ORIGINAL RESEARCH

Adiposity and asthma in adults: a bidirectional Mendelian randomisation analysis of The HUNT Study

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ABSTRACT

Background We aimed to investigate the potential causal associations of adiposity with asthma overall, asthma by atopic status or by levels of symptom control in a large adult population and stratified by sex. We also investigated the potential for reverse causation between asthma and risk of adiposity.

Methods We performed a bidirectional one-sample Mendelian randomisation (MR) study using the Norwegian Nord-Trøndelag Health Study population including 56 105 adults. 73 and 47 genetic variants were included as instrumental variables for body mass index (BMI) and waist-to-hip ratio (WHR), respectively. Asthma was defined as ever asthma, doctor-diagnosed asthma and doctor-diagnosed active asthma, and was further classified by atopic status or levels of symptom control. Causal OR was calculated with the Wald method.

Results The ORs per 1 SD (4.1 kg/m^2) increase in genetically determined BMI were ranged from 1.36 to 1.49 for the three asthma definitions and similar for women and men. The corresponding ORs for non-atopic asthma (range 1.42–1.72) appeared stronger than those for the atopic asthma (range 1.18–1.26), but they were similar for controlled versus partly controlled doctor-diagnosed active asthma (1.43 vs 1.44). There was no clear association between genetically predicted WHR and asthma risk or between genetically predicted asthma and the adiposity markers.

Conclusions Our MR study provided evidence of a causal association of BMI with asthma in adults, particularly with non-atopic asthma. There was no clear evidence of a causal link between WHR and asthma or of reverse causation.

Key messages

What is the key question?
► Is adiposity causally associated with the risk of asthma in adults, and does reverse causation exist?

What is the bottom line?
► This study demonstrated evidence of a causal association of body mass index with asthma risk in adults, particularly with non-atopic asthma. There was no clear evidence of a causal link between waist-to-hip ratio (WHR) and asthma or of reverse causation between asthma and risk of adiposity.

Why read on?
► This is the first study to assess a potential causal association between WHR and asthma in adults, and it is one of the few studies to assess the reverse causation.

Observational studies have limitations to assess causal association due to confounding and reverse causation. The Mendelian randomisation (MR) approach attempts to overcome these limitations with the use of genetic variants that serve as instrumental variables for the exposure of interest.[6 7]

Two MR studies in children found genetically determined increase in BMI being associated with a higher risk of asthma[8 9]; the magnitude of the effect of BMI, however, differed by sex. The studies also identified a stronger effect on non-atopic than atopic asthma and an association between genetically determined fat mass or waist-to-hip ratio (WHR) and asthma risk.[8 9] Two MR studies were performed in adults using the individual-level data[10 11]; one study reported a 7% increase in risk for asthma associated with 1 kg/m^2 increase in genetically predicted BMI,[10] while the other reported a marginal association.[11] None of the studies in adults has evaluated the potential effect modification by sex. Nor have they evaluated if WHR, a marker for central adiposity, plays a causal role in asthma risk independent of BMI.[10 11] Moreover, a possible causal association of adiposity with asthma symptom control has not been investigated in the previous MR studies.

Adults with asthma have a higher prevalence of obesity than their healthy peers.[12] This may be explained by less physical activity among adults with asthma.[13] An evaluation of the reverse causation,

INTRODUCTION

The relationship between adiposity and asthma has been extensively investigated in children and adults.[1 2] A systematic review and meta-analysis of prospective observational studies has summarised that there is a similar association between adiposity, measured by body mass index (BMI), and asthma risk in women and men.[1] Later, in a prospective cohort study using the Norwegian Nord-Trøndelag Health Study (HUNT) population we confirmed this association in both sexes.[3] We also found an association between adiposity measured by waist circumference (WC) and asthma risk in women after adjustment for BMI.[3] However, findings of the relationship between waist size independent of BMI and asthma risk have been inconsistent in observational studies.[4 5]

that is, if asthma leads to increased adiposity, is thus warranted. In a large and homogenous population of adults, we aimed to investigate (1) if there was a causal association between adiposity and risk of asthma; (2) if there was effect modification by sex; (3) what was the magnitude of causal effect of adiposity on asthma by atopic status or by levels of asthma symptom control; and (4) if there was a potential reverse causation between asthma and the risk of adiposity. To achieve these aims, we performed a bidirectional one-sample MR study using the Norwegian HUNT population in which BMI and WHR were studied as markers of general and central adiposity, respectively.

