory burden score as proposed by other researchers. This score should be further validated and standardized in studies including other populations. The use of the respiratory burden score provides a better description of the total burden of respiratory symptoms, as well as the symptoms as a continuum.(87) This dissertation has

generated interesting data regarding the frequency of sick leave in participants with asthma and obesity; however, it lacks more detailed data regarding the cause of sick leave, the duration of each sick-leave period, and the number of periods per year. To remedy this, future studies could be linked with national registries. This approach is also recommended by Thorsen et al.(93)

In our future studies in Telemark, we aim to have a longer observation period and use a job-exposure matrix or other instruments to assess occupational exposure. We also plan to include objective data from the participants, such as spirometry and inflammatory markers in airways and blood over time. In cases where we need to increase statistical power, the Telemark study will cooperate with other similar studies on respiratory health.

12 Reference list

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13 Appendices

13.1 Questionnaire (Q_{main}), English version

SYKEHUSET TELEMARK

TELEMARK STUDIEN

THE TELEMARK STUDY

- A health research project

Personal information

Today's date (ddmmyy):

☐

Gender:

☐ Female

☐ Male

Height: ☐ *cm*

Weight: ☐,☐ *kg*

What is your marital status?

☐ Single

☐ Married

☐ Partner

☐ Divorced/separated

☐ Widow

How many years of school do you have?

(Starting with the first class of primary school up to the last fully completed academic year).

☐ Years

What is your highest level education?
(Are you currently in secondary/vocational school/college/university? Please cross off your highest completed level of formal education).

☐ Elementary school/grade school

☐ Basic courses/1-2 year(s) of education after elementary school

☐ Secondary/high school/vocational school (3-years)

☐ Certificate

☐ University/College - 4 years or less

☐ University/College - more than 4 years

☐ Other: _____

We assume that your employability, when it was at its best would rate 10 points. How many points would you give to rate your employability?

(0 means that you cannot work and 10 that your employability is at its best right now).

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Working conditions

1. *Have you ever been in work?*

☐ No (go to question 10)

☐ Yes (go to question 2)

2. ***Describe your employment and work tasks with their associated time frames.***
If you have worked less than three months you do not need to respond.

If you have had many employers with similar works tasks merge them into one and proceed through the questionnaire. (Example: Building and construction, excavator driver with Selmer/Pavement/Ripper-Smith, 1993-2009). If you have been self-employed consider this as employment and proceed through the questionnaire.

Examples:

Yara/ Fertilizer Manufacturer	*Process operator*	*2008*	*2010*
Teaching	*Teacher at the vocational school*	*2010*	*2011*
Consulting	*Consultant company*	*2011*	*present day*

Sector/industry	***Profession (title)/work tasks***	***Year started***	***Year ended***

3. *Have you been engaged in paid work for **the past 12 months**?*

☐ No

☐ Yes

Supplementary questions about your work tasks in various employment situations: Many of these questions are specific to certain professions. If the question does not apply to you; answer no and move on to the next question.

4. *Have you in your work been subjected to: Gas, smoke or dust?*

☐ No

☐ Yes

5. *If you have been exposed to the gas, smoke or dust over the course of **the last five years** - how often? (Cross off an average)*

- ☐ Daily, for large parts of the working day
- ☐ Daily, but for short periods
- ☐ Weekly
- ☐ Less often

6. *Have you **ever,** in your **work,** been exposed to:*

	No	Yes	Last year of exposure
Smoke from frying	☐	☐	☐☐☐☐
Car/engine exhaust	☐	☐	☐☐☐☐
Strong acids, ammonia or formalin	☐	☐	☐☐☐☐
Stone dust	☐	☐	☐☐☐☐
Flour dust	☐	☐	☐☐☐☐
Wood dust	☐	☐	☐☐☐☐
Paper dust	☐	☐	☐☐☐☐
Textile dust	☐	☐	☐☐☐☐
Metal dust	☐	☐	☐☐☐☐

At work have you worked with:	No	Yes	Last year of exposure
Cleaning/disinfection agents	☐	☐	☐☐☐☐
If YES, do/did you use spray?	☐	☐	☐☐☐☐
Superglue or similar	☐	☐	☐☐☐☐
Painting or varnishing work	☐	☐	☐☐☐☐
Welding or other metal smoke	☐	☐	☐☐☐☐
Sewage or treatment plants	☐	☐	☐☐☐☐
Hair care products	☐	☐	☐☐☐☐
Animals	☐	☐	☐☐☐☐

If YES, which animals? _____

Gas, dust or damp not mentioned above

_____ ☐☐☐☐

8.

Have you worked in offices with:	No	Yes	Last year of exposure
Visible moisture damage	☐	☐	
Visible mold	☐	☐	
Smell of mildew (basement smell)	☐	☐	
Cold (in the cold room or outdoors in winter)	☐	☐	
Have you had physically strenuous work (so that you have been out of breath and sweaty)	☐	☐	
Have you had work with repetitive heavy lifting?	☐	☐	

9. *Have you used respiratory protection (safety/dust mask) at work during **the last 12 months?***

☐ Always/almost always
☐ From time to time
☐ Never/almost never

Have you only used respiratory protection in cases of high exposure?

☐ No
☐ Yes

10. *Have you had an accident at work or in your leisure time where you have been exposed to high levels of gas, smoke or dust?*

☐ No
☐ Yes

If YES, did you experience respiratory problems (coughing, shortness of breath, wheezing/rasping) when the accident happened or immediately afterwards?

☐ No
☐ Yes

Respiratory symptoms

			No
11.1		Have you had wheezing or whistling in the chest at some point over the course **of the last 12 months**? If NO, go to question 11.2, if YES:	☐
	a	Have you ever felt out of breath due to wheezing or whistling in your chest?	☐
	b	Have you had whistling or wheezing in your chest without having a cold?	☐
11.2		Have you woken up with a feeling of tightness in your chest at any time in **the last 12 months**?	☐ ☐
11.3		Have you woken up with breathing difficulties over the course of **the last 12 months?**	☐ ☐
11.4		Have you woken up due to coughing attacks during **the last 12 months?**	☐ ☐
11.5		Have you experienced an asthma attack in **the last 12 months**?	☐ ☐
		Do you currently use any medication (spray, inhalation powder or tablets) for asthma?	
11.6		Do you have allergies that cause nasal symptoms, including hay fever?	☐ ☐
11.7		Have you during the last years had a prolonged/cronich cough?	☐ ☐
11.8		Do you usually cough up phlegm or have mucus in the lungs that is hard to get up? If NO go to question 11.9, if YES:	☐ ☐
	a	Do you cough or bring up phlegm in this way nearly every day for at least three months each year?	☐ ☐
	b	Have you had periods with similar symptoms for at least two consecutive years?	☐ ☐
	c	How old were you when these problems started? ☐ Years	
11.9		Have you ever had whistling or wheezing in the chest? If Yes, how old were you when you experienced whistling or wheezing in the chest the first time? ☐ Years	☐ ☐
11.10		Do you have, or have you ever had asthma? If NO go to question, 11.11, if YES:	☐ ☐

a Has a doctor/physician ever diagnosed you with asthma? ☐ ☐

b How old were you when you first experienced asthma symptoms? ___ years

d What year did you last experience asthma symptoms? ____ (yyyy)

11.11 Has a doctor ever told you that you have chronic obstructive pulmonary disease (COPD)? ☐ ☐

If Yes, how old were you when you first experienced symptoms of COPD? ___ years

11.12 Have you ever experienced nasal symptoms such as stuffy nose, runny nose or sneeze attacks without having a cold? ☐ ☐

If NO go to question 11.13, if YES:

a How old were you when you first experienced these nasal symptoms? ___ years

b Have you had nasal symptoms over **the course of the last 12 months?** ☐ ☐

c During which season are your symptoms worse? (select only one option)

☐Spring ☐Summer ☐Autumn ☐Winter ☐Always ☐Don't know

11.13 Have you ever had a blocked nose **for more than 12 weeks over the course of the last 12 months?** ☐ ☐

11.14 Have you had pain or pressure around the forehead, nose, or eyes **for more than 12 weeks over the course of the last 12 months?** ☐ ☐

11.15 Have you had discolored nose secretions (snot) or discolored mucus in the throat for **more than 12 weeks over the course of the last 12 months?** ☐ ☐

11.16 Has your sense of smell been impaired or lost for **more than 12 weeks over the course of the last 12 months?** ☐ ☐

Respiratory symptoms and work

12. *Have you ever had recurring respiratory symptoms (cough, heavy breathing, wheezing, whistling) at work?*

☐ No (continue to question 15)
☐ Yes
☐ Yes, in the last 12 months

How serious were the respiratory symptoms?
(0 means that you did not have ailments and 10 that you had very serious ailments.)

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

13. *Were your complaints better:*

	No	Yes
- on weekends?	☐	☐
- during the holidays?	☐	☐
- during other absence from work?	☐	☐
- when changing your job/workplace?	☐	☐

14. *If you use/have used medicine to treat respiratory symptoms; can/could you reduce its use/dosage?*

	No	Yes
- on weekends?	☐	☐
- during the holidays?	☐	☐
- during other absence from work?	☐	☐
- when changing your job/workplace?	☐	☐

15. *Have you ever changed your job because the job has affected your breathing?*

☐ No

☐ Yes

If Yes, when was it (in which year)?

Year ☐☐☐☐ Year ☐☐☐☐

If YES, which place of work (work tasks) did you have at that time?

_____

16. *Have you ever changed your job because of: Hay fever, or other nasal problems?*

☐ No

☐ Yes

If Yes, when was it (what or which year)?

Year ☐☐☐☐ Year ☐☐☐☐

If YES, which place of work (work tasks) did you have at that time?

_____

17. *Have you ever changed job due to other health problems/illnesses?*

☐ No

☐ Yes

18. *Have you been on sick leave over* **the course of the last 12 months?**

☐ No

☐ Yes

If YES, for how many days? Choose only one option

☐ 1-7 days ☐ 8 -14 days ☐ 15 days - 12 weeks ☐ More than 12 weeks

Have you been off work due to breathing problems in ***the last 12 months****?*

☐ No

☐ Yes

Smoking and snuff

19.

	No	Yes
Do you smoke daily (even if you only smoke a few cigarettes, cigars or a pipe daily)?	☐	☐
Do you smoke only occasionally (not daily, but weekends, party smoking or the like)?	☐	☐
Did you use to smoke previousy?	☐	☐

If the answer is NO to question 19, go to question 25.

20. *How much did you smoke? (Give an average)*

☐ Cigarettes per day or ☐ cigarettes per **week**

☐ Cigars per week

☐ Packs of rolling tobacco-/pipe tobacco per week

21. *How old were you when you started smoking?*

☐ Years

22. *How many years have you smoked (this applies to both current and former smoking)?*

☐ Years

23. *If you smoked in the past, when did you quit?*

☐ Year

24. *Do you use, or have you used snuff?*

☐ No, never ☐ Yes from time to time

☐ Yes, but I stopped ☐ Yes, daily

*If you have **never** taken snuff, go to question 26.*

If YES:

How old were you when started to take snuff? ☐ *years*

How many tins of snuff do/did you use per month? ☐ *tins*

If you have stopped taking snuff, how old were you stopped? ☐ *years*

Living conditions

26. *What type of residence do you live in? (Choose two options)*

☐ Detached house ☐ Apartment/lodgings

☐ Row house/Semi-detached ☐ Other

27. *When did you move into your current residence?*

☐ year

How many hours per day do you normally spend in your home?

Weekdays ☐ hours Weekends ☐ hours

28. Is tobacco smoked inside your current residence? Choose only one option.

☐ Almost daily ☐ 1-4 times/week ☐ 1-4 times/week ☐ Never

29. Have you had any of the following in your residence?

	No	Yes	The number of years	The last year you were exposed.
Water damage/damage from damp inside the dwelling on walls, floors or ceilings?	☐	☐	☐	☐
"Warped" plastic mats, yellowed plastic coating or wood flooring that has become dark due to moisture?	☐	☐	☐	☐
Visible mold on walls, floors or ceilings?	☐	☐	☐	☐
Have you at any time over the course of the last 10 years seen signs of moisture damage, water leakage or mildew in your home?	☐	☐	☐	☐

30. *Is your bedroom window near a street (less than 20 m)? Choose only one option*

☐ No ☐ Yes, with moderate traffic

☐ Yes, with light traffic ☐ Yes, with a lot of traffic

31. *How much time do you usually spend travelling along a moderate-to very busy road in the course of a normal day?*

About ☐ minutes/day

Which of following heating methods were used in your home when you were five years old? Select more than one option if applicable.

☐ Wood
☐ Coal
☐ Paraffin
☐ Electricity
☐ Gas
☐ Oil
☐ Water-borne/district heating

32. *What word best describes the place you lived most of the time when you were under five years old? Choose only one option* Choose only one option

☐ Farm with animals
☐ Farm without animals
☐ Hamlet/village
☐ Small town/close to a town
☐ Large city

33. *Have you over the past 12 months used spray products regularly for cleaning at home?*

☐ No

☐ Yes

Childhood and family

34.

	No	Yes	Do not know
Did you as a child, have a severe respiratory infection before the age of 5?	☐	☐	☐
Did your mother smoke regularly when you were a child?	☐	☐	☐
Did your father smoke regularly when you were a child?	☐	☐	☐
Did anyone else in your home smoke on a regular basis when you were a child?	☐	☐	☐

35. *Do you have parents who have, or have had, the following diseases (provide a response also for deceased parents)?* Use a cross mark if the answer is YES

	Mother	Father
Asthma	☐	☐
Chronic bronchitis, emphysema or COPD	☐	☐
Heart disease	☐	☐
High blood pressure	☐	☐
Brain hemorrhage/stroke	☐	☐
Diabetes (diabetic)	☐	☐
Cancer	☐	☐

Physical activity and diet

36. *How often do you exercise? (Give an average)*

☐ Never
☐ Less than 1 time per week
☐ 1 time per week
☐ 2-3 times per week
☐ Daily/almost daily (4-7) times per week

37. *If you exercise once per week or more:*

How hard do you exercise?

☐ Take it easy without getting sweaty or out of breath
☐ I am out of breath and/or sweaty

☐ I am almost exhausted

38. *For how long do you usually work out? (Give an average)*

☐ Less than 15 minutes ☐ 30 minutes to 1 hour

☐ 15-29 minutes ☐ More than 1 hour

39. *Do you usually have at least 30 minutes of physical activity every day?*

☐ No ☐ Yes

40. *How often do you usually eat these foods? Make a cross in the box*

	0-3 times per month	1-3 times per week	4-6 times per week	1 time per day	2 times or more per day
Fruit/berries	☐	☐	☐	☐	☐
Vegetables	☐	☐	☐	☐	☐
Chocolate/candy	☐	☐	☐	☐	☐
Boiled potatoes	☐	☐	☐	☐	☐
Pasta/rice	☐	☐	☐	☐	☐
Sausages/hamburgers	☐	☐	☐	☐	☐
Oily fish (salmon, trout, herring, mackerel, redfish as toppings at dinner)	☐	☐	☐	☐	☐

41. *Do you use the following supplements? Make a cross in the box*

	Yes, daily	Occasionally	No
Cod liver oil	☐	☐	☐
Omega-3 capsules/supplements	☐	☐	☐
Vitamin-and/or mineral supplements	☐	☐	☐

Other diseases and symptoms

42. If you answer YES to the questions below, fill in your age on the far right.

(Cross either no or yes to all questions)

	No	Yes	If Yes, how old were you the **first** time?
Have you been told by a doctor that you have high blood pressure?	☐	☐	☐☐ year
Has a doctor told you that you have diabetes?	☐	☐	☐☐ year
Have you been hospitalized with a heart attack or heart cramp (angina)?	☐	☐	☐☐ year
Has a doctor ever told you that have heart failure (a weak heart, water in the lungs or swollen legs)?	☐	☐	☐☐ year

43. *Do you have, or have you ever had any of these diseases/complaints?*

Make a cross to indicate either no or yes to all the questions)

	No	Yes	If Yes, how old were you on the **first** occurrence?
Stroke/aneurism	☐	☐	☐☐ year
Atrial fibrillation?	☐	☐	☐☐ year
Eczema on the hands (with the exception of psoriasis)?	☐	☐	☐☐ year
Chronic lung disease other than asthma or COPD?	☐	☐	☐☐ year
Have you ever had mental problems that you have sought help for?	☐	☐	☐☐ year

13.2 Questionnaire ($Q_{spesical}$), English version

Sykehuset Telemark

Important
Simple
Free

Lung survey in Telemark

This is a questionnaire for participants in the major lung survey currently being carried out in Telemark. By participating you will be making an important contribution to medical research. All participants are of equal importance, whether they are currently affected by lung problems or not. The more people who participate, the easier it will be to find out why many people experience by respiratory problems.

Please return the completed questionnaire in the enclosed prepaid envelope.

You can read more about the questionnaire on the information sheet or on our website: www.sthf.no/asthma

Thank you for your help!

Yours Sincerely

[signature removed]

Bess Margrete Frøyshov
Administrerende direktør, STHF

Tomm Bernklev
Forskningssjef, STHF

Johny S. Kongerud
Professor Det medisinske fakultet, Oslo

If you have any questions, please ring one of the project staff at Telemark Hospital on: +47 953 69 315 (from 09.00–15.00).

Today's date (ddmmyy) : ☐☐☐☐☐☐ *Gender:* ☐ Female ☐ Male

Working conditions

If this question does not apply to you, please proceed to the next question.

1. *Have you been exposed to gas, dust or smoke at work in **the last 12 months**?*
☐ No ☐ Yes

2. *Have you been exposed to any of the following **at work**?:*

	Yes	In last 12 mnths?	From year (last two figures)	To year (last two figures)	How often? Daily	Weekly	Rarely
Grain dust or hay/straw	☐	☐	☐☐	☐☐	☐	☐	☐
Fire smoke	☐	☐	☐☐	☐☐	☐	☐	☐
Plastic dust	☐	☐	☐☐	☐☐	☐	☐	☐
Fertiliser or calcium nitrate dust	☐	☐	☐☐	☐☐	☐	☐	☐
Chlorine gas	☐	☐	☐☐	☐☐	☐	☐	☐
Nitrous gases	☐	☐	☐☐	☐☐	☐	☐	☐
Ammonia	☐	☐	☐☐	☐☐	☐	☐	☐
Acids (e.g.: nitric/hydrochloric/sulphuric)	☐	☐	☐☐	☐☐	☐	☐	☐
Cutting fluids/cutting oils	☐	☐	☐☐	☐☐	☐	☐	☐
Formalin/formaldehyde	☐	☐	☐☐	☐☐	☐	☐	☐
Tobacco smoke (passively)	☐	☐	☐☐	☐☐	☐	☐	☐
Smoke from frying	☐	☐	☐☐	☐☐	☐	☐	☐
Car/engine exhaust	☐	☐	☐☐	☐☐	☐	☐	☐
Stone dust	☐	☐	☐☐	☐☐	☐	☐	☐
Flour dust	☐	☐	☐☐	☐☐	☐	☐	☐
Wood dust	☐	☐	☐☐	☐☐	☐	☐	☐
Paper dust	☐	☐	☐☐	☐☐	☐	☐	☐
Textile dust	☐	☐	☐☐	☐☐	☐	☐	☐
Metal dust	☐	☐	☐☐	☐☐	☐	☐	☐

3. ***Have you ever worked with the following at your workplace?***

	Yes	In last 12 mnths?	From year (last two figures)	To year (last two figures)	How often? Daily	Weekly	Rarely
Birds	☐	☐	☐☐	☐☐	☐	☐	☐
Farming/agriculture	☐	☐	☐☐	☐☐	☐	☐	☐
Laboratory chemicals	☐	☐	☐☐	☐☐	☐	☐	☐
Mineral wool (Glava, Rockwool etc.)	☐	☐	☐☐	☐☐	☐	☐	☐
Solvents	☐	☐	☐☐	☐☐	☐	☐	☐
Wood impregnation	☐	☐	☐☐	☐☐	☐	☐	☐
Hot asphalt	☐	☐	☐☐	☐☐	☐	☐	☐
Epoxy (paint, varnish, glue)	☐	☐	☐☐	☐☐	☐	☐	☐
Acrylates	☐	☐	☐☐	☐☐	☐	☐	☐
Polyurethane	☐	☐	☐☐	☐☐	☐	☐	☐
Renovation work/waste handling	☐	☐	☐☐	☐☐	☐	☐	☐
Soldering	☐	☐	☐☐	☐☐	☐	☐	☐
Metal production (smelting work)	☐	☐	☐☐	☐☐	☐	☐	☐
Welding or other metal smoke	☐	☐	☐☐	☐☐	☐	☐	☐
Welding: rust-proof/acid-proof	☐	☐	☐☐	☐☐	☐	☐	☐
Welding: black steel and similar	☐	☐	☐☐	☐☐	☐	☐	☐
Cleaning/disinfection agents	☐	☐	☐☐	☐☐	☐	☐	☐
If YES, do/did you use spray?	☐	☐	☐☐	☐☐	☐	☐	☐
Superglue or similar	☐	☐	☐☐	☐☐	☐	☐	☐
Painting or varnishing work	☐	☐	☐☐	☐☐	☐	☐	☐
Sewage or treatment plants	☐	☐	☐☐	☐☐	☐	☐	☐
Hair care products	☐	☐	☐☐	☐☐	☐	☐	☐
Gas, dust or damp not mentioned above: **Which**?_____	☐	☐	☐☐	☐☐	☐	☐	☐
Animals	☐	☐	☐☐	☐☐	☐	☐	☐

If YES, which animal(s)? _____

4. *Have you changed job in **the last 12 months**?*

☐ No ☐ Yes

5. *Have you worked (full or part-time) in **the last 12 months?***

☐ No ☐ Yes

6. *List your various periods of employment including work tasks performed in the **LAST TWO YEARS**. If you are still in work, write d.d. under "Finished".*

Examples:

Industry/sector	***Profession (title)/work tasks***	***Started***	***Finished***
Yara/Fertiliser factory	*Process operator*	*0 5 1 3*	*1 1 1 3*
Consultancy	*Self-employed consultant*	*0 1 1 4*	*d. d.*
Industry/sector	***Profession (title)/work tasks***	***mmyy***	***mmyy***

7. *Have you ever changed job because your work was affecting your breathing?*

☐ No ☐ Yes

***If YES**, when (which year[s])?*

Year ____ Which workplace/work tasks:_____

Year ____ Which workplace/work tasks: _____

8. *Have you used breathing equipment (protective/dust masks) at work?*

☐ No ☐ Yes

***If YES**,* ☐ Last 12 mnths

Any earlier years From ____ To ____ (mmyy)

How often did/do you use a mask for work tasks:

For <u>normal/moderate</u> amounts of dust, gas or smoke?

☐ Always ☐ Occasionally ☐ Never

For <u>higher than normal</u> amounts of dust, gas or smoke?

☐ Always ☐ Occasionally ☐ Never

9. *Have you suffered an accident at work or in your leisure time in which you were exposed to high levels of gas, smoke or dust in **the last 12 months**?*

Work: ☐ No ☐ Yes

Leisure: ☐ No ☐ Yes

***If YES**,* Which type of gas, smoke or dust were you exposed to?_____

Did you experience respiratory problems (coughing, shortness of breath, wheezing/rasping) when the accident happened or immediately afterwards?

Work: ☐ No ☐ Yes

Leisure: ☐ No ☐ Yes

Respiratory problems

10.

		No	Yes
9.1	Do you suffer from, or have you ever suffered from asthma? If NO go to question 9.2, **If YES**:	☐	☐
	How old were you when you first experienced asthma symptoms? ☐☐ year		
	In which year did you last experience asthma symptoms? ☐☐☐☐ (year)		
	Has a doctor ever diagnosed you with asthma?	☐	☐
	How old were you then? ☐☐ years		
9.2	Have you experienced wheezing or rasping in your chest at any time in **the last 12 months**? If NO, go to question 9.3, **If YES**:	☐	☐
	Have you experienced shortness of breath with wheezing or rasping in your chest in **the last 12 months**?	☐	☐
	Have you experienced wheezing or rasping in your chest without having a cold in **the last 12 months**?	☐	☐
9.3	Have you woken up with a feeling of tightness in your chest at any time in **the last 12 months**?	☐	☐
9.4	Have you been woken up by breathing difficulties at any time in **the last 12 months**?	☐	☐
9.5	Have you experienced breathing difficulties when at rest at any time in **the last 12 months**?	☐	☐
9.6	Have you experienced breathing difficulties after being exposed to cold at any time in **the last 12 months**?	☐	☐
9.7	Have you experienced breathing difficulties after exerting yourself at any time in **the last 12 months**?	☐	☐
9.8	Have you been woken up by a coughing attack in **the last 12 months**?	☐	☐
9.9	Have you experienced an asthma attack in **the last 12 months**?	☐	☐
9.10	Have you had a blocked nose **for more than 12 weeks in the last 12 months**?	☐	☐
9.11	Have you experienced pains or pressure around your forehead, nose or eyes **for more than 12 weeks in the last 12 months**?	☐	☐
9.12	Have you experienced discoloured nasal secretions (mucus) or discoloured mucus in your throat **for more than 12 weeks in the last 12 months**?	☐	☐
9.13	Has your sense of smell been reduced or absent for **more than 12 weeks in the last 12 months**?	☐	☐
9.14	Have you visited a doctor or accident/emergency unit due to acute breathing difficulties at any time in **the last 12 months**?	☐	☐
9.15	Have you taken extra cortisone medication or increased your cortisone inhalation at any time in **the last 12 months**?	☐	☐
9.16	Have been hospitalised due to breathing difficulties at any time in **the last 12 months**?	☐	☐

		No	Yes
9.17	Have you ever experienced problems breathing?	☐	☐
9.18	Have you ever experienced difficulties taking deep breaths?	☐	☐
9.19	Do you suffer from soreness in your chest (musculature)?	☐	☐
9.20	Do you suffer from nausea or a bloated stomach?	☐	☐
9.21	Do you suffer from itching, irritation or dryness in your eyes, nose or throat?	☐	☐

11.

Do you experience breathing difficulties if you are exposed to/involved in:	No	Yes
Perfume, hairspray, paint, cleaning/washing agents or exhaust fumes?	☐	☐
Tobacco smoke or bonfire smoke?	☐	☐
Stress or situations of conflict?	☐	☐
Physical activity?	☐	☐

Living conditions

12.

	No	Yes
Have you lived in a fire-damaged home in **the last 12 months**?	☐	☐
Have you experienced water damage/damp patches on the walls, floors or ceilings in your home in **the last 12 months**?	☐	☐
Have you performed renovation work in your home in **the last 12 months**?	☐	☐

If YES, were you exposed to:

☐ Dust ☐ Paint/varnish

Have you through your hobbies or leisure activities been exposed to gas, dust or smoke in **the last 12 months**?	☐	☐

If YES, state which _____

Other illnesses and conditions

13.

Do you suffer from, or have you ever suffered from, any of these illnesses/conditions?

	No	Yes	If YES, how old were you the **first** time?
Heart attack	☐	☐	☐☐ years
Angina pectoris	☐	☐	☐☐ years
Heart failure	☐	☐	☐☐ years

Other heart disease	☐	☐	☐☐	years
Stroke/brain haemorrhage	☐	☐	☐☐	years
Kidney disease	☐	☐	☐☐	years
Diabetes	☐	☐	☐☐	years
Psoriasis	☐	☐	☐☐	years
Eczema on your hands	☐	☐	☐☐	years
Cancer	☐	☐	☐☐	years
Epilepsy	☐	☐	☐☐	years
Rheumatoid arthritis	☐	☐	☐☐	years
Ankylosing spondylitis	☐	☐	☐☐	years
Sarcoidosis	☐	☐	☐☐	years
Osteoporosis	☐	☐	☐☐	years
Fibromyalgia	☐	☐	☐☐	years
Arthrosis	☐	☐	☐☐	years

Allergies

14. *Do you suffer from any form of allergy?*

☐ No ☐ Yes

***If YES**,*

Do you suffer from hay fever/pollen allergies or other allergic respiratory problems?

☐ No ☐ Yes

Do you suffer from eczema or any other skin allergy?

☐ No ☐ Yes

Are you allergic to anything else? (cross all that apply)

☐Dogs ☐Cats ☐Other animals ☐Foods ☐Cosmetics ☐Metals ☐Other

15. *Does your biological **mother** have an allergy? Does your biological **mother** have asthma?*

☐ No ☐ Yes ☐ Don't know ☐ No ☐ Yes ☐ Don't know

16. *Does your biological **father** have an allergy? Does your biological **father** have asthma?*

☐ No ☐ Yes ☐ Don't know ☐ No ☐ Yes ☐ Don't know

Family illnesses and conditions

17. *Do your biological parents have any of these symptoms/conditions (now or previously)?*

	Biological **mother**			Biological **father**		
	No	Yes	Don't know	No	Yes	Don't know
Heart attack	☐	☐	☐	☐	☐	☐
Angina pectoris	☐	☐	☐	☐	☐	☐
Heart failure	☐	☐	☐	☐	☐	☐
Other heart disease	☐	☐	☐	☐	☐	☐
Stroke/brain haemorrhage	☐	☐	☐	☐	☐	☐
Kidney disease	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐
Psoriasis	☐	☐	☐	☐	☐	☐
Eczema on your hands	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Epilepsy	☐	☐	☐	☐	☐	☐
Rheumatoid arthritis	☐	☐	☐	☐	☐	☐
Ankylosing spondylitis	☐	☐	☐	☐	☐	☐
Sarcoidosis	☐	☐	☐	☐	☐	☐
Osteoporosis	☐	☐	☐	☐	☐	☐
Fibromyalgia	☐	☐	☐	☐	☐	☐
Arthrosis	☐	☐	☐	☐	☐	☐

Physical activity and diet

18. *How often do you normally eat these foods?*

	Rarely or never	1–3 times per month	1–2 times per week	3–4 times per week	5–7 times per week
Potatoes (boiled, baked, mashed)	☐	☐	☐	☐	☐
Oily fish (salmon, trout, mackerel, herring as a filling/meal)	☐	☐	☐	☐	☐
Other fish (cod, pollack etc.)	☐	☐	☐	☐	☐
Fishcakes, fish balls, deep-fried fish etc.	☐	☐	☐	☐	☐
Red meat (pure cuts of beef, pork, lamb, game, e.g. chops, roasts, steaks)	☐	☐	☐	☐	☐
White meat (chicken, turkey)	☐	☐	☐	☐	☐
Hot dogs, hamburgers, kebabs, rissoles or other meals with mince	☐	☐	☐	☐	☐

Readymade pizza	☐	☐	☐	☐	☐
Chips	☐	☐	☐	☐	☐
Rice	☐	☐	☐	☐	☐
Pasta	☐	☐	☐	☐	☐
Biscuits, cakes, waffles, rolls etc.	☐	☐	☐	☐	☐
Ice cream	☐	☐	☐	☐	☐
Chocolate/sweets	☐	☐	☐	☐	☐
Salted snacks (crisps, peanuts)	☐	☐	☐	☐	☐

19. *How often do you normally eat these foods?*

	Rarely or never	1–2 times per week	3–4 times per week	5–7 times per week	Several times a day
Coarse bread and other coarse wheat products	☐	☐	☐	☐	☐
White bread or other refined wheat products	☐	☐	☐	☐	☐
Normal cheese (all types, white/brown)	☐	☐	☐	☐	☐
Reduced fat cheese (all types, white/brown)	☐	☐	☐	☐	☐
Jams and other sweet spreads	☐	☐	☐	☐	☐

21. *How many portions of vegetables or fruit/berries do you eat each day?*

One portion could be, e.g., 1 medium-sized fruit or 1 carrot, 1 slice of turnip or 1 portion of salad.

	0 portions	½ portion	1 portion	2 portions	3 portions	4 portions	5 or more portions
Vegetables (excl. potatoes)	☐	☐	☐	☐	☐	☐	☐
Fruit or berries (incl. juice, max 1 glass)	☐	☐	☐	☐	☐	☐	☐

22. *How often do you eat these meals?:*

	Rarely/ Never	1–2 times a week	3–4 times a week	5–6 times a week	Every day
Breakfast	☐	☐	☐	☐	☐
Lunch	☐	☐	☐	☐	☐
Evening meal	☐	☐	☐	☐	☐
Supper	☐	☐	☐	☐	☐

23. *How often do you eat something between the above meals?*

Rarely/ never	1–2 times a week	3–4 times a week	5–6 times a week	Every day	Several times a day
☐	☐	☐	☐	☐	☐

24. *Are you happy with your weight?*

☐ No, I'm too light ☐ No, I'm too heavy ☐ Yes

25. *Have you tried to slim in the last 10 years?*

☐ No ☐ Yes, occasionally ☐ Yes, frequently

26. *How often do you exercise? (On average)*

☐ Never
☐ Less than once a week
☐ Once a week
☐ 2–3 times a week
☐ Most days (4–7 times a week)

27. *Do you usually perform at least 30 minutes' physical activity each day?*

☐ No ☐ Yes

28. *How many hours' physical activity do you take on average each week?*

Low intensity, do not get out of breath or sweat (easy walks, light housework and gardening work and similar) ☐ hours

Moderate intensity, get out of breath and sweat (jogging, cycling or swimming at moderate intensity, strenuous housework and gardening work) ☐ hours

High intensity, hard physical training that pushes you close to your limit (interval training, intense strength training, high intensity spinning or aerobic and similar) ☐ hours

Smoking and snuff habits

Even if you have already answered these questions, please could you answer them again one year later. Many thanks in advance!

29.

	No	Yes
Do you smoke every day (also applies if you only smoke a few cigarettes or cigars, or light a pipe each day)?	☐	☐
Do you only smoke occasionally (not each day, but at weekends, parties or similar)?	☐	☐
Did you use to smoke?	☐	☐

If you have answered NO all items in question 29, go to question 34.