METHODS
Study population
The study was based on data from the second survey of The HUNT Study (HUNT2, 1995–1997). HUNT2 included 65 227 subjects 20 years or older living in Nord-Trøndelag in Norway (participation rate 70%).[14] All participants completed two general questionnaires regarding health, lifestyle and socioeconomic status, and attended a clinical examination.

BMI, WHR and associated genetic variants
Body weight, height, and waist and hip circumferences were measured by trained nurses as described elsewhere.[14] Genotyping was performed using Illumina HumanCoreExome arrays.[15] Seventy-seven single-nucleotide polymorphisms (SNP) were selected as instrumental variables for BMI based on a large genome-wide association study (GWAS) from the Genetic Investigation of ANthropometric Traits (GIANT) consortium[16]; these SNPs were associated with BMI in adults of European ancestry at a genome-wide significance ($p < 5 \times 10^{-8}$), and the same SNPs were suggested for women and men. Data of two SNPs (rs12016871 and rs2033732) were not available in The HUNT Study population. Two SNPs (rs13021737 and rs16951275) were associated with smoking status and were therefore excluded, leaving 73 SNPs as instruments for BMI in the current study. An externally weighted BMI genetic risk score (GRS) was calculated by multiplying the number of BMI-increasing alleles for each variant by the variant's coefficient for BMI from the GIANT study,[16] and summing across the 73 variants. The BMI GRS showed an F statistic of 1122 and explained 2.0% of the variance in BMI in the HUNT2 Study.

Forty-nine SNPs were chosen as instruments for sex-combined WHR from adults of mainly European ancestry in the GIANT study at $p < 5 \times 10^{-8}$ [17]; sex-specific instruments were suggested including 48 SNPs for women and 33 SNPs for men at $p < 0.05$. In HUNT2, data of 47, 46 and 32 SNPs were available and used to generate weighted WHR GRS for total, women and men, respectively. None of these SNPs was associated with smoking or other potential confounders. The weights in GRS for total, women and men were coefficients for WHR from sex-combined or sex-specific analyses in the GIANT study.[17] The WHR GRS showed an F statistic of 174 and explained 0.3% of the variation in WHR in the total HUNT2 cohort. As HUNT was part of the GIANT study, we acknowledge that the calculation of weighted BMI and WHR GRS may be minimally biased.

Asthma and associated genetic variants
Asthma was defined as ever asthma, doctor-diagnosed asthma and doctor-diagnosed active asthma based on self-report. Ever asthma was defined according to an affirmative answer to the question, 'Do you have or have you had asthma?' Doctor-diagnosed asthma was based on participant's response to the question, 'Have you been diagnosed as having asthma by a doctor?' Individuals with doctor-diagnosed active asthma also confirmed wheezing symptoms and/or use of asthma medication in the last 12 months. Having atopic status was defined as those who reported having allergic rhinitis in combination with reported use of allergy medication or with reported allergic symptoms to pollen or pets. Based on questions about (1) daytime symptoms, (2) night awakes, (3) reliever medication use, and (4) activity limitations,[18] levels of asthma symptom control were classified as controlled (0 of the above items) versus partly controlled (1–4 items) in the doctor-diagnosed active asthma individuals. The classification was adapted from the 2015 Global Initiative for Asthma Global Strategy for Asthma Management and Prevention.[19]

In the HUNT2 Study, seven asthma-associated SNPs from the GABRIEL (a multidisciplinary study to identify the genetic and environmental causes of asthma in the European community) study ($p < 5 \times 10^{-8}$ for asthma risk at all ages), a large GWAS on asthma in people with European ancestry,[20] were used in a weighted asthma GRS. The weighted asthma GRS explained about 0.4% (based on pseudo-R^2) of the variation in liability for ever asthma in the HUNT2 cohort. In a two-sample MR, 26 of 34 SNPs derived from a latest GWAS on asthma ($p < 5 \times 10^{-8}$ for adult-onset asthma)[21] were used as instrumental variables for asthma. Data of the 26 SNPs were not accessible in the HUNT2 Study. Three of the 26 SNPs were in linkage disequilibrium ($R^2 > 0.1$) with three of the seven SNPs used in the HUNT2 Study.

Statistical analysis
First, we evaluated the potential causal BMI–asthma association among 56 105 participants who had complete information on the BMI SNPs, BMI and asthma. We performed one-sample MR analyses applying the Wald method,[22] with which MR-derived OR and 95% CI were calculated by the natural exponential function of the ratio of coefficient of GRS–outcome (asthma) association over coefficient of GRS–exposure (BMI) association. The coefficient of the GRS–asthma association was derived after adjustment for family history of asthma and education because there were associations of the BMI GRS with the two variables after a correction of multiple testing (online supplementary table S1). The coefficient of the GRS–BMI association was derived after adjustment for sex, age and age-squared.[16] The MR-derived OR corresponded to an effect of 1 SD increase in genetically determined BMI.

Second, we evaluated the potential causal WHR–asthma association in 55 671 of the 56 105 adults who had complete information on the WHR SNPs, WHR and asthma. A similar approach was employed to calculate the MR-derived OR corresponding to 1 SD increase in genetically determined WHR. The coefficient of the GRS–asthma association was derived without adjustment for other variables as the WHR GRS was not associated with the potential confounders. The coefficient of the GRS–WHR association was derived after adjustment for sex, age, age-squared and BMI.[17]

Third, we performed sensitivity analyses to test the robustness of the BMI–asthma association using the inverse-variance weighted (IVW) method and the MR-Egger method. The IVW method combines ratio estimates derived from each genetic variant in a random effects meta-analysis model.[23] Additionally, we tested for heterogeneity among the 73 BMI SNPs by presenting the I^2 value in the IVW method.[24] The MR-Egger method is relatively robust to horizontal pleiotropy,[25] by which

Table 1 Description of the HUNT2 cohort, 1995–1997

	Total	Women	Men
Subjects (n)	56 105	29 678	26 427
Age (years)*	49.6±16.6	49.5±16.8	49.6±16.3
Body mass index (kg/m²)*	26.3±4.1	26.2±4.6	26.5±3.5
Waist-to-hip ratio*†	0.84±0.08	0.80±0.06	0.90±0.06
Family history of asthma, % (no/yes)	85.7/14.3	83.6/16.4	88.1/11.9
Smoking, % (never/ever/unknown)	42.2/55.9/1.9	46.7/51.0/2.3	37.1/61.4/1.5
Physical activity, % (inactive/active/unknown)	21.3/48.5/30.2	22.9/42.7/34.4	19.6/54.9/25.5
Education (years), % (<10/≥10/unknown)	34.1/61.3/4.6	37.5/57.4/5.1	30.2/65.7/4.1
Economic difficulties, % (no/yes/unknown)	49.8/21.6/28.6	50.2/22.9/27.0	49.4/20.2/30.4

*Data are given as mean±SD.
†Data are available for 55 671 adults including 29 291 women and 26 380 men.
HUNT2, The Nord-Trøndelag Health Study Survey 2.

we calculated the intercept and 95% CI of the MR-Egger regression line.[25] Substantial horizontal pleiotropy is less likely if the intercept does not deviate markedly from zero. We also performed two-sample MR analyses to provide more evidence on the central adiposity–asthma relationship using the publicly accessible MR Base[26]; summary-level statistics were extracted from the GIANT consortium on WHR/WC[17] and the GABRIEL study on doctor-diagnosed asthma.[20]

At last, we evaluated the possibility of reverse causation between asthma and adiposity using both one-sample MR in the HUNT2 Study and two-sample MR with summary statistics from the GWAS.[16 17 21] In the HUNT2, the effect estimate was calculated as the ratio of coefficient of asthma GRS–BMI association over the coefficient of asthma GRS–asthma association, and it corresponded to the effect of one unit increase in ln (OR) of genetically determined asthma on the BMI values. A similar approach was employed for the causal asthma–WHR association. Effect estimates of the two-sample MR were derived using the MR Base.[26]

We also conducted observational analyses between adiposity markers and prevalent asthma in the HUNT2 cohort, in which we adjusted for important confounders including age (as a continuous variable), family history of asthma (yes and no), active smoking (never, former (0–10.0, 10.1–20.0, ≥20.1 pack-years), current (0–10.0, 10.1–20.0, ≥20.1 pack-years) and unknown), physical activity (inactive, low, moderate, high and unknown), education (<10, 10–12, ≥13 years and unknown) and having economic difficulties (yes, no and unknown).