30. *How old were you when you started smoking?* ☐ *years*

31. *How long have you smoked (only applies to current and previous smoking)?* ☐ *years*

32. *Do you smoke e-cigarettes (applies even if you only smoke a few cigarettes)?*

No, never ☐ Yes, occasionally ☐
Yes, but I have stopped ☐ Yes, daily ☐

33. *If you used to smoke, when did you stop?* ☐☐☐☐ *year*

34. *Do you take/have you ever taken snuff?*

No, never ☐ Yes, occasionally ☐

Yes, but I have stopped ☐ Yes, daily ☐

If YES:

How old were you when you started to take snuff? ☐☐ *years*

How many tins of snuff do/did you use per month? ☐☐ *tins*

If you have stopped taking snuff, how old were you when you stopped? ☐☐ *Years*

Respiratory problems and work

35. *Have you experienced repeated respiratory problems (cough, shortness of breath, rasping, wheezing)* ***at work in the last 12 months****?*

☐ No

☐ Yes

If yes, *how serious were your respiratory problems?*

(0 means you experienced no problems and 10 you experienced very serious problems).

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

36. *Do these problems improve:*

	No	Yes
- at the weekends?	☐	☐
- in the holidays?	☐	☐
- on other absents from work?	☐	☐
- after changing job/work location?	☐	☐

37. *If you take/have taken medication for respiratory problems can/could you reduce your usage/dose?*

	No	Yes
- at the weekends?	☐	☐
- in the holidays?	☐	☐
- on other absents from work?	☐	☐
- after changing job/work location?	☐	☐

Thank you for taking the time to answer ☺

13.3 Asthma control test (ACT) questionnaire, English version

1. **In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?**
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ None of the time

2. **During the past 4 weeks, how often have you had shortness of breath?**
    - ☐ More than once a day
    - ☐ Once a day
    - ☐ 3 – 6 times a week
    - ☐ 1-2 a week
    - ☐ Not at all

3. **During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing shortness of breath, chest tightness or pain) wake you up at night, or earlier than usual in the morning?**
    - ☐ 4 or more nights a week
    - ☐ 2-3 nights a week
    - ☐ 1 time a week
    - ☐ 1 or 2 times
    - ☐ Not at all

4. **During the past 4 weeks, how often have you used your recue inhaler or nebulizer medication?**
    - ☐ 3 or more times per day
    - ☐ 1-2 times per day
    - ☐ 2-3 time per week
    - ☐ One a week or less
    - ☐ Not at all

5. **How would you rate your asthma control during the past 4 weeks?**
    - ☐ Not controlled at all
    - ☐ Poorly controlled
    - ☐ Somewhat controlled
    - ☐ Well controlled
    - ☐ Completely controlled

14 Paper I to III

I

II

BMJ Open Respiratory Research

Influence of asthma and obesity on respiratory symptoms, work ability and lung function: findings from a cross-sectional Norwegian population study

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ABSTRACT

Background Although asthma and obesity are each associated with adverse respiratory outcomes, a possible interaction between them is less studied. This study assessed the extent to which asthma and overweight/obese status were independently associated with respiratory symptoms, lung function, Work Ability Score (WAS) and sick leave; and whether there was an interaction between asthma and body mass index (BMI) ≥25 kg/m^2 regarding these outcomes.

Methods In a cross-sectional study, 626 participants with physician-diagnosed asthma and 691 without asthma were examined. All participants completed a questionnaire and performed spirometry. The association of outcome variables with asthma and BMI category were assessed using regression models adjusted for age, sex, smoking status and education.

Results Asthma was associated with reduced WAS (OR=1.9 (95% CI 1.4 to 2.5)), increased sick leave in the last 12 months (OR=1.4 (95% CI 1.1 to 1.8)) and increased symptom score (OR=7.3 (95% CI 5.5 to 9.7)). Obesity was associated with an increased symptom score (OR=1.7 (95% CI 1.2 to 2.4)). Asthma was associated with reduced prebronchodilator and postbronchodilator forced expiratory volume in 1 s (FEV_1) (β=−6.6 (95% CI −8.2 to −5.1) and −5.2 (95% CI −6.7 to −3.4), respectively) and prebronchodilator forced vital capacity (FVC) (β=−2.3 (95% CI −3.6 to −0.96)). Obesity was associated with reduced prebronchodilator and postbronchodilator FEV_1 (β=−2.9 (95% CI −5.1 to −0.7) and −2.8 (95% CI −4.9 to −0.7), respectively) and FVC (−5.2 (95% CI −7.0 to −3.4) and −4.2 (95% CI −6.1 to −2.3), respectively). The only significant interaction was between asthma and overweight status for prebronchodilator FVC (β=−3.6 (95% CI −6.6 to −0.6)).

Conclusions Asthma and obesity had independent associations with increased symptom scores, reduced prebronchodilator and postbronchodilator FEV_1 and reduced prebronchodilator FVC. Reduced WAS and higher odds of sick leave in the last 12 months were associated with asthma, but not with increased BMI. Besides a possible association with reduced FVC, we found no interactions between asthma and increased BMI.

Key messages

- Are asthma and increased body mass index (BMI) independently associated with respiratory health outcomes, and is there a possible interaction between asthma and BMI?
- Asthma and obesity were independently associated with an increased respiratory symptom score, reduced prebronchodilator and postbronchodilator forced expiratory volume in 1 s and reduced prebronchodilator forced vital capacity (FVC), and the only interaction was between asthma and overweight for prebronchodilator FVC.
- A better understanding of respiratory outcomes and interaction may aid clinical decision-making and inform more personalised treatments in patients with asthma and increased BMI.

INTRODUCTION

Asthma is characterised by variable respiratory symptoms, such as wheezing and dyspnoea during rest or exercise and variable airflow limitation. Studies have found more sick leave and disability among patients with asthma compared with healthy controls.[1 2] Similarly, obesity may also cause shortness of breath and wheezing both at rest and following activity.[3 4] The effect of obesity on lung function has been described in several review studies,[5–8] showing an association between obesity and reduced forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC).[5] Obesity has also been associated with a higher frequency and longer duration of sick leave.[9 10] Work ability in subjects with obesity has been less studied, but an association between reduced work ability and higher body mass index (BMI) has been found in employed subjects.[11]

A recent review concluded that there is sufficient evidence for a causal relationship between BMI and asthma.[12] Obesity may increase the risk of de novo asthma, complicate asthma or worsen respiratory symptoms.[13] Studies indicate that asthma is a risk factor for obesity in children[14] and adults.[15] Low-grade

systemic inflammation and altered lung mechanics have been demonstrated in both asthma and obesity.[16] Obesity and asthma have several common comorbidities, such as obstructive sleep apnoea, gastro-oesophageal reflux and anxiety.[17] Previous studies of patients with both asthma and obesity have classified obese asthma as a distinct phenotype, characterised by late onset asthma, increased respiratory symptoms, reduced lung function and poorer response to treatment compared with patients with asthma without obesity.[13 18–20]

While asthma and obesity are each separately associated with adverse respiratory outcomes, a possible interaction between them is less studied. A better understanding of the combined effects of asthma and obesity may help inform new and more personalised treatment and follow-up for such patients. Nicolacakis *et al* assessed the interaction between asthma and obesity using different lung function tests.[21] This study found no synergistic interaction, but the study sample was small, and the analyses were not adjusted for smoking status. To the best of our knowledge, there are no other studies assessing the possible interaction between asthma and BMI and the effect on respiratory outcomes.

In the present study of asthma cases and controls without asthma, we studied the extent to which asthma and overweight/obese status were independently associated with respiratory symptoms, lung function, work ability and sick leave; and whether there is an interaction between asthma and BMI ≥25 kg/m^2 regarding these outcomes.

METHODS

Study population

The study population was a sample of 626 participants in the cross-sectional baseline survey of the Telemark study who answered affirmative to the question: 'Has a doctor/physician ever diagnosed you with asthma?'. A random sample of those who did not state that they had physician-diagnosed asthma (n=691) was included as controls (hereafter the term 'healthy controls' is used). The Telemark study is a population-based study that started in 2013 and is described in detail in a previous publication.[22] In brief, the Telemark study started with a random sample of 50 000 inhabitants living in Telemark county in Norway, aged 16–50 years, who received a postal questionnaire. Of these, 48 142 were eligible, and 16 099 responded (response rate: 33%).[23] The responders included 1857 (11.5%) who reported having physician-diagnosed asthma.

For the present study, all 1857 subjects with physician-diagnosed asthma and 1989 computer-randomised healthy subjects were invited to undergo further medical examinations in 2014 or 2015. Figure 1 shows a flowchart of the subjects in the present study and indicates the number of subjects excluded and reasons for exclusion.

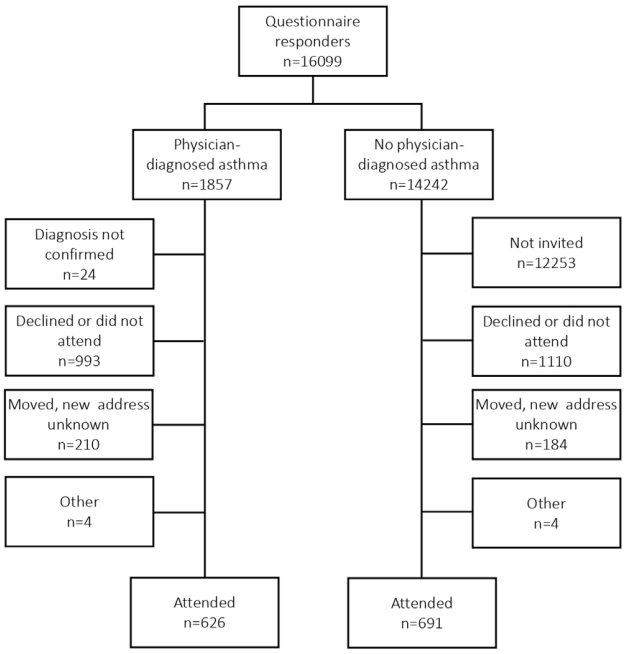

Figure 1 Flow chart of study subjects, including those excluded and the reasons for exclusion.

Questionnaire

All participants (n=1317) completed a questionnaire regarding respiratory symptoms, smoking status and other variables. The questionnaire was based on the European Community Respiratory Health Survey questionnaire as well as a questionnaire from a similar study conducted in Sweden.[24] Physician-diagnosed asthma was defined as an affirmative answer to the question: 'Has a doctor/physician ever diagnosed you with asthma?'. All missing data regarding symptoms and sick leave were recorded as not having that symptom or any sick leave. Age and sex were confirmed for accuracy using the Norwegian National Population Register. We calculated a score based on respiratory symptoms experienced within the last 12 months for each individual by adding all positive answers to questions Q1 to Q9 listed in online supplemental table 1, giving a maximum score of 9. The cut-off for dichotomising the symptom score was set at ≥3, which represented the upper tertile of the scores. Use of current asthma medication was defined as an affirmative answer to the question: 'Are you currently using any medications for asthma (spray, inhalation powder or tablets)?'. All subjects with physician-diagnosed asthma and respiratory symptoms during the past 12 months completed the Asthma Control Test (ACT) questionnaire, and a score was calculated.[25] In this questionnaire, answers are given a score of 1–5, where five is the best, and the maximum score is 25. A total score <19 indicates poorly controlled asthma.[25]

In the baseline study questionnaire the subjects were asked to state if they ever had sarcoidosis, other chronic lung diseases than asthma and Chronic obstructive pulmonary disease (COPD), sought help for mental

problems, physician-diagnosed COPD, and if they suffer from hay fever, pollen allergy or other allergic respiratory problems.

Anthropometric measures

All participants underwent a physical examination. Trained study personnel using the same instruments for all participants measured the subjects' height and weight. BMI was calculated as kg/m^2 and stratified into the following categories recommended by the WHO: normal weight (including underweight) <25.0 kg/m^2, overweight 25.0–29.9 kg/m^2 and obese ≥30 kg/m^2.[26]

Lung function tests

Spirometry was performed in accordance with the American Thoracic Society/European Respiratory Society guidelines[27] using Jaeger Master Screen Pulmonary Function Testing (Erich Jaeger GmbH & Co. KG, Würzburg, Germany). FVC, FEV_1 and FEV_1/FVC-ratio were recorded. Two trained physicians (GK and JK) manually validated all tests. If a participant had no valid curves, the results were not included. All reference values were calculated using Global Lung Function Initiative equations.[28]

Reversibility testing

All participants with at least one acceptable spirometry test (n=1258, 96%) were asked to inhale 0.4 mg salbutamol, and spirometry was repeated after 10–15 min.[29] All tests were manually validated, and tests without an acceptable curve were excluded. In total, 1091 (83%) participants had an acceptable test. Reasons for not performing the reversibility test included refusal by participants (n=91 (7%)), no valid curves (n=28 (2%)), contraindications (n=14 (1%)) or other reasons (n=15 (1%)).

Work ability

Work ability was defined via self-report using the first question of the Work Ability Index (WAI) questionnaire.[30] This question is referred to as the Work Ability Score (WAS).[30] The participants were asked to grade their current work ability on a scale from 0 ('I cannot work at all') to 10 ('my work ability is at its best right now'). WAS can be categorised into normal (score ≥8) and reduced (score <8) work ability.[31] Previous studies have demonstrated a strong association between WAS and the results of a complete WAI questionnaire.[31 32]

Sick leave

Sick leave was defined as an affirmative answer to the question, 'Have you been on sick leave over the course of the last 12 months?'. The subjects selected how many days they had been on sick leave from the following categories: 1–7 days, 8–14 days, 15 days–12 weeks and >12 weeks. A cut-off of 14 days was chosen to differentiate short-term from long-term sick leave. The cut-off and categorisation were chosen to reflect the official Norwegian sick leave system and important follow-up time points. Analyses of sick leave were restricted to subjects employed in paid work within the previous 12 months (n=1143).

Patient and public involvement

A representative from the Norwegian Asthma and Allergy Association (NAAA) was a member of the study steering committee and contributed to the development of questionnaires and examination methods. NAAA representatives have also been involved in study planning, design piloting and transfer of knowledge to the patient group.

Statistical analyses

The study participants were grouped into six categories according to their BMI and asthma status. To analyse differences between the groups, Pearson χ^2 and Fisher's exact tests were used for categorical data, and one-way analysis of variance (ANOVA) was applied to continuous data.

The association of outcome variables with asthma and BMI was assessed using logistic and linear regression models adjusted for age, sex, smoking status and education. To assess interaction, a separate regression model was fit for each outcome and included covariates for asthma, BMI categories, asthma ×BMI interaction, age, sex, smoking and education. Additive interactions for dichotomous outcomes were assessed via the methods described by Andersson *et al* using the Synergy Index (SI), with a null value of 1.0 and a 95% CI.[33]

For responders and non-responders, we have self-reported data from the baseline survey on BMI, age, sex, education, smoking, sick leave and WAS. We used a conditional logistic regression model to test whether attendance at the medical examination was associated with these variables. In other analyses performed on the Telemark study population,[22] the inverse probability of participation weights was used to minimise selection bias from non-participation. Because this did not substantially change the exposure-outcome associations compared with the use of non-weighted variables in that study, weights were not used in the present study.

All analyses were performed using the statistical package SPSS V.25.0 (IBM SPSS). Statistical significance was defined as $p<0.05$, and $0.05 \leq p < 0.10$ was considered borderline statistically significant.

RESULTS

Table 1 shows the characteristics for all subjects stratified by BMI-category and asthma status. Subjects with asthma and obesity had a higher age of onset of symptoms (mean 16.6 years of age), more frequently used asthma medication (65%) and had a poorer asthma control (43% with ACT score 5–19) than the subjects with normal weight and asthma. The subjects with asthma reported more

Table 1 Characteristics for subjects stratified by BMI-category and physician-diagnosed asthma

	No physician-diagnosed asthma			Physician-diagnosed asthma			P value
	Normal weight (BMI <25 kg/m^2)	Overweight (BMI 25–29.9 kg/m^2)	Obesity (BMI ≥30 kg/m^2)	Normal weight (BMI <25 kg/m^2)	Overweight (BMI 25–29.9 kg/m^2)	Obesity (BMI ≥30 kg/m^2)	(Comparing all strata)
	(n=309)	(n=255)	(n=127)	(n=228)	(n=230)	(n=168)	
Sex							**<0.001***
Women, N (%)	216 (70%)	132 (52%)	62 (49%)	157 (69%)	125 (54%)	110 (66%)	
Men N (%)	93 (30%)	123 (48%)	65 (51%)	71 (31%)	105 (46%)	58 (35%)	
Smoking status							0.16*
Never smoker N (%)	183 (59%)	140 (55%)	55 (43%)	134 (59%)	111 (48%)	83 (49%)	
Former smoker N (%)	68 (22%)	63 (25%)	39 (31%)	53 (23%)	65 (28%)	47 (28%)	
Occasional smoker N (%)	27 (9%)	25 (10%)	10 (8%)	17 (8%)	21 (9%)	13 (8%)	
Daily smoker N (%)	31 (10%)	27 (11%)	23 (18%)	24 (11%)	33 (14%)	25 (15%)	
Highest completed education							0.24*
Elementary N (%)	35 (11%)	30 (12%)	18 (14%)	37 (16%)	27 (12%)	24 (14%)	
Upper secondary N %)	98 (32%)	106 (42%)	52 (41%)	81 (36%)	87 (38%)	76 (45%)	
University N (%)	165 (53%)	111 (44%)	54 (43%)	102 (45%)	108 (47%)	65 (39%)	
Other/missing N (%)	11 (4%)	8 (3%)	3 (2%)	8 (4%)	8 (4%)	3 (2%)	
Age at examination, years, SEM categories, SD total	39.4 (0.55)	42.7 (0.48)	42.4 (0.74)	36.1 (0.68)	42.3 (0.63)	42.1 (0.59)	**<0.001****
Age of onset of asthma symptoms, years of age	NA	NA	NA	13.1 (0.75)	16.2 (0.88)	16.6 (0.89)	**0.005****
Current use of any asthma medication (spray, inhalation powder or tablets)							
▶ No	NA	NA	NA	109 (48%)	103 (45%)	59 (35%)	
▶ Yes	NA	NA	NA	119 (52%)	127 (55%)	109 (65%)	**0.036***
ACT score							
▶ Well controlled (20–25 points)	NA	NA	NA	109 (72%)	84 (65%)	63 (57%)	**0.034***
▶ Not controlled (5–19 points)	NA	NA	NA	45 (29%)	45 (35%)	48 (43%)	
Ever had sarcoidosis, yes N (%)	1	0	3	0	3	2	0.051*
Ever sought help for mental problems, yes N (%)	50 (19%)	44 (21%)	23 (18%)	56 (25%)	55 (24%)	46 (27%)	**0.014***

Continued

Table 1 Continued

	No physician-diagnosed asthma			Physician-diagnosed asthma			P value
	Normal weight (BMI <25 kg/m^2)	Overweight (BMI 25–29.9 kg/m^2)	Obesity (BMI ≥30 kg/m^2)	Normal weight (BMI <25 kg/m^2)	Overweight (BMI 25–29.9 kg/m^2)	Obesity (BMI ≥30 kg/m^2)	(Comparing all strata)
	(n=309)	(n=255)	(n=127)	(n=228)	(n=230)	(n=168)	
Ever had other chronic lung diseases than asthma and COPD, yes N (%)	1	4	3	12 (5%)	25 (11%)	12 (7%)	**<0.001***
Physician-diagnosed COPD, yes N (%)	1	1	0	7	6	6	**0.006***
Allergy with respiratory symptoms, yes N (%)	98 (32%)	76 (30%)	43 (34%)	138 (61%)	134 (58%)	112 (67%)	**<0.001***

P values are calculated using *χ^2 or ** One.way analysis of variance (ANOVA). NA=not applicable. Statistically significant findings, p<0.05, are bolded
ACT, Asthma Control Test; BMI, body mass index; COPD, Chronic obstructive pulmonary disease.

frequently other respiratory conditions such as respiratory allergy than the healthy controls.

In the logistic regression model to test whether attendance at the medical examination was associated with BMI, age, sex, education, smoking, sick leave and WAS, we observed positive associations with the age categories of 30–39 years (OR=2.2 (95% CI 1.8 to 2.7)) and 40–50 years (OR=3.8 (95% CI 3.2 to 4.6)) with 18–29 years as the reference. Negative associations were observed with male sex (OR=0.8 (95% CI 0.71 to 0.98)) and current smoking (OR=0.61 (95% CI 0.49 to 0.77)).

The prevalence of outcomes by possible confounders is presented in table 2 and shows an association of most outcomes with sex and smoking status. Additionally, most lung function variables were associated with age and education.

Table 3 shows the WAS, sick leave in the last 12 months, symptom score and mean % of predicted prebronchodilator and postbronchodilator spirometry for the six groups defined by asthma and BMI status. Overweight subjects with asthma had significantly reduced WAS and were more frequently on sick leave compared with overweight subjects without asthma. There was no significant difference in sick leave >14 days within the two groups. Comparing obese subjects with and without asthma to their normal weight counterparts, we found a significantly increased symptom score (p=0.02 and p=0.01, respectively). Lung function prebronchodilator and postbronchodilator was significantly lower in the groups with asthma than in those without, with the exception of pre-FVC and post-FVC for normal weight and obese subjects. The results also demonstrated that, regardless of asthma status, subjects with obesity had reduced FEV_1 and FVC both prebronchodilator and postbronchodilator compared with normal weight subjects. However, the FEV_1/FVC-ratio was similar. The frequencies of each respiratory symptom by asthma and BMI categories are presented in online supplemental table 1.

Table 4 shows adjusted coefficients, interaction terms and SIs from the regression models. The adjusted ORs for the categorical outcomes show that asthma is significantly associated with a reduced WAS (OR=1.9 (95% CI 1.4 to 2.5)), an increased likelihood of sick leave in the last 12 months (1.4 (95% CI 1.1 to 1.8)) and an increased symptom score (7.3 (95% CI 5.5 to 9.7)). Obesity was associated with an increased symptom score (1.7 (95% CI 1.2 to 2.4)) but not WAS or sick leave, and overweight was associated with none of these three outcomes. The models for each respiratory symptom showed that obesity was associated with several symptoms (online supplemental table 2). The SI was used to evaluate additive interactions. An elevated SI was found for the combination of overweight and asthma with WAS and the two sick leave outcomes, but none of these index values were statistically significant (table 4). Multiplicative interactions for the dichotomous outcomes were not significant, although asthma and overweight had a borderline statistically significant interaction (p=0.095) for reduced WAS.

Table 2 Work Ability Score, sick leave, respiratory symptom score and % of predicted FEV_1, FVC and FEV_1/FVC-ratio prebronchodilator and postbronchodilator by possible confounders: sex, smoking status, highest completed education and age category

Outcome, summary statistics		Sex			Smoking status				Highest completed education				Age category			
	Number	Male	Female	P value	Never smoker	Former smoker	Daily smoker	P value	Elementary	Upper secondary	University	P value	18–30	31–40	41–52	P value
Work Ability Score <8, n/n total in group (%)	261/1295 (20%)	85/508 (17%)	176/787 (22%)	**0.016**	112/697 (16%)	78/328 (24%)	71/270 (27%)	**<0.001**	52/168 (31%)	130/525 (25%)	79/602 (13%)	**<0.001**	26/212 (12%)	66/310 (21%)	169/773 (22%)	0.007
Sick-leave in the last 12 months, n/n total in group (%)	413/1143 (36%)	113/453 (25%)	300/690 (43%)	**<0.001**	182/610 (30%)	125/297 (42%)	106/236 (45%)	**<0.001**	44/116 (38%)	180/464 (39%)	189/563 (34%)	0.203	47/156 (30%)	108/237 (46%)	258/714 (36%)	0.148
Sick leave >14 days, n/n total in group (%)	199/1143 (17%)	43/453 (9%)	156/690 (23%)	**<0.001**	78/610 (13%)	63/297 (21%)	58/236 (25%)	**<0.001**	20/116 (17%)	88/464 (19%)	91/563 (16%)	0.428	15/156 (10%)	57/237 (24%)	127/714 (18%)	0.060
Symptom score ≥3, n/n total in group (%)	403/1317 (31%)	120/515 (23%)	283/802 (35%)	**<0.001**	194/706 (27%)	107/335 (32%)	102/276 (37%)	**0.012**	50/171 (29%)	177/541 (33%)	176/605 (29%)	0.379	63/216 (29%)	96/314 (31%)	244/787 (31%)	0.874
Symptom score, n, mean (SEM)	1317	515 1.87 (0.11)	802 2.58 (0.10)	**<0.001**	706 2.10 (0.10)	335 2.37 (0.15)	276 2.72 (0.18)	**0.004**	171 2.26 (0.21)	541 2.49 (0.12)	605 2.14 (0.11)	0.095	216 2.26 (0.18)	314 2.26 (0.15)	787 2.33 (0.10)	0.911
Pre-FEV_1 % of predicted value, n, mean (SEM)	1257	489 94.26 (0.67)	768 96.00 (0.49)	**0.033**	671 95.44 (0.52)	322 96.57 (0.77)	264 93.50 (0.99)	**0.031**	158 93.12 (1.08)	515 94.06 (0.63)	584 97.02 (0.58)	**<0.001**	199 94.45 (0.83)	296 96.11 (0.81)	762 95.25 (0.54)	0.428
Pre-FVC % of predicted value n, mean (SEM)	1257	489 98.25 (0.44)	768 98.25 (0.56)	**0.028**	671 98.86 (0.46)	322 100.14 (0.68)	264 98.93 (0.82)	0.284	158 97.37 (0.99)	515 98.34 (0.54)	584 100.46 (0.50)	**0.002**	199 99.25 (0.81)	296 99.91 (0.66)	762 98.92 (0.47)	0.498
Pre-FEV_1/ FVC-ratio in %, n, mean (SEM)	1257	489 0.79 (0.002)	768 0.77 (0.003)	**<0.001**	671 0.79 (0.002)	322 0.77 (0.003)	264 0.76 (0.005)	**<0.001**	158 0.79 (0.006)	515 0.77 (0.003)	584 0.78 (0.003)	0.093	199 0.81 (0.005)	296 0.79 (0.004)	762 0.77 (0.002)	**<0.001**
Post-FEV_1 % of predicted value, n, mean (SEM)	1091	425 96.79 (0.67)	666 99.16 (0.50)	0.004	588 98.22 (0.53)	279 99.88 (0.76)	224 96.25 (1.00)	**0.009**	131 95.97 (1.16)	442 97.10 (0.64)	518 99.78 (0.57)	**<0.001**	177 97.99 (0.84)	264 99.10 (0.78)	650 97.95 (0.55)	0.478
Post-FVC % of predicted value, n, mean (SEM)	1091	425 98.57 (0.58)	666 99.88 (0.46)	0.077	588 98.78 (0.49)	279 100.67 (0.70)	224 99.28 (0.80)	0.093	131 97.21 (1.12)	442 98.85 (0.56)	518 100.36 (0.51)	**0.012**	177 98.92 (0.85)	264 100.03 (0.69)	650 99.23 (0.48)	0.559

Continued

Table 2 Continued

Outcome, summary statistics	Number	Sex			Smoking status				Highest completed education				Age category			
		Male	Female	P value	Never smoker	Former smoker	Daily smoker	P value	Elementary	Upper secondary	University	P value	18–30	31–40	41–52	P value
Post-FEV_1/FVC ratio in %, n, mean (SEM)	1091	425 0.78 (0.004)	666 0.81 (0.002)	**<0.001**	588 0.81 (0.003)	279 0.80 (0.003)	224 0.78 (0.005)	**<0.001**	131 0.81 (0.006)	442 0.80 (0.003)	518 0.81 (0.003)	**0.029**	177 0.85 (0.005)	264 0.81 (0.004)	650 0.79 (0.003)	**<0.001**

P values were calculated using Fisher's exact, Pearson χ^2 or one-way ANOVA.Statistically significant findings, p<0.05, are bolded
ANOVA, Analysis of variance; FEV, forced expiratory volume; FEV_1, forced expiratory volume after 1 s; FVC, forced vital capacity.

We found no statistically significant multiplicative or additive interactions between asthma status and elevated BMI category with any specific respiratory symptom (online supplemental table 2).

Adjusted linear regression models showed that asthma was significantly associated with a higher symptom score (2.4 points (95% CI 2.2 to 2.7)), reduced prebronchodilator and postbronchodilator FEV_1 %-predicted (β=−6.6 (95% CI −8.2 to −5.1) and −5.2 (95% CI −6.7 to −3.4)), prebronchodilator FVC %-predicted (β=−2.3 (95% CI −3.6 to −0.96)) and prebronchodilator and postbronchodilator FEV_1/FVC-ratio (−0.04 (95% CI −0.05 to −0.03) and −0.03 (95% CI −0.04 to −0.03)) (table 4). Overweight status was associated only with an increased prebronchodilator FEV_1/FVC-ratio (β=0.01 (95% CI 0.003 to 0.020)). Obesity was associated with a higher symptom score (0.6 points (95% CI 0.3 to 0.97)) and reduced FEV_1 and FVC % of predicted prebronchodilator and postbronchodilator (FEV_1 β=−2.9 (95% CI −5.1 to −0.7) and −2.8 (95% CI −4.9 to −0.7), FVC β=−5.2 (95% CI −7.0 to −3.4) and −4.2 (95% CI −6.1 to −2.3), respectively). The interaction between asthma and overweight status was statistically significant for prebronchodilator FVC (β=−3.6 (95% CI −6.6 to −0.6)), but not for postbronchodilator FVC (β=−3.1 (95% CI −6.3 to 0.05)). We found no other interactions between asthma and overweight or obesity status when analysing lung function and the other continuous variables.

DISCUSSION

In the present study, we found that asthma and increased BMI were independently associated with an increased respiratory symptom score and reduced lung function. Asthma, but not increased BMI, was associated with reduced self-reported work ability and more frequent sick leave in the last 12 months. The only statistically significant interaction we found was between asthma and overweight for prebronchodilator FVC %.

All groups with asthma, regardless of BMI category, reported a higher symptom score compared with the group with no asthma in the same BMI category. As expected, in the adjusted model, we found an elevated OR for increased symptom scores in subjects with asthma. Obese subjects with and without asthma reported a significantly higher symptom score compared with the normal-weight group. In the adjusted model, obesity was associated with an increased symptom score with an OR of 1.7 (95% CI 1.2 to 2.4), which was substantially lower than that for asthma (7.3 (95% CI 5.5 to 9.7)). The same contrast was evident when modelling symptom score as a continuous variable, with effect estimates greater for asthma (2.4 (95% CI 2.2 to 2.7)) than obesity (0.6 (95% CI 0.3 to 0.97)) and for individual symptoms as dichotomous outcomes (online supplemental table 2). The stronger association of symptoms with asthma was expected because asthma is a respiratory disease, while obesity is not.

Table 3 Work Ability Score, sick leave, respiratory symptom score and % of predicted FEV_1, FVC and FEV_1/FVC-ratio prebronchodilator and postbronchodilator, stratified by physician-diagnosed asthma and BMI category†‡

	BMI category			P values for elevated vs normal weight within asthma strata	
Outcome, summary statistics	**Normal weight (BMI <25 kg/m²)**	**Overweight (BMI 25–29.9 kg/m²)**	**Obesity (BMI ≥30 kg/m²)**	**Overweight vs normal**	**Obesity vs normal**
Work ability score <8, n/n total in group (%)					
No asthma	46/308 (15%)	36/250 (14%)	23/125 (18%)	0.86	0.37
Asthma	45/223 (20%)	65/223 (29%)	46/166 (27%)	**0.03**	0.08
P values for asthma vs no asthma within BMI categories	0.11	**>0.001**	0.07		
Sick leave in the last 12 months, n/n total in group (%)					
No asthma	87/269 (32%)	69/230 (30%)	41/111 (37%)	0.57	0.39
Asthma	74/193 (38%)	80/202 (40%)	62/138 (45%)	0.80	0.23
P values for asthma vs no asthma within BMI categories	0.18	**0.04**	0.20		
Sick leave >14 days, n/n total in group (%) *					
No asthma	37/85 (43%)	29/69 (42%)	18/41 (44%)	0.85	0.97
Asthma	39/74 (53%)	42/80 (53%)	34/62 (55%)	0.98	0.80
P values for asthma vs no asthma within BMI categories	0.25	0.20	0.28		
Symptom score ≥3, n/n total in group (%)					
No asthma	35/309 (11%)	25/255 (10%)	26/127 (21%)	0.60	**0.01**
Asthma	109/228 (48%)	107/230 (47%)	101/168 (60%)	0.78	**0.02**
P values for asthma vs no asthma within BMI categories	**>0.001**	**>0.001**	**>0.001**		
Symptom score, mean (SEM)					
No asthma	1.04 (0.10)	0.98 (0.11)	1.57 (0.19)	0.70	**0.01**
Asthma	3.46 (0.18)	3.37 (0.19)	4.15 (0.23)	0.75	**0.02**
P values for asthma vs no asthma within BMI categories	**>0.001**	**>0.001**	**>0.001**		
Pre-FEV_1 % of predicted value, mean (SEM)					
No asthma	98.6 (0.68)	100.2 (0.77)	95.4 (1.27)	0.13	**0.01**
Asthma	92.9 (0.93)	93.1 (1.01)	87.8 (1.30)	0.97	**>0.001**
P values for asthma vs no asthma within BMI categories	**>0.001**	**>0.001**	**>0.001**		
Pre-FVC % of predicted value, mean (SEM)					
No	100.9 (0.62)	102.0 (0.76)	96.5 (1.17)	0.37	**>0.001**
Yes	100.4 (0.82)	98.1 (0.82)	93.6 (1.10)	**0.04**	**>0.001**
P values for asthma vs no asthma within BMI categories	0.59	**0.001**	0.08		
Pre-FEV_1/FVC-ratio in %, mean (SEM)					
No asthma	79.7 (0.39)	79.3 (0.35)	79.8 (0.47)	0.54	0.82
Asthma	76.3 (0.54)	76.4 (0.50)	75.7 (0.65)	0.94	0.56