All statistical analyses were performed in R (V.3.5.1) or STATA/MP V.15.1 (College Station, TX, USA).

RESULTS
The characteristics of the HUNT2 cohort are described in table 1. The prevalence of ever asthma, doctor-diagnosed asthma and doctor-diagnosed active asthma in the HUNT2 population was 8.9%, 5.5% and 3.7%, respectively, and it was comparable in women and men. The MR estimates demonstrated a larger

Table 2 Associations between BMI and ever asthma, doctor-diagnosed asthma and doctor-diagnosed active asthma in the HUNT2 Study

	Asthma/no asthma (n)	Observational estimates		MR estimates	
		OR*	95% CI	OR†	95% CI
Total (n=56 105)					
Ever asthma	4987/51 118	1.17	(1.14 to 1.21)	1.36	(1.10 to 1.68)
Doctor-diagnosed asthma	3061/53 044	1.15	(1.11 to 1.19)	1.49	(1.14 to 1.94)
Doctor-diagnosed active asthma	2083/54 022	1.17	(1.12 to 1.22)	1.40	(1.02 to 1.93)
Women (n=29 678)					
Ever asthma	2588/27 090	1.21	(1.17 to 1.25)	1.47	(1.12 to 1.93)
Doctor-diagnosed asthma	1624/28 054	1.20	(1.15 to 1.25)	1.64	(1.17 to 2.30)
Doctor-diagnosed active asthma	1134/28 544	1.21	(1.15 to 1.28)	1.39	(0.93 to 2.07)
Men (n=26 427)					
Ever asthma	2399/24 028	1.12	(1.06 to 1.17)	1.24	(0.88 to 1.74)
Doctor-diagnosed asthma	1437/24 990	1.07	(1.00 to 1.14)	1.31	(0.85 to 2.03)
Doctor-diagnosed active asthma	949/25 478	1.08	(1.00 to 1.17)	1.43	(0.84 to 2.43)

*Per SD (4.1 kg/m²) increase in BMI. Model was adjusted for sex, age, family history of asthma, pack-years of active smoking, physical activity, education and economic difficulties.
†Per SD (4.1 kg/m²) increase in genetically determined BMI after adjustment for family history of asthma and education. Wald method was applied for calculating MR estimates using externally weighted BMI genetic risk score (GRS). The weighted BMI GRS was calculated by multiplying the number of BMI-increasing alleles for each variant by the variant's coefficient for BMI from the Genetic Investigation of Anthropometric Traits (GIANT) study,[16] and summing across the 73 variants.
BMI, body mass index; HUNT2, The Nord-Trøndelag Health Study Survey 2; MR, Mendelian randomisation.

Table 3 Associations of BMI with atopic/non-atopic asthma and with asthma symptom control in the HUNT2 Study (n=56 105)

| | Atopic/non-atopic asthma (n) | Observational estimates | | | | MR estimates | | | |
| | | Atopic asthma | | Non-atopic asthma | | Atopic asthma | | Non-atopic asthma | |
		OR*	95% CI	OR*	95% CI	OR†	95% CI	OR†	95% CI
Ever asthma	1838/3149	1.18	(1.13 to 1.23)	1.17	(1.13 to 1.21)	1.25	(0.89 to 1.77)	1.42	(1.09 to 1.85)
Doctor-diagnosed asthma	1440/1621	1.16	(1.11 to 1.22)	1.15	(1.09 to 1.20)	1.26	(0.86 to 1.85)	1.72	(1.20 to 2.46)
Doctor-diagnosed active asthma	1001/1082	1.16	(1.09 to 1.23)	1.18	(1.12 to 1.25)	1.18	(0.74 to 1.86)	1.65	(1.06 to 2.55)
	Controlled/partly controlled asthma (n)	**Observational estimates**				**MR estimates**			
		Controlled asthma		**Partly controlled asthma**		**Controlled asthma**		**Partly controlled asthma**	
		OR*	95% CI	OR*	95% CI	OR†	95% CI	OR†	95% CI
Doctor-diagnosed active asthma‡	561/1500	1.21	(1.11 to 1.30)	1.16	(1.10 to 1.21)	1.43	(0.78 to 2.61)	1.44	(0.99 to 2.10)