Continued

Table 3 Continued

Outcome, summary statistics	BMI category			P values for elevated vs normal weight within asthma strata	
	Normal weight (BMI <25 kg/m^2)	Overweight (BMI 25–29.9 kg/m^2)	Obesity (BMI ≥30 kg/m^2)	Overweight vs normal	Obesity vs normal
P values for asthma vs no asthma within BMI categories	**>0.001**	**>0.001**	**>0.001**		
Post-FEV$_1$ % of Post-FEV$_1$ % of predicted value, mean (SEM)predicted value, mean (SEM)					
No asthma	101.0 (0.70)	102.3 (0.82)	97.4 (1.43)	0.31	**0.003**
Asthma	96.6 (0.93)	96.0 (0.97)	93.2 (1.30)	0.81	**0.02**
P values for asthma vs no asthma within BMI categories	**>0.001**	**>0.001**	**0.03**		
Post-FVC % of predicted value, mean (SEM)					
No asthma	100.4 (0.66)	101.5 (0.82)	95.9 (1.25)	0.38	**>0.001**
Asthma	100.4 (0.86)	98.7 (0.82)	95.9 (1.14)	0.20	**0.001**
P values for asthma vs no asthma within BMI categories	0.99	**0.02**	0.99		
Post-FEV$_1$/FVC ratio in %, mean (SEM)					
No asthma	82.1 (0.42)	81.2 (0.36)	82.0 (0.51)	0.12	0.59
Asthma	79.4 (0.55)	78.5 (0.49)	78.5 (0.66)	0.26	0.31
P values for asthma vs no asthma within BMI categories	**>0.001**	**>0.001**	**>0.001**		

Prebronchodilator spirometry: 661 acceptable tests among controls, 596 acceptable tests among cases.
Postbronchodilator spirometry: 559 acceptable tests among controls, 532 acceptable tests among cases.
Statistically significant findings are given in bold.
*The participants with reported sick leave >14 days were limited to those who reported taking sick leave in the last 12 months.
†P values were based on χ^2 test for categorical variables and one-way ANOVA for continuous variables.
‡The distribution by BMI category for all 691 participants without asthma was 269 normal weight, 230 overweight and 111 obese; for all 626 participants with asthma, 193 had normal weight, 202 had overweight and 138 had obese. The actual numbers varied by outcome variable, depending on the number of missing values.
ANOVA, Analysis of variance; BMI, body mass index; FEV, forced expiratory volume; FEV$_1$, forced expiratory volume after 1 s; FVC, forced vital capacity.

Reduced WAS and sick leave in the last 12 months were both associated with asthma but not with overweight or obesity status. When assessing lung function, both asthma and obesity were associated with reduced spirometry. This was not the case for postbronchodilator FVC % of predicted for asthma and prebronchodilator and postbronchodilator FEV$_1$/FVC ratio for obesity. The results are consistent with greater effect estimates for FEV$_1$ than FVC for asthma and the reverse for obesity (table 4).

Jarvis *et al* employed some of the same questions as in the present study and assessed the associations between increased BMI and respiratory symptoms.[4] In line with our findings, these authors reported more wheezing in the absence of cold and shortness of breath following strenuous activity; significantly more wheezing with shortness of breath and waking with shortness of breath was also reported (online supplemental table 2). Other studies have reported an increase in self-reported dyspnoea and wheezing at rest and exertion in obese subjects compared with normal-weight subjects,[3] but to our knowledge, no other studies used a respiratory symptom score. As expected, all groups with physician-diagnosed asthma reported a higher symptom score compared with subjects without asthma in the same BMI category (table 3). Our previous study of the same population of physician-diagnosed subjects showed no statistically significant difference between obese and normal weight asthma cases for any specific respiratory symptom, but the group with obesity did have a higher symptom score.[34] Other studies have shown that some respiratory symptoms are more prevalent among patients with asthma and obesity, but the literature is conflicting.[35–37] Bildstrup *et al* demonstrated an increased incidence of severe cough and tightness in the chest with increased BMI in patients with asthma, whereas wheezing and shortness of breath were not related to BMI.[38] The findings in previous studies were observed mainly for the BMI category ≥35 kg/m^2 or for groups with an average

Table 4 Association of work ability, sick leave, respiratory symptom score and spirometry with asthma and BMI categories and tests of interaction**

Health-related outcome, effect estimate or units	Coefficients from regression models (95% CI)*			Coefficients for interaction terms in regression models† for all outcomes and Synergy Index for dichotomous outcomes			
		Elevated BMI vs normal weight		Interaction terms in regression models (95% CI)†		Synergy Index (95% CI)‡	
	Asthma, yes vs no	Overweight	Obesity	Asthma×overweight	Asthma×obesity	Asthma×overweight	Asthma×obesity
Dichotomous outcomes							
Work Ability Score ≤8, OR	**1.9 (1.4 to 2.5)**	1.2 (0.8 to 1.6)	1.2 (0.8 to 1.7)	1.76 (0.90 to 3.41) §	1.08 (0.51 to 2.28)	3.3 (0.35 to 32)	1.26 (0.35–4.5)
Sick leave in the last 12 months, OR¶	**1.4 (1.1 to 1.8)**	1.05 (0.8 to 1.4)	1.3 (0.9 to 1.8)	1.28 (0.71 to 2.30)	1.01 (0.51 to 2.00)	2.75 (0.06 to 112)	1.17 (0.21 to 6.45)
Sick leave >14 days, OR¶	1.5 (0.99 to 2.2)	0.9 (0.6 to 1.5)	0.9 (0.6 to 1.6)	1.35 (0.64 to 2.86)	1.05 (0.45 to 2.47)	2.50 (0.05 to 129)	1.22 (0.13 to 11.4)
Symptom score ≥3, OR	**7.3 (5.5 to 9.7)**	0.9 (0.7 to 1.3)	**1.7 (1.2 to 2.4)**	1.05 (0.54 to 2.04)	0.71 (0.35 to 1.44)	0.94 (0.61 to 1.47)	1.37 (0.87 to 2.17)
Continuous outcomes							
Symptom score (0–9), score	**2.4 (2.2 to 2.7)**	–0.03 (–0.3 to 0.3)	**0.6 (0.3 to 0.97)**	–0.1 (–0.7 to 0.5)	0.01 (–0.7 to 0.7)		
Pre-FEV_1 % of predicted	**–6.6 (–8.2 to –5.1)**	1.7 (–0.2 to 3.5)	**–2.9 (–5.1 to –0.7)**	–1.7 (–5.1 to 1.7)	–2.2 (–6.2 to 1.8)		
Pre-FVC, % of predicted	**–2.3 (–3.6 to –0.96)**	–0.08 (–1.6 to 1.5)	**–5.2 (–7.0 to –3.4)**	**–3.6 (–6.6 to –0.6)**	–2.4 (–6.0 to 1.2)		
Pre-FEV_1/FVC-ratio, %	**–0.04 (–0.05 to – 0.03)**	**0.01 (0.003 to 0.020)**	0.009 (–0.001 to 0.019)	1.3 (–0.4 to 2.9)	–0.3 (–2.2 to 1.7)		
Post-FEV_1, % of predicted	**–5.2 (–6.7 to –3.4)**	1.1 (–0.7 to 2.8)	**–2.8 (–4.9 to –0.7)**	–2.0 (–5.4 to 1.5)	0.1 (–4.0 to 4.2)		
Post-FVC, % of predicted	–1.0 (–2.5 to 0.4)	–0.05 (–1.7 to 1.6)	**–4.2 (–6.1 to –2.3)**	–3.1 (–6.3 to 0.05) §	0.03 (–3.7 to 3.8)		
Post-FEV_1/FVC ratio, n %	**–0.03 (–0.04 to – 0.03)**	0.008 (–0.001 to 0.02)	0.009 (–0.001 to 0.02)	0.9 (–0.8 to 2.5)	–0.1 (–2.0 to 1.9)		

Predilator spirometry: 661 acceptable tests among controls, 596 acceptable tests among cases.
Postdilator spirometry: 559 acceptable tests among controls, 532 acceptable tests among cases.
*A separate regression model was fit for each outcome and included covariates for asthma, BMI categories, age, sex, smoking and education.
†A separate regression model was fit for each outcome and included covariates for asthma, BMI categories, asthma ×BMI interaction, age, sex, smoking and education. The coefficients for the interaction terms test for interaction on the multiplicative scale for dichotomous outcomes and on the additive scale for continuous outcomes.
‡Synergy Index is an indicator of an additive interaction for dichotomous outcomes and has a null value of 1.0.
§Results are borderline statistically significant, 0.05<p<0.10.
¶Results for sick leave are limited to the 1143 participants employed in the last 12 months.
**Statistically significant findings are given in bold. The operational definitions of asthma and BMI categories are described in the Methods section.
BMI, body mass index; FEV_1, forced expiratory volume after 1 s; FEV, forced expiratory volume; FVC, forced vital capacity.

BMI in the top BMI group that was higher than in our study.

When using WAS to assess self-reported work ability, we found a reduced WAS associated with asthma but not increased BMI. A Danish cross-sectional study by Andersen *et al* demonstrated reduced work ability with increasing BMI in working subjects.[11] They found an OR of 1.69 (95% CI 1.10 to 2.62) for lower work ability among working subjects with BMI ≥40 kg/m^2. For BMI of 30 to <35 kg/m^2, the OR was 1.11 (95% CI 1.01 to 1.22); however, the researchers used a different instrument to evaluate work ability that focused on physical demands. This may explain the different results compared with our study, as WAS is a measure of total work ability. In a review by Neovius *et al*, obesity was associated with higher frequency and longer duration of sick leave.[9] A Dutch review, using only longitudinal studies, had similar conclusions.[10] Two other studies have found more frequent sick leave among patients with asthma regardless of weight compared with healthy controls.[1 2] Hansen *et al* showed that patients with asthma receive more welfare, sick leave and disability compared with subjects without asthma.[1] In the present study, we found more frequent sick leave within the past 12 months among subjects with asthma, but there was no indication of increased duration of sick leave longer than 14 days. This finding may suggest that subjects with asthma are more frequently on sick leave, but that the sick leave periods are relatively short. A limitation of this study is that we do not have data on the cause for the sick leave.

Increased BMI alone was not associated with more sick leave in our study. There are several possible explanations for these conflicting results on self-reported work ability and sick leaves for the current study vs other studies.[9 10] First, we had few subjects with BMI >40 kg/m^2 (n=22); thus, we lacked the statistical power to show an effect. Neovius *et al* reported an OR of 1.3–2.1 for frequency of sick leave in studies comparing subjects with obesity to those with normal weight and found that subjects with obesity had about ten additional days of sick leave per person year compared with those with normal weight.[9] In the present study, the subjects were relatively young (the oldest was 52 years old) and all subjects were working, which possibly introduced a healthy worker effect bias. Moreover, in Norway, there is a high awareness of reducing sick leave and employers will make great efforts to adjust work tasks and provide alternative jobs so that the workers can stay at work.

Among subjects without asthma, we found a significant negative effect on FVC both prebronchodilator and postbronchodilator among subjects with BMI ≥30 kg/m^2 compared with those with normal weight. In a review by Dixon and Peters, the authors concluded that FVC and FEV_1 were slightly reduced in the presence of obesity and that the FEV_1/FVC ratio was often unaffected unless BMI was over 60 kg/m^2. They also found that body fat distribution was more strongly associated with lung function than BMI and weight.[39] The effect of obesity on lung function has also been described in other review studies,[5–8] showing an effect on both FEV_1 and FVC.[5] Several studies have shown an effect of overweight/obesity status on spirometry among patients with asthma,[40–42] but there are also studies that do not find an effect.[38] In meta-analyses, the effect on FVC and FEV_1 among subjects with asthma and obesity was confirmed.[8] Thus, our results seem to be in line with those of previous studies indicating an independent effect of both obesity and asthma on lung function.

To our knowledge, few studies have assessed the possible interactions between asthma and obesity. Nicolacakis *et al* found no synergistic interaction between asthma and obesity and concluded that the effects on lung function were a result of the combined effects.[21] However, this was a small study (n=210 divided into four groups), and the results were not adjusted for smoking status. The researchers attributed the lack of interaction to the existence of different pathways: obesity reduces lung volumes and influences the thoracic wall movement, while asthma affects the smooth muscle tone, leading to airway obstruction. However, we found only a possible interaction of asthma and overweight with FVC, and no interaction with the other assessed outcomes.

Strengths and limitations

An important limitation of our study was that the outcomes, apart from lung function, were self-reported. However, we used validated questions from questionnaires used in other large epidemiological studies on respiratory health. Validated questionnaires may improve the accuracy of the responses; however, they may still introduce recall bias and random errors that could distort estimates of associations.

Epidemiological studies are susceptible to bias due to selection and non-response. The controls were randomly selected from the Telemark study baseline cohort for medical examination, and all asthma cases were invited to reduce selection bias. Another important limitation is the relatively low response rate among the invited participants, which may have introduced selection bias. Nevertheless, non-response analyses of our baseline study indicated that the frequency of respiratory symptoms was similar between participants and non-participants.[23] Analyses of the baseline population showed that non-response was associated with younger age, living in rural areas, male sex and past smoking status, and responders more frequently used asthma medications and had more chronic cough.[23] While more robust participation by somewhat older individuals and women and reduced participation by current smokers may have altered prevalence estimates, they were unlikely to have biased the estimates of associations examined in this study. However, such a bias cannot be ruled out entirely. To decrease the likelihood of confounding factors, all analyses were adjusted for age, smoking status, sex and educational level.

In the present study, asthma was defined by a self-reported physician-diagnosis of asthma. Using our current study design, we could not verify the diagnosis of asthma. However, validation studies of self-reported physician-diagnosed asthma have found good sensitivity (68%) and high specificity (94%).[43] Our study design included cases of childhood asthma, without any recent symptoms. This may lower the frequency of positive responses among the cases. To assess this possibility, we performed a sensitivity analysis restricted to participants with active asthma, defined as having any respiratory symptoms in the last 12 months. The analysis showed comparable results, with somewhat higher estimates for all three BMI groups with asthma (data not shown).

BMI is widely used but may not necessarily be the best measure of obesity and its effects.[39] According to WHO, BMI can be classified into six categories.[44] Even though our study was of reasonable size (N=1317), the use of categories defined by the WHO led to small sample sizes in the extreme BMI categories. This resulted in uncertainty in the analyses owing to statistical power issues. Larger studies or study designs other than population-based studies may be needed to better assess the effect of asthma with obesity grade II (35–39.9 kg/m^2) and III (>40 kg/m^2). Some effects of obesity may occur at higher BMI than most of our cases; thus, we may lack the statistical power to replicate the results reported by some other studies.

As this was a cross-sectional study, we could not assess causality. The participants may have had a debut of asthma in childhood with normal weight but were now obese and still had asthma. However, as we have shown, it is possible to examine the interaction between obesity and asthma. As recommended by Knol and VanderWeele, we assessed interaction on additive and multiplicative scales for dichotomous outcomes.[45] There are several measures of interaction on an additive scale, for example, relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) and the SI. In the present study, SI was used because it is regarded to be more stable across strata of potential confounders than RERI and AP.[46]

A strength of this study is that it is based on a relatively large sample from the general population aged between 16 and 52 years and residing in Telemark county. We also included a control group from the same population, reducing the possibility of systematic differences. A few well-trained healthcare workers performed all medical examinations.

In conclusion, asthma and obesity were independently associated with an increased respiratory symptom score, reduced prebronchodilator and postbronchodilator FEV_1 and reduced prebronchodilator FVC. The association between symptom score and asthma was considerably stronger than that with obesity. Reduced WAS and higher odds of sick leave in the last 12 months were associated with asthma but not increased BMI in the adjusted models. Other than the additive interaction of asthma and overweight status on prebronchodilator FVC, we found no other significant additive or multiplicative interactions between asthma and BMI. Due to the small number of participants with BMI ≥35 kg/m^2 in our study, we recommend further studies on this subpopulation.

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Supplementary Table 1. Specific respiratory symptoms stratified by physician-diagnosed asthma and BMI category*

		BMI category			P values for elevated vs normal weight within asthma strata	
Outcome, summary statistics		**Normal weight (BMI <25 kg/m²)**	**Overweight (BMI 25–29.9 kg/m²)**	**Obesity (BMI ≥30 kg/m²)**	**Overweight vs normal**	**Obesity vs normal**
Q1: Wheezing or whistling in the chest in the last 12 months, -yes, n/n total in group (%)	No asthma Asthma	42/309 (13%) 126/228 (55%)	41/255 (16%) 114/230 (49%)	32/127 (25%) 105/168 (63%)	0.41 0.22	**0.003** 0.15
	P values for asthma vs no asthma within BMI categories	**<0.001**	**<0.001**	**<0.001**		
Q2: Wheezing or whistling with dyspnoea in the last 12 months, -yes n/n total in group (%)	No asthma Asthma	37/309 (12%) 108/228 (47%)	26/255 (10%) 104/230 (45%)	20/127 (16%) 95/168 (57%)	0.51 0.64	0.29 0.07
	P values for asthma vs no asthma within BMI categories	**<0.001**	**<0.001**	**<0.001**		
Q3: Wheezing or whistling in the chest without a cold in the last 12 months, -yes n/n total in group (%)	No asthma Asthma	30/309 (10%) 108/228 (47%)	29/255 (11%) 93/230 (40%)	23/127 (18%) 96/168 (57%)	0.52 0.14	**0.015** 0.05
	P values for asthma vs no asthma within BMI categories	**<0.001**	**<0.001**	**<0.001**		
Q4: Dyspnoea at rest in the last 12 months, -yes, n/n total in group (%)	No asthma Asthma	19/309 (6%) 154/228 (24%)	12/255 (5%) 64/230 (28%)	14/127 (11%) 53/168 (32%)	0.45 0.31	0.08 0.08
	P values for asthma vs no asthma within BMI categories	**<0.001**	**<0.001**	**<0.001**		
Q5: Dyspnoea after exposure to cold in the last 12 months, -yes, n/n total in group (%)	No asthma Asthma	19/309 (6%) 78/228 (34%)	11/225 (4%) 78/230 (34%)	16/127 (13%) 76/168 (45%)	0.33 0.95	**0.02** **0.03**
	P values for asthma vs no asthma within BMI categories	**<0.001**	**<0.001**	**<0.001**		

Q6: Dyspnoea following strenuous activity in the last 12 months, -yes, n/n total in group (%)	No asthma Asthma	62/309 (20%) 125/228 (55%)	45/225 (18%) 119/230 (52%)	39/127 (31%) 110/168 (65%)	0.47 0.51	**0.02** **0.03**
	P values for asthma vs no asthma within BMI categories	**<0.001**	**<0.001**	**<0.001**		
Q7: Woken by a coughing attack in the last 12 months, -yes, n/n total in group (%)	No asthma Asthma	65/309 (21%) 68/228 (30%)	49/225 (19%) 80/230 (35%)	28/127 (22%) 65/168 (39%)	0.59 0.26	0.82 0.07
	P values for asthma vs no asthma within BMI categories	**0.02**	**<0.001**	**0.002**		
Q8: Woken by a feeling of tightness in the chest in the last 12 months, -yes, n/n total in group (%)	No asthma Asthma	32/309 (10%) 80/228 (35%)	24/225 (9%) 81/230 (35%)	18/127 (14%) 65/168 (39%)	0.71 0.98	0.26 0.46
	P values for asthma vs no asthma within BMI categories	**<0.001**	**<0.001**	**<0.001**		
Q9: Woken by dyspnoea in the last 12 months, - n/n total in group (%)	No asthma Asthma	15/309 (5%) 41/228 (18%)	13/225 (5%) 42/230 (18%)	9/127 (7%) 33/168 (20%)	0.90 0.94	0.35 0.68
	P values for asthma vs no asthma within BMI categories	**<0.001**	**<0.001**	**0.002**		

*Statistically significant findings are shown as bold. P-values were based on the chi-square test. The distribution by BMI category for all 691 participants without asthma was 269 with normal weight, 230 with overweight, and 111 with obesity; for all 626 participants with asthma, 193 had normal weight, 202 had overweight, and 138 had obesity.

Supplementary Table 2. Association of specific respiratory symptoms with asthma, BMI categories, and tests of interaction

	Coefficients from regression models (95% CI) [a]			Coefficients for interaction terms in regression models[b] for all outcomes and synergy Index for dichotomous outcomes			
		Elevated BMI vs. normal weight		Interaction terms in regression models (95% CI) [b]		Synergy Index (95% CI) [c]	
Health-related outcome, effect estimate	**Asthma, yes vs no**	**Overweight**	**Obesity**	**Asthma x overweight**	**Asthma x obesity**	**Asthma x overweight**	**Asthma x obesity**
Q1: Wheezing or whistling in the chest in the last 12 months	**6.0 (4.7, 7.8)**	0.9 (0.7, 1.3)	**1.6 (1.1, 2,2)**	0.65 (0.36, 1.18)	0.61 (0.32, 1.19)	0.65 (0.43, 1.00)[d]	1.16 (0.74, 1.81)
Q2: Wheezing or whistling with dyspnoea in the past 12 months	**6.9 (5.2, 9.1)**	0.9 (0.7, 1.3)	**1.4 (1.0, 2.0)**	1.08 (0.56, 2.07)	1.02 (0.50, 2.09)	0.94 (0.60, 1.48)	1.40 (0.88, 2.23)
Q3: Wheezing or whistling in the chest without a cold in the last 12 months	**6.8 (5.1, 9.0)**	0.8 (0.6, 1.2)	**1.6 (1.1, 2.2)**	0.60 (0.31, 1.17)	0.69 (0.34, 1.43)	0.65 (0.42, 1.02)[d]	1.25 (0.79, 1.97)
Q4: Dyspnoea at rest in the last 12 months	**5.4 (3.8,7.7)**	1.1 (0.7, 1.6)	1.4 (0.96, 2.2)	1.36 (0.76, 2.43)	1.15 (0.65, 2.02)	1.36 (0.76, 2.43)	1.15 (0.65, 2.02)
Q5: Dyspnoea after exposure to cold in the last 12 months	**8.1 (5.7, 11)**	0.9 (0.7, 1.4)	**1.7 (1.2, 2.5)**	1.06 (0.66, 1.72)	1.36 (0.85, 2.15)	1.06 (0.66, 1.72)	1.36 (0.85, 2.15)
Q6: Dyspnoea following strenuous activity in the last 12 months	**4.8 (3.8, 6.2)**	0.9 (0.6, 1.2)	**1.6 (1.1, 2.2)**	0.88 (0.54, 1.46)	1.31 (0.80, 2.15)	0.88 (0.54, 1.46)	1.31 (0.80, 2.15)
Q7: Woken by a coughing attack in the last 12 months	**2.0 (1.5, 2.5)**	1.2 (0.9, 1,6)	1.4 (0.98, 1.9)	1.84 (0.68, 5.02)	1.55 (0.57, 4.24)	1.84 (0.68, 5.02)	1.55 (0.57, 4.24)
Q8 :Woken by a feeling of tightness in the chest in the last 12 months	**4.7 (3.5, 6.3)**	1.0 (0.7, 1.4)	1.3 (0.9, 1.8)	1.06 (0.72, 1.55)	1.02 (0.60, 1.74)	1.06 (0.72, 1.55)	1.02 (0.60, 1.74)
Q9: Woken by dyspnoea in the last 12 months	**4.1 (2.8, 6.1)**	1.0 (0.6, 1.5)	1.1 (0.7, 1.7)	0.91 (0.55, 1.49)	0.86 (0.43, 1.71)	0.91 (0.55, 1.49)	0.86 (0.43, 1.71)

*Statistically significant findings are bolded. The operational definitions of asthma and BMI categories are described in the Methods section.

[a] A separate regression model was fit for each outcome and included covariates for asthma, BMI categories, age, sex, smoking, and education.

[b] A separate regression model was fit for each outcome and included covariates for asthma, BMI categories, asthma × BMI interaction, age, gender, smoking, and education. The coefficients for interaction terms test for interaction on multiplicative and additive scales for dichotomous outcomes.

[c] Synergy Index is an indicator of additive interaction for dichotomous outcomes and has a null value of 1.0.

[d] Results are borderline statistically significant, $0.05<p<0.10$

III

BMJ Open Respiratory Research

Association of respiratory symptoms with body mass index and occupational exposure comparing sexes and subjects with and without asthma: follow-up of a Norwegian population study (the Telemark study)

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ABSTRACT

Background Occupational exposure and increased body mass index (BMI) are associated with respiratory symptoms. This study investigated whether the association of a respiratory burden score with changes in BMI as well as changes in occupational exposure to vapours, gas, dust and fumes (VGDF) varied in subjects with and without asthma and in both sexes over a 5-year period.

Methods In a 5-year follow-up of a population-based study, 6350 subjects completed a postal questionnaire in 2013 and 2018. A respiratory burden score based on self-reported respiratory symptoms, BMI and frequency of occupational exposure to VGDF were calculated at both times. The association between change in respiratory burden score and change in BMI or VGDF exposure was assessed using stratified regression models.

Results Changes in respiratory burden score and BMI were associated with a β-coefficient of 0.05 (95% CI 0.04 to 0.07). This association did not vary significantly by sex, with 0.05 (0.03 to 0.07) for women and 0.06 (0.04 to 0.09) for men. The association was stronger among those with asthma (0.12; 0.06 to 0.18) compared with those without asthma (0.05; 0.03 to 0.06) (p=0.011). The association of change in respiratory burden score with change in VGDF exposure gave a β-coefficient of 0.15 (0.05 to 0.19). This association was somewhat greater for men versus women, with coefficients of 0.18 (0.12 to 0.24) and 0.13 (0.07 to 0.19), respectively (p=0.064). The estimate was similar among subjects with asthma (0.18; −0.02 to 0.38) and those without asthma (0.15; 0.11 to 0.19).

Conclusions Increased BMI and exposure to VGDF were associated with increased respiratory burden scores. The change due to increased BMI was not affected by sex, but subjects with asthma had a significantly larger change than those without. Increased frequency of VGDF exposure was associated with increased respiratory burden score but without statistically significant differences with respect to sex or asthma status.

Key messages

What is already known on this topic

- Increased body mass index (BMI) and occupational exposure are associated with respiratory symptoms.
- It is not known if change in respiratory burden score is associated with changes in BMI and occupational exposure to vapours, gas, dust and fumes and what the potential associations between sex and asthma status are.

What this study adds

- Increased BMI and occupational exposure were associated with increase in respiratory burden score.
- Both associations did not differ at the level of statistical significance between sexes, but the association with change in BMI was stronger with a positive asthma status.

How this study might affect research, practice And/Or policy

- Further studies are needed to confirm our findings, but this study contributes to a better understanding of how respiratory burden is affected by occupational exposure and BMI.
- This knowledge may aid clinical decision-making and inform more personalised treatments in patients with asthma, obesity and occupational exposure.

INTRODUCTION

Increased body mass index (BMI) (≥25 kg/m^2) and occupational exposure to vapours, gas, dust and fumes (VGDF) are associated with respiratory symptoms.[1 2] Obesity is associated with exertional dyspnoea, an increased risk of asthma and reduced asthma control.[1] Furthermore, patients with extremely high BMI (>50 kg/m^2) show a significant lung function improvement after weight loss following bariatric surgery.[3]

Peralta *et al*[4] demonstrated that a moderate and high weight gain over 20 years was associated with accelerated lung function decline (forced vital capacity and forced expiratory volume in 1 s) among adults, while weight loss improved this excessive decline. However, few studies have assessed the changes in respiratory symptoms due to weight gain or loss. Ekström *et al* showed that obesity is strongly associated with increased activity-related breathlessness[5] and that subjects with increased BMI since their 20s had more breathlessness compared with those with stable weight.

Occupational exposure to VGDF is common. For instance, in Norway, it is estimated that 23% of the workers are exposed.[6] Current evidence strongly suggests that exposure to VGDF can affect the airways in subjects with and without asthma.[2 5 7–11] Multiple studies have shown that exposure to VGDF is associated with chronic obstructive pulmonary disease (COPD)[8] and asthma,[9 10 12] and that occupational exposure to VGDF can also be a risk factor for asthma exacerbation.[11 13]

Female sex is associated with a higher frequency of respiratory symptoms and severe asthma[14] and is at an increased risk of asthma.[15 16] Women exposed to dust report more shortness of breath, and in particular inorganic dust exposure is associated with asthma in women, while men only reported occasional wheezing and reduced lung function.[17]

Although the associations between respiratory symptoms and increased BMI and VGDF exposure are well documented, there is a lack of prospective studies on how change in BMI or VGDF exposure affects respiratory symptoms. In addition, there is a lack of knowledge on the influence of asthma status and sex over these effects. A better understanding of how changes in VGDF exposure or BMI affect respiratory symptoms, particularly in vulnerable subjects, will improve prevention and help guide personalised treatments.

The present study aimed to assess whether the association of a change in respiratory burden score with changes in BMI and occupational VGDF exposure varied with self-reported, physician-diagnosed asthma status and sex.

METHODS

Study population

The Telemark study is a population-based survey that started in 2013 with a random sample of 50 000 inhabitants living in Telemark County, Norway, aged 16–50 years, who received a postal questionnaire. Of these, 48 142 were eligible and 16 099 responded (response rate: 33%).[18] In 2018, all eligible 2013 responders (n=15 681) were invited to complete the questionnaire again. Four hundred and eighteen subjects could not be traced or were excluded. Subjects not providing height and weight and thus impeding BMI calculation at both baseline and follow-up were excluded from the present study.

Questionnaire

The questionnaire included questions regarding occupational exposure, physician-diagnosed asthma, respiratory symptoms ever and in the last 12 months, height, weight, and possible confounders. The questionnaire was based on the European Community Respiratory Health Survey questionnaire and a validated questionnaire from a similar study in Sweden.[19]

Exposure variables

BMI, measured in kg/m^2, was calculated for each participant in 2013 and 2018 using the self-reported weight and height from the questionnaires. BMI was stratified into the following categories recommended by the WHO: normal weight (including underweight) <25.0 kg/m^2, overweight 25.0–29.9 kg/m^2 and obese ≥30 kg/m^2, and was used as a continuous variable.[20] As only 85 subjects (1.3%) were classified as underweight (BMI ≤18.5 kg/m^2), they were included in the normal weight category. Change in BMI was calculated for each participant by subtracting the BMI value in 2013 from that in 2018.

VGDF exposure in 2013 was defined as an affirmative answer to the question 'Have you ever been exposed to gas, smoke, or dust at work?' All exposed participants in 2013 were then asked to grade their average exposure in the past 5 years into one of the following categories: 'Daily, for large parts of the working day' (exposure=4 points), 'Daily, but for short periods' (exposure=3 points), 'Weekly' (exposure=2 points), 'Less often' (exposure=1 point) and 'never' (no exposure=0 points). In 2018, the subjects were asked the same question with the options 'No', 'Yes' or 'Yes, in the last 12 months', and in case of an affirmative answer in the last 12 months the participants were asked to classify the exposure into the same categories as in 2013. Exposure change was calculated by subtracting the exposure points in 2013 from those in 2018. A positive or negative number indicates that the exposure frequency increased or decreased, respectively. The analyses were restricted to subjects engaged in paid work in the last 12 months of 2013. Subjects engaged in paid work in the last 12 months in 2013 but not in 2018 were included in the analyses as unexposed in 2018. Subjects with missing data for VGDF exposure were excluded from the analyses on change in VGDF.

Outcome variable

The questionnaire enquired about seven respiratory symptoms in the last 12 months and the current use of any medication for asthma (online supplemental table 1). A missing answer was recoded as not having that symptom or not using medication for asthma. We calculated a respiratory burden score for each participant in 2013 and 2018 by adding positive answers to the questions to a maximum score of 8. We then calculated the change in respiratory burden score by subtracting the score in 2013 from that in 2018, such that a positive number represented more respiratory symptoms in

2018 than in 2013. We chose to use a respiratory burden score to better describe the total respiratory symptom burden, and because it also provides increased statistical power and better describes symptoms as a continuum.[21] Although current use of asthma medication is not a respiratory symptom, we included this question in the respiratory burden score as respiratory symptoms can lead to medication usage. Similar scores based on these symptoms have been previously used in other studies on subjects with asthma.[21 22]

Background and adjustment variables

Asthma was defined by an affirmative response to the following question: 'Has a physician ever diagnosed you with asthma?' Age and sex were confirmed using the Norwegian National Population Registry.

At both time points, smoking habits were classified as daily smokers, occasional smokers and former smokers in case of an affirmative answer to the following question: 'Do you smoke every day (also applies if you only smoke a few cigarettes, cigars, or light a pipe each day)?', 'Do you smoke occasionally (not each day, but weekends, parties, or similar)?' and 'Did you used to smoke?', respectively. Those who did not answer any of the three questions were defined as missing and those with three negative responses were categorised as never smokers. The variable for smoking habit changes between 2013 and 2018 was divided into the three following categories: same, increased or decreased.

Participants' educational levels were categorised into the following categories: elementary education (≤10 years), upper secondary school and certificate (additional 3–4 years), and university and university college. In addition, we included a category for other education and missing data.

Statistical analyses

To compare the longitudinal changes in background variables from 2013 to 2018, we used a paired t-test for continuous variables and a McNemar's test for categorical variables. Changes in BMI and VGDF exposure frequency were calculated by subtracting the values in 2013 from those in 2018. We used linear regression models to assess the associations between change in respiratory burden score as an outcome variable and changes in BMI or VGDF exposure frequency. In the unadjusted linear regression models, we used change in respiratory burden score as the outcome variable and changes in BMI or VGDF exposure or possible confounding variables as the exposure variable. In the adjusted models to estimate the effect of changes in BMI or VGDF exposure frequency, we adjusted for age, sex, educational category in 2013, smoking habit category in 2013, change in smoking habit, BMI category in 2013, physician-diagnosed asthma in 2013, VGDF exposure in 2013 and respiratory burden score in 2013 (full model). The models were then stratified for sex and physician-diagnosed asthma in 2013, and interaction terms were used to test differences in strata-specific effect estimates.