*Per SD increase in BMI. Model was adjusted for sex, age, family history of asthma, pack-years of active smoking, physical activity, education and economic difficulties.
†Per SD increase in genetically determined BMI after adjustment for family history of asthma and education. Wald method was applied for calculating MR estimates using externally weighted BMI genetic risk score (GRS). The weighted BMI GRS was calculated by multiplying the number of BMI-increasing alleles for each variant by the variant's coefficient for BMI from the Genetic Investigation of Anthropometric Traits (GIANT) study,[16] and summing across the 73 variants.
‡22 individuals with doctor-diagnosed active asthma were excluded due to missing of the asthma symptom control variables.
BMI, body mass index; HUNT2, The Nord-Trøndelag Health Study Survey 2; MR, Mendelian randomisation.

effect of BMI than the observational estimates, that is, 36%–49% vs 15%–17% higher ORs for asthma by the three definitions per 1 SD (4.1 kg/m^2) increase in BMI (table 2). Although the ORs per 1 SD (4.1 kg/m^2) in men were generally lower than those in women in the MR analyses, statistical tests showed little evidence of effect modification by sex (all p>0.30).

The proportion of atopic versus non-atopic asthma was 36.9% vs 63.1% for ever asthma, 47.0% vs 53.0% for doctor-diagnosed asthma and 48.1% vs 51.9% for doctor-diagnosed active asthma (table 3). In the observational analyses, BMI was similarly associated with atopic and non-atopic asthma. However, the MR analyses showed larger ORs for non-atopic than atopic asthma (42%–72% vs 18%–26% increased ORs for the three asthma definitions, respectively). The proportions of controlled versus partly controlled doctor-diagnosed active asthma were 26.9%

vs 72.0% (table 3). The effect of BMI on controlled asthma was similar to that on the partly controlled asthma. Similar patterns for asthma by atopic status or by levels of symptom control were observed in women and men despite the reduced statistical power by stratification (online supplementary tables S2 and S3).

There were positive associations between WHR and asthma in the total cohort and by sex in the observational analysis after additional adjustment for BMI (table 4). However, the MR estimates showed little evidence of an association between genetically determined WHR and asthma, and no sex difference was found (all p>0.27).

Results from the IVW method were comparable with those from the Wald method (online supplementary table S4). The I^2 values showed relatively low heterogeneity among the 73 BMI genetic variants. Results from the MR-Egger method showed

Table 4 Associations between WHR and ever asthma, doctor-diagnosed asthma and doctor-diagnosed active asthma in the HUNT2 Study

| | Asthma/no asthma (n) | Observational estimates | | MR estimates | |
		OR*	95% CI	OR†	95% CI
Total (n=55 671)					
Ever asthma	4954/50 717	1.24	(1.18 to 1.30)	1.00	(0.61 to 1.63)
Doctor-diagnosed asthma	3042/52 629	1.23	(1.16 to 1.30)	1.01	(0.55 to 1.86)
Doctor-diagnosed active asthma	2073/53 598	1.26	(1.18 to 1.34)	1.17	(0.56 to 2.44)
Women (n=29 291)					
Ever asthma	2562/26 729	1.18	(1.11 to 1.25)	1.11	(0.70 to 1.78)
Doctor-diagnosed asthma	1607/27 684	1.12	(1.04 to 1.21)	0.95	(0.53 to 1.70)
Doctor-diagnosed active asthma	1125/28 166	1.18	(1.08 to 1.29)	1.22	(0.61 to 2.43)
Men (n=26 380)					
Ever asthma	2392/23 988	1.35	(1.26 to 1.45)	0.48	(0.14 to 1.61)
Doctor-diagnosed asthma	1435/24 945	1.42	(1.30 to 1.55)	0.73	(0.16 to 3.37)
Doctor-diagnosed active asthma	948/25 432	1.40	(1.26 to 1.56)	0.61	(0.09 to 3.96)