All analyses were performed using the statistical package IBM SPSS V.26.0. Statistical significance was set at $p<0.05$.

Patient and public involvement

A representative from the Norwegian Asthma and Allergy Association (NAAA) was a member of the study steering committee and contributed to the development of questionnaires. NAAA representatives have also been involved in the study planning and transfer of knowledge to the patient group.

RESULTS

Figure 1 shows a flow chart of the participant inclusion and exclusion procedures. Briefly, 7952 subjects responded to the questionnaire in both 2013 and 2018. Of these, 6368 reported weight and height on both questionnaires to allow calculation of BMI changes. All subjects with a BMI change >±20 points were excluded (n=18). This was based on a scatter plot and performed to exclude extreme values and errors in recorded weight due to automatic scanning of the questionnaires. Thus, 6350 subject questionnaires were included for further analyses.

Table 1 shows the characteristics of the population in 2013 and 2018.

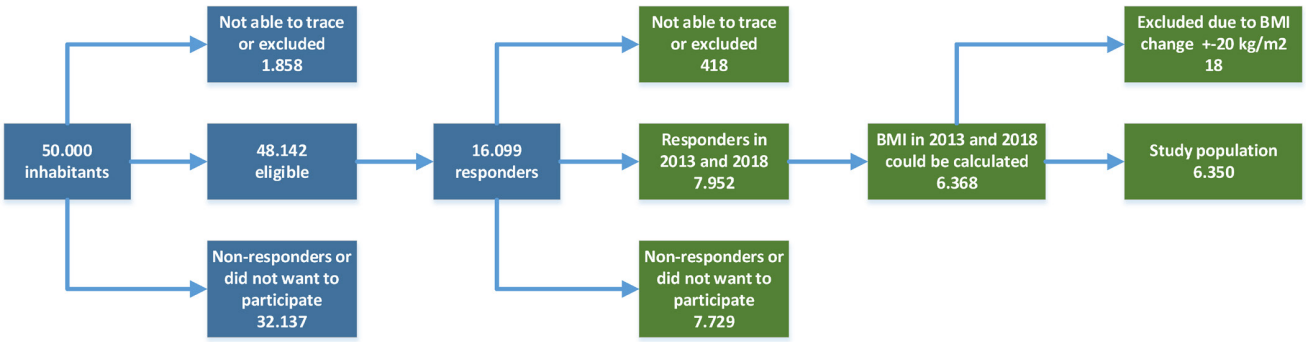

Figure 1 Flow chart of study subjects, including subjects excluded and the rationale for exclusion. BMI, body mass index.

Table 1 Study population characteristics in 2013 and 2018 (N=6350)

	2013	2018	P value
Sex, n (%)			NA
Male	2688 (42)		
Female	3662 (58)		
Age group (in years) in 2013, n (%)			NA
16–30	1485 (23)		
31–40	1670 (26)		
41–50	3195 (50)		
Age in years, mean (SD)	38.0 (9.45)		NA
Highest completed education, n (%)			**<0.001***
Elementary	756 (12)	494 (8)	
Upper secondary and certificate	2311 (36)	2205 (35)	
University/university college	3103 (49)	3536 (56)	
Other and missing	180 (3)	115 (2)	
Smoking status, n (%)			**<0.001***
Never smoker	3593 (57)	3594 (57)	
Former smoker	1398 (22)	1591 (25)	
Occasional smoker	544 (9)	483 (8)	
Daily smoker	781 (12)	571 (9)	
Missing	34 (1)	111 (2)	
BMI category, n (%)			**<0.001***
Normal weight (<24.9 kg/m^2)	3245 (51)	2877 (45)	
Overweight (25–29.9 kg/m^2)	2212 (35)	2429 (38)	
Obese (>30 kg/m^2)	893 (14)	1044 (16)	
BMI, mean (SD)	25.55 (4.38)	26.10 (4.44)	**<0.001†**
Employed in the past 12 months, n (%)			**0.014***
Yes	5541 (87)	5643 (89)	
No	809 (13)	707 (11)	
Frequency of exposure to VGDF‡, n (%)			**<0.001***
Daily, most of the day	292 (5)	201 (4)	
Daily, short periods of the day	505 (9)	336 (6)	
Weekly	554 (10)	410 (7)	
Seldom	1418 (26)	1186 (21)	
Never	2705 (49)	2856 (52)	
Missing	67 (1)	552 (10)	
Physician-diagnosed asthma, n (%)			**<0.001***
No	5697 (90)	5576 (88)	
Yes	653 (10)	774 (12)	
Physician-diagnosed chronic obstructive pulmonary disease, n (%)			**<0.001***
No	6299 (99)	6279 (99)	
Yes	51 (1)	71 (1)	

Statistically significant findings (p<0.05) are in bold.
*P value is calculated using McNemar's test.
†P value is calculated using paired t-test.
‡Frequency of exposure is restricted to subjects employed in the last 12 months in 2013 (n=5541).
BMI, body mass index; NA, not applicable; VGDF, vapours, gas, dust and fumes.

In 2018, more subjects reported having a degree from a university, while fewer had elementary school as their highest educational level, compared with 2013. The number of subjects reporting daily or occasional smoking was significantly lower in 2018 than in 2013. In the study population, BMI significantly increased from 25.5 kg/m^2 to 26.1 kg/m^2 over the 5-year study period (p<0.001), and there were more overweight subjects or with obesity. The prevalence of physician-diagnosed asthma increased from 10% to 12% (p<0.001). The frequency of exposure to VGDF in the last 12 months was reduced for all exposure categories, and the 'never exposed' category was larger in 2018 than in 2013. In 2013, 104 (3.4%) women were exposed daily and most of the day and 207 (6.7%) were exposed daily but in shorter periods of the day. The corresponding numbers were greater for men at 188 (7.9%) and 298 (12.6%), respectively. Approximately 3% of each question about respiratory symptoms in the last 12 months were missing.

Univariable analyses (table 2) with changes in respiratory burden score as the outcome variable in a linear regression model showed a β-coefficient of 0.05 (95% CI 0.033 to 0.066) for change in BMI.

This means that a one-point change in BMI was associated with an increase of 0.05 points in respiratory burden score. There was no significant association between change in respiratory burden score and age, sex or educational level in 2013. The average respiratory burden score in 2013 was 1.12 (SD: 1.78) and was negatively associated with change in respiratory burden score (β-coefficient −0.46; 95% CI −0.48 to −0.44). Daily smoking was associated with change in respiratory burden score with β-coefficients of −0.39 (−0.52 to −0.27) in 2013 and −0.15 (−0.30 to −0.005) in 2018. Increased smoking was associated with higher respiratory burden score (β=0.21; 0.03 to 0.38), whereas a reduction was associated with reduced respiratory burden score (β=−0.30; −0.45 to −0.16) over time. Change in respiratory burden score was positively associated with change in VGDF exposure, with a β-coefficient of 0.07 (0.03 to 0.11). We found no significant associations between change in burden score and 2013 exposure frequency in the last 5 years. When adjusting for respiratory burden score in 2013, significant associations were found for daily smoking, asthma, obesity in 2013 and daily exposure to VGDF in 2013, as well as change in BMI and VGDF.

Table 3 shows the univariable and adjusted β-coefficients in linear regression models for change in respiratory burden score as an outcome variable and change in BMI or VGDF exposure as the exposure variable.

The models were also stratified by sex and physician-diagnosed asthma in 2013. The adjusted full regression models showed an association between change in respiratory burden score and change in BMI, with a β-coefficient of 0.05 (0.04 to 0.07). Stratified by sex, the association was 0.05 (0.03 to 0.07) and 0.06 (0.04 to 0.09) for women and men, respectively, and 0.05 (0.03 to 0.06) and 0.12 (0.06 to 0.18) for subjects without and with asthma, respectively, which differed significantly (p=0.011). The association between change in respiratory burden score and change in VGDF exposure was significant, with a β-coefficient of 0.15 (0.05 to 0.19) in the adjusted full model. In the stratified models, individually, men and women had a significant association, with β-coefficients of 0.18 (0.12 to 0.24) and 0.13 (0.07 to 0.19), respectively, but without differences between sexes. The estimate (β=0.18; −0.02 to 0.38) among subjects with asthma was higher but not significantly different from subjects without asthma (β=0.15; 0.11 to 0.19).

DISCUSSION

In this study, we showed that change in BMI is associated with change in respiratory burden score. This effect was larger in subjects with asthma than in those without. As shown in table 3, for BMI changes, we found an adjusted β-coefficient of 0.05 for change in respiratory burden score. This means a 0.05 increase in respiratory burden score for a one-point increase in BMI. These results suggest that if a subject gains the weight equivalent to an increase in BMI of 10 points (eg, from 25 kg/m^2 to 35 kg/m^2), this will result in an average increase of 0.5 symptoms in the respiratory burden score. In our study, 24 subjects (0.4%) had a BMI increase ≥10 points. For patients with asthma, the average increase was 1.12 symptoms per 10 BMI points. We observed a positive association between respiratory burden score and VGDF exposure change, but this effect was not affected when stratifying for sex and asthma status. The longitudinal effect of VGDF exposure change was statistically significant, with an adjusted β-coefficient of 0.15 respiratory burden score change for both, all participants and those without asthma. The comparable estimate for subjects with asthma was 0.18 (not statistically significant). These results indicate that a person with asthma only had a slightly greater respiratory burden score increase associated with a VGDF exposure increase.

The univariable analyses (table 2) showed some surprising results; for example, daily smoking in 2013 was negatively associated with change in respiratory burden score, possibly reflecting regression to the mean. Regression to the mean is a statistical phenomenon that can make natural variation in repeated data look like real change and unusually happens when large or small measurements tend to be followed by measurements that are closer to the mean.[23] When adjusting for respiratory burden score in 2013, the associations were more as expected, showing the importance of adjusting for respiratory burden scores at baseline.

In line with Ekström *et al*,[5] we found that increased BMI was associated with increased respiratory burden score. However, as the outcomes are different (breathlessness vs burden score), it is difficult to directly compare the estimates. Unfortunately, our study did not contain any questions regarding activity-related breathlessness. Since obese subjects have an increased workload, they may

Table 2 Results from a series of linear regression models with change in respiratory burden score, with a single exposure variable and also adjusted for baseline respiratory burden score

Exposure variable	n (%) or mean (SD)	Coefficients from regression model (95% CI)	Coefficient from regression model adjusted for respiratory burden score in 2013 (95% CI)
Sex, n (%)			
Female	3662 (58)	Reference category	Reference category
Male	2688 (42)	0.040 (–0.04 to 0.12)	–0.07 (–0.14 to 0.005)
Age in 2013, mean (SD)	38.05 (9.45)	0.00 (–0.004 to 0.004)	0.002 (–0.001 to 0.006)
Education, n (%)			
Elementary school	756 (12)	Reference category	Reference category
Upper secondary	2311 (36)	–0.45 (–0.18 to 0.04)	–0.11 (–0.23 to 0.006)
University	3103 (49)	–0.4 (–0.17 to 0.09)	**–0.13 (–0.25 to –0.02)**
Other and missing	180 (3)	0.21 (–0.06 to 0.05)	0.20 (–0.03 to 0.44)
Smoking status in 2013, n (%)			
Never	3596 (57)	Reference category	Reference category
Past	1398 (22)	–0.06 (–0.11 to 0.96)	0.12 (–0.01 to 0.25)
Occasional	544 (9)	–0.10 (–0.25 to 0.05)	0.09 (–0.98 to 0.27)
Daily	781 (12)	**–0.39 (–0.52 to –0.27)**	0.07 (–0.10 to 0.24)
Smoking status in 2018, n (%)			
Never	3594 (57)	Reference category	Reference category
Past	1591 (25)	–0.01 (–0.11 to 0.08)	0.07 (–0.02 to 0.15)
Occasional	483 (8)	–0.04 (–0.19 to 0.12)	0.04 (–0.09 to 0.18)
Daily	571 (9)	**–0.15 (–0.30 to –0.01)**	**0.26 (0.13 to 0.38)**
Change in smoking habit, n (%)			
No	5278 (83)	Reference category	Reference category
Yes, decreased	566 (9)	**–0.30 (–0.45 to –0.16)**	**–0.13 (–0.26 to –0.01)**
Yes, increased	362 (6)	**0.21 (0.03 to 0.38)**	**0.23 (0.08 to 0.38)**
Physician-diagnosed asthma in 2013, n (%)			
No	5697 (90)	Reference category	Reference category
Yes	653 (10)	**–0.59 (–0.72 to –0.46)**	**0.89 (0.75 to 1.0)**
BMI category in 2013, n (%)			
Normal weight (<24.9 kg/m^2)	3245 (51)	Reference category	Reference category
Overweight (25–29.9 kg/m^2)	2212 (35)	**–0.10 (–0.19 to –0.12)**	0.008 (–0.67 to 0.09)
Obese (>30 kg/m^2)	893 (14)	**–0.19 (–0.31 to –0.067)**	**0.15 (0.05 to 0.26)**
Change in BMI (kg/m^2), mean (SD)	0.56 (2.43)	**0.050 (0.033 to 0.066)**	**0.045 (0.03 to 0.06)**
Symptom score in 2013, burden score (SD)	1.12 (1.78)	**–0.46 (–0.48 to –0.44)**	**Not applicable**
Change in VGDF exposure* score (SD)	–0.15 (1.03)	**0.07 (0.03 to 0.11)**	**0.068 (0.03 to 0.11)**
VGDF exposure in 2013*†, n (%)			
Never	2705 (49)	Reference category	Reference category
Seldom	1418 (26)	–0.07 (–0.17 to 0.04)	–0.01 (–0.09 to 0.09)
Weekly	554 (10)	–0.07 (–0.22 to 0.08)	0.08 (–0.05 to 0.21)
Daily, short	505 (9)	0.03 (–0.12 to 0.19)	**0.18 (0.05 to 0.32)**
Daily, most	292 (5)	–0.07 (–0.26 to 0.13)	**0.18 (0.10 to 0.35)**

Statistically significant findings (p<0.05) are in bold.
Missing values for smoking are not included in the models.
*Exposure to VGDF is restricted to subjects employed in the last 12 months in 2013 (n=5541).
†67 subjects did not provide a response to this question.
BMI, body mass index; VGDF, vapours, gas, dust and fumes.

Table 3 Model showing change in respiratory burden score as the outcome variable for the full model and stratified by sex and asthma status*

Exposure variable	Full model		Sex: male		Sex: female		P value comparing sexes	Asthma: yes		Asthma: no		P value comparing asthma status
	Unadjusted β (95% CI)	Adjusted β† (95% CI)	Unadjusted β (95% CI)	Adjusted β† (95% CI)	Unadjusted β (95% CI)	Adjusted β† (95% CI)		Unadjusted β (95% CI)	Adjusted β† (95% CI)	Unadjusted β (95% CI)	Adjusted β† (95% CI)	
Change in BMI	**0.05 (0.03 to 0.07)**	**0.05 (0.04 to 0.07)**	**0.05 (0.03 to 0.08)**	**0.06 (0.04 to 0.09)**	**0.05 (0.03 to 0.07)**	**0.05 (0.03 to 0.07)**	0.57	**0.13 (0.07 to 0.20)**	**0.12 (0.06 to 0.18)**	**0.04 (0.02 to 0.05)**	**0.05 (0.03 to 0.06)**	**0.011**
Change in VGDF exposure‡	**0.07 (0.02 to 0.11)**	**0.15 (0.10 to 0.19)**	**0.11 (0.05 to 0.17)**	**0.18 (0.12 to 0.24)**	0.04 (−0.20 to 0.10)	**0.13 (0.07 to 0.19)**	0.064	0.15 (−0.04 to 0.35)	0.18 (−0.02 to 0.38)	**0.06 (0.01 to 0.10)**	**0.15 (0.11 to 0.19)**	0.412

Significant findings at p<0.05 shown in bold.
*Regression models for change in respiratory burden score were fit separately for the exposure variables change in BMI and change in VGDF exposure.
†Adjusted for age, sex, education in 2013, smoking in 2013, change in smoking habit, BMI category in 2013, asthma, VGDF exposure in 2013 and respiratory burden score in 2013.
‡Restricted to the employed in the last 12 months in 2013.
BMI, body mass index; VGDF, vapours, gas, dust and fumes.

report more breathlessness during activity. However, our respiratory burden score included symptoms at rest and night, indicating symptoms also at rest.

In the stratified model, the adjusted effect estimates for BMI change did not differ between sexes, but subjects with asthma had a higher estimate than those without. This is in line with a previous cross-sectional analysis from the 2013 Telemark study, where subjects with asthma and obesity had higher respiratory burden score compared with subjects with asthma and normal weight.[22] Subjects with a distinct obese asthma phenotype report more respiratory symptoms and reduced asthma control and use more asthma medications.[24–27] Weight loss in this group has been shown to improve respiratory symptoms and lung function.[3]

Studies have shown that pulmonary diseases affect sexes differently.[28] There seems to be a difference in how men and women perceive respiratory symptoms, and possibly the kind of symptoms they report.[29] A previous study has shown that as subjects became obese, male subjects had greater increase in wheezing without a cold, while female subjects had greater increase in asthma.[30] In the present study, there was no significant difference between sexes in changes in respiratory burden score with increasing weight. We speculate that this might be attributed to the respiratory symptoms attributed to increased BMI being the same in both sexes or that, in addition, women have other symptoms not reflected in our study. The health response to air pollution has been shown to differ between male and female subjects, but whether this is a result of sex-linked biological differences or exposure pattern differences is unclear.[31] Sex differences in respiratory signs and symptoms in occupational settings have been described in a review, but there is little evidence of a clear pattern of susceptibility and the results are not consistent between studies.[32] In population-based studies, more consistent sex differences have been found, but whether occupational exposure exacerbates sex differences in respiratory symptoms warrants further research.[32] Skorge *et al*[33] showed that exposure to dust, fumes and gas was significantly more strongly associated with an increased incidence of respiratory symptoms in women than in men. In our study, we did not detect any sex difference (p=0.064), but the groups including exposed women were small.

To our knowledge, few studies have investigated how changes in VGDF exposure affect respiratory symptoms in subjects without any respiratory disease. In a Polish follow-up study comparing subjects exposed to dust with those not exposed, a lower OR was found for chronic cough when removing exposure compared with continued exposure.[34] Skorge *et al*[33] conducted a follow-up study over 11 years and showed that occupational airborne exposure to dust, fumes and gas is weakly related with the incidence of respiratory symptoms, but significantly more so for women. However, this study did not describe how changes in exposures affect the incidence or prevalence of respiratory symptoms.

Previous studies have shown that VGDF exposure is associated with asthma exacerbation. In a study, severe asthma exacerbation was associated with high occupational exposure to dust, gas and fumes (relative risk (RR) 3.1, 95 % CI 1.9 to 5.1) compared with lack of exposure.[11] In a Cochrane review, compared with continued exposure, reduction or removal of exposure for patients with occupational asthma was associated with improvement in symptoms.[35] The reduction of exposure increased the likelihood of reporting the *absence* of symptoms (RR 2.65; 1.24–5.68), while for removal of exposure the RR was 2.80 (1.67–13.86). This review did not include any studies on the *improvement* of asthma symptoms after a reduction in exposure, while for the removal from exposure the RR was 2.47 (1.26–4.84). In the present study, reduced exposure to VGDF did not lead to a statistically significant improvement in burden score in subjects with asthma. This might be because subjects with asthma included all types of cases, not just those with occupational asthma.

To our knowledge, a well-recognised and validated respiratory burden score for subjects without asthma or other respiratory diseases is not available. However, similar scores including some of the questions in our questionnaire have been used in subjects with asthma or other respiratory diseases.[21 22] We developed our score to better describe the burden of respiratory symptoms, including the use of medication, and to reflect a continuum in respiratory symptoms. Contingency table analyses with Cramer's V test as an effect measure of the association indicated an association among the three wheezing questions, but the other questions in the score had a low level of association (data not shown). When using only one of the wheezing questions in the respiratory burden score, the estimates were as expected lower, but the associations were the same and the reliability was reduced. The respiratory burden score had good internal consistency, with a Cronbach's alpha value of 0.83. In the 2013 survey, we did not enquire about breathlessness or dyspnoea in the last 12 months, but we included these questions in the 2018 survey. When comparing participants' respiratory burden score in 2018 with a score including questions on breathlessness, we found that the scores showed high agreement, with an intraclass correlation coefficient of 0.91 (0.90–0.91). The Bland-Altman plot indicates that our respiratory burden score showed less agreement in high scores, probably because one of the scores included more items (symptoms).

Strengths and limitations

A strength of this study is its relatively large and unselected sample from the general population. The study was a prospective study over 5 years using the same questions at baseline and follow-up. Adjusting for important possible confounders, such as smoking, obesity and occupational exposure, is considered another strength. However, there was a significant loss to follow-up (51%) in this study. Online supplemental table 2 shows a comparison between responders (n=7952) and not responders, including those not eligible in 2018 (n=8174). Briefly, there were more men, more current smokers, more subjects with asthma or with lower educational level, and fewer employed in the last 12 months among subjects lost to follow-up compared with those included in the study. The subjects lost to follow-up were also younger and had more respiratory symptoms and current use of asthma medication. The mean BMI was not significantly different, but the distribution by BMI categories showed more overweight or obese subjects among those included. These variables were included and adjusted for in the analysis. Although the differences may have altered prevalence estimates, they were unlikely to have biased the estimates of associations, although such bias cannot be ruled out entirely.

An important limitation of our study was the self-reported outcomes. Even though the questionnaires contained validated questions used in large epidemiological studies on respiratory health, validated questionnaires may improve response accuracy but may still introduce recall bias and random errors. A review found that subjects tend to overestimate height and underestimate weight and BMI when using self-reported data and that this bias is greater in overweight and obese subjects.[36] However, the outcome variable used was the difference in BMI, and we have no reason to believe that the bias from self-reported height and weight was substantially different between the two time points. Asthma was defined as self-reported, physician-diagnosed asthma. Using our current study design, we could not verify the diagnosis. However, validation studies of self-reported, physician-diagnosed asthma have found good sensitivity (65%) and high specificity (94%).[37] This question is susceptible to misclassification of asthma and COPD among older subjects. To assess this point, we also performed analyses restricted to subjects with asthma onset ≤30 years of age (n=679). The results are shown in online supplemental table 4 and were comparable with the analyses in which all subjects with asthma were included. Underweight (BMI ≤18.5 kg/m^2) has been associated with more respiratory disability in other studies. In our study underweight and normal-weight subjects are merged into one category. However, only 1.3% of the subjects reported underweight and excluding underweight subjects from the analyses made minimal difference (online supplemental table 3).

Another limitation is that we did not have direct measurements of occupational exposure for each participant nor information regarding exposure between 2013 and 2017, which could lead to misclassification of exposure. The question refers to the frequency, but the exposure levels may have been reduced after implementing better ventilation, use of personal protective equipment or a change in production methods. However, the question regarding VGDF exposure is commonly used in occupational epidemiology and has been tested against a 16-item battery assessing specific inhalation exposures and a job-exposure matrix, which appears to delineate

exposure risk as well as a multiple-item battery and has a modest agreement with the job-exposure matrix.[38 39] In this study, we assumed equal steps between exposure frequencies, and that an increase in exposure at one point has an equal but opposite effect on the respiratory burden score as a one-point reduction in exposure. Following this approach, we might have underestimated the effect of reduction of exposure in the most exposed subjects and overestimated the effect of reduction in the least exposed subjects. Another limitation is that approximately 50% of the subjects have never been exposed to VGDF, and 5% were exposed daily and most of the day in 2013 and 7% in 2018. A larger number of subjects in these exposure categories would have contributed to narrower CIs for estimates of association. Future studies should include more respiratory symptom questions, objective measures such as spirometry and more detailed occupational exposure data.

In this study we have shown that respiratory burden in the form of respiratory symptoms and asthma medication use increases with increasing BMI and occupational exposure, but further studies are needed to estimate the clinical effect of this. Weight loss may improve respiratory symptoms by increasing pulmonary function and reducing workload and the low-grade inflammation associated with obesity.[1] Similarly, reducing occupational VGDF exposure may reduce respiratory burden by reducing airway inflammation.[40]

In conclusion, the present study showed that BMI changes and occupational exposure to VGDF were associated with increased respiratory burden score. The change due to increased BMI was not affected by sex, but subjects with asthma had a larger change than subjects without. Increased frequency of VGDF exposure was associated with increased respiratory burden score, but stratified analyses showed no statistical difference between sexes or with respect to asthma status.

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Contributors GK drafted the paper and was involved in study design, data collection, data management, data analyses, data interpretation and accept responsibility for the overall content as guarantor. CB supervised the statistical analyses and was involved in data interpretation and critical revision of the manuscript. PKH, JK, KT and AKMF were involved in study design, data analyses, data interpretation and critical revision of the manuscript. All authors approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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Ethics approval This study involves human participants and was approved by the Regional Committee for Medical and Health Research Ethics in Norway (REC 2012/1665). Written informed consent was obtained from all study participants. Participants gave informed consent to participate in the study before taking part.

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Supplementary table 1. Comparison of frequencies of respiratory symptoms in the burden score and any respiratory symptoms in 2013 and 2018

Respiratory symptom	2013	2018	P value
Wheezing or whistling in chest in the last 12 months, yes N (%)	1197 (19%)	976 (15%)	**<0.001**
Wheezing or whistling with dyspnoea in the last 12 months, yes N (%)	847 (13%)	699 (11%)	**<0.001**
Wheezing or whistling in chest without a cold in the last 12 months, yes N (%)	832 (13%)	715 (11%)	**<0.001**
Do you currently use medication (spray, powder, or tablets) for asthma, yes N (%)	424 (7%)	482 (8%)	**0.001**
Have you in the last years had prolonged cough, yes N (%)	1293 (20%)	1310 (21%)	0.665
Woken by a coughing attack in the last 12 months, yes N (%)	1468 (23%)	1449 (23%)	0.64
Woken by a feeling of tightness in chest in the last 12 months, yes N (%)	837 (13%)	691 (11%)	**<0.001**
Woken by dyspnoea in the last 12 months, yes N (%)	430 (7%)	282 (4%)	**<0.001**
Any respiratory symptoms, yes N (%)	2646 (42%)	2515 (40%)	**<0.001**

McNemar's test was used to compare frequency of symptoms in 2013 to 2018.
Statistically significant findings at p<0.05 are shown in bold.

Supplementary table 2. Comparison between the study population to subjects lost to follow up in frequency of respiratory symptoms in the burden score and any respiratory symptoms in 2013 and 2018

Variable	Study population N, (%) or Mean (SD)	Lost to follow up population N, (%) or Mean (SD)	P value
Sex**, N (%)			**<0.001**
Female	4651 (58%)	4289 (53%)	
Male	3301 (41%)	3858 (47%)	
Age in 2013, Years, SD*	38.0 (9.52)	33.38 (10.51)	**<0.001**
Education**, N (%)			**<0.001**
Elementary School	947 (12%)	1668 (21%)	
Upper secondary	2861 (36%)	3468 (43%)	
University	3861 (49%)	2616 (31%)	
Other and missing	283 (4%)	395 (5%)	
Smoking in 2013**, N (%)			**<0.001**
Never	4482 (57%)	4453 (55%)	
Past	1783 (23%)	1508 (19%)	
Occasional	674 (9%)	783 (10%)	
Daily	969 (12%)	1329 (17%)	
Asthma in 2013**, N (%)			**<0.001**
No	7120 (90%)	7122 (87%)	
Yes	832 (11%)	1025 (13%)	
BMI (kg/m^2) *, Mean (SD)	25.61 (4.60)	25.49 (5.10)	0.155
BMI category in 2013**, N (%)			**0.004**
Normal weight (BMI <24.9 kg/m^2)	3320 (51%)	3688 (53%)	
Overweight (BMI 25-29.9 kg/m^2)	2272 (35%)	2242 (32%)	
Obese (BMI > 30 kg/m^2)	924 (14%)	1043(15%)	
Symptom score in 2013*, Mean (SD)	1.14 (1.83)	1.30 (1.96)	**<0.001**
VGFD exposure in 2013**, N (%)			**<0.001**

Never	4039 (52%)	4102 (51%)	
Seldom	1927 (25%)	1751 (22%)	
Weekly	752 (10%)	787 (10%)	
Daily, short periods	704 (9%)	796 (10%)	
Daily, most of the day	406 (5%)	574 (7%)	
Employed past 12 months**, N (%)			**<0.001**
Yes	6913 (87%)	6402 (79%)	
No	1039 (13%)	1745 (21%)	
Wheezing or whistling in chest in the last 12 months, yes N (%) **	1460 (18%)	1766 (22%)	**<0.001**
Wheezing or whistling with dyspnoea in the last 12 months, yes N (%) **	1043 (13%)	1254 (15%)	**<0.001**
Wheezing or whistling in chest without a cold in the last 12 months, yes N (%) **	1004 (13%)	1268 (16%)	**<0.001**
Do you currently use medication (spray, power or tablets) for asthma, yes N (%) **	539 (7%)	632 (8%)	**0.017**
Have you in the last years had prolonged cough, yes N (%) **	1608 (20%)	1711 (21%)	0.221
Woken by a coughing attack in the last 12 months, yes N (%) **	1843 (23%)	1997 (25%)	**0.047**
Woken by a feeling of tightness in chest in the last 12 months, yes N (%) **	1047 (13%)	1268 (16%)	**<0.001**
Woken by dyspnoea in the last 12 months, yes N (%) **	532 (7%)	647 (8%)	**0.002**

P values are calculated with independent t-test* or Chi Square test**
Statistically significant findings at p<0.05 are shown in bold.
Study population= all responders in both 2013 and 2018.
Lost to follow up= all responders only in 2013.

Supplementary table 3: Model showing the change in respiratory symptom score as outcome variables for the full model and stratified by sex and asthma status[a]. Restricted to BMI over 18.5 kg/m^2

	Full model		Sex-male		Sex-female		p-value comparing sexes	Asthma-Yes		Asthma-No		p-value comparing asthma status
Exposure variable	Unadjusted β (95% CI)	Adjusted* β (95% CI)	Unadjusted β (95% CI)	Adjusted* β (95% CI)	Unadjusted β (95% CI)	Adjusted* β (95% CI)		Unadjusted β (95% CI)	Adjusted* β (95% CI)	Unadjusted β (95% CI)	Adjusted* β (95% CI)	
Change in BMI	**0.05 (0.03, 0.06)**	**0.05 (0.04, 0.07)**	**0.05 (0.03, 0.08)**	**0.07 (0.04, 0.09)**	**0.04 (0.02, 0.07)**	**0.05 (0.03, 0.07)**	0.55	**0.13 (0.07, 0.20)**	**0.12 (0.06, 0.19)**	**0.04 (0.02, 0.05)**	**0.05 (0.03, 0.06)**	**0.011**
Change in VGDF exposure**	**0.07 (0.02, 0.11)**	**0.15 (0.11, 0.20)**	**0.11 (0.05, 0.17)**	**0.19 (0.12, 0.25)**	0.04 (-0.20, 0.10)	**0.13 (0.07, 0.19)**	0.063	0.16 (-0.04, 0.35)	**0.21 (0.01, 0.42)**	**0.05 (0.01, 0.10)**	**0.15 (0.10, 0.19)**	0.35

* Adjusted for age, sex, education in 2013, smoking in 2013, change in smoking habit, BMI category in 2013, asthma, vapours, gas, dust, and fumes (VGDF) exposure in 2013 and burden score in 2013

**Restricted to employed in the last 12 months in 2013

Significant findings at p<0.05 shown in bold.

[a]Regression models for change in respiratory burden score were fit separately for the exposure variables change in BMI and change in VGDF exposure

Supplementary table 4: Model showing the change in respiratory symptom score as outcome variables for the full model and stratified by sex and asthma status[a]. Restricted to asthma debut before 30 years of age

	Full model		Sex-male		Sex-female		p-value comparing sexes	Asthma-Yes		Asthma-No		p-value comparing asthma status
Exposure variable	Unadjusted β (95% CI)	Adjusted* β (95% CI)	Unadjusted β (95% CI)	Adjusted* β (95% CI)	Unadjusted β (95% CI)	Adjusted* β (95% CI)		Unadjusted β (95% CI)	Adjusted* β (95% CI)	Unadjusted β (95% CI)	Adjusted* β (95% CI)	
Change in BMI	**0.05 (0.03, 0.06)**	**0.05 (0.04, 0.07)**	**0.06 (0.03, 0.09)**	**0.07 (0.04, 0.09)**	**0.04 (0.02, 0.06)**	**0.05 (0.03, 0.07)**	0.28	**0.13 (0.06, 0.20)**	**0.12 (0.05, 0.18)**	**0.04 (0.02, 0.05)**	**0.05 (0.03, 0.06)**	**0.012**
Change in VGDF exposure**	**0.07 (0.02, 0.11)**	**0.15 (0.10, 0.19)**	**0.11 (0.05, 0.17)**	**0.19 (0.13, 0.26)**	0.04 (-0.20, 0.10)	**0.12 (0.06, 0.18)**	**0.03**	0.15 (-0.06, 0.36)	0.20 (-0.02, 0.42)	**0.06 (0.01, 0.10)**	**0.15 (0.10, 0.19)**	0.59

* Adjusted for age, sex, education in 2013, smoking in 2013, change in smoking habit, BMI category in 2013, asthma, vapours, gas, dust, and fumes (VGDF) exposure in 2013 and burden score in 2013

**Restricted to employed in the last 12 months in 2013

Significant findings at p<0.05 shown in bold.

[a]Regression models for change in respiratory burden score were fit separately for the exposure variables change in BMI and change in VGDF exposure