*Per SD increase in WHR. Model was adjusted for sex, age, body mass index, family history of asthma, pack-years of active smoking, physical activity, education and economic difficulties.
†Per SD increase in genetically determined WHR. Wald method was applied for calculating MR estimates using externally weighted WHR genetic risk score (GRS). The weighted WHR GRS was calculated by multiplying the number of WHR-increasing alleles for each variant by the variant's coefficient for WHR in Shungin et al's[17] study, and summing across the 47, 46 and 32 variants in total, women and men, respectively.
HUNT2, The Nord-Trøndelag Health Study Survey 2; MR, Mendelian randomisation; WHR, waist-to-hip ratio.

Table 5 MR estimates of association between asthma and BMI in the HUNT2 Study (n=56 105)

Exposure	BMI (kg/m^2)		
	Coefficient*	95% CI	P value
Ever asthma	−0.03	(−0.24 to 0.17)	0.73
Doctor-diagnosed asthma	−0.04	(−0.24 to 0.17)	0.73
Doctor-diagnosed active asthma	−0.04	(−0.24 to 0.17)	0.73

*Per unit increase in ln (OR) of genetically determined asthma. Wald method was applied for MR estimates using externally weighted allele score. The externally weighted asthma allele score was calculated by multiplying the number of asthma risk-increasing alleles for each variant by the variant's coefficient for asthma from the GABRIEL (a multidisciplinary study to identify the genetic and environmental causes of asthma in the European community) study,[20] and summing across the seven variants.

BMI, body mass index; HUNT2, The Nord-Trøndelag Health Study Survey 2; MR, Mendelian randomisation.

consistent evidence for ever asthma and doctor-diagnosed asthma (online supplementary table S4), and the corresponding intercepts did not deviate from zero. However, the causal OR for doctor-diagnosed active asthma was inconsistent and the intercept showed deviation from zero. The two-sample MR analyses showed little evidence on a causal association of WHR (online supplementary table S5) or WC (online supplementary table S6) with doctor-diagnosed asthma.

Regarding the reverse asthma–adiposity relationship, genetically determined asthma was not associated with BMI (table 5) or WHR (online supplementary table S7) in the HUNT2 Study. In two-sample MR of asthma on BMI/WHR we found similar results (online supplementary table S8).

DISCUSSION
Main findings
We observed evidence of an association between genetically determined BMI and asthma in an adult population overall and by sex. The causal association appeared stronger for non-atopic than atopic asthma, but it was similar for controlled and partly controlled asthma. Genetically determined WHR (after adjustment for BMI), however, was not associated with the asthma risk in this adult population. There was little evidence to support a reverse association between genetically determined asthma and the adiposity markers.

Comparison with previous studies
Our finding on the BMI–asthma causal association in the overall population was consistent with results from the previous MR studies in children and adults.[8–11] A most recent two-sample MR study using publicly available summary data further confirmed this causal direction in adults.[27] The similar association between genetically determined BMI and asthma in women and men in the current study was supported by prospective cohort studies.[13] However, it was not supported by the paediatric MR studies in which one reported a stronger causal association in girls[8] and the other reported a stronger association in boys.[9] Regarding a stronger effect of BMI on non-atopic asthma, our finding was supported by the paediatric studies,[8 9] but not by an adult MR study that seemed to report a stronger effect on atopic asthma.[10] Misclassification of atopic status was possible in the latter study as it was defined by reported allergic rhinitis only,[10] whereas our definition was based on report of having allergic rhinitis in combination with reported use of allergy medication or with reported allergic symptoms.

We did not observe an association of genetically determined WHR with asthma. This was supported by results from the two-sample MR analyses on the WHR/WC–doctor-diagnosed asthma associations using data from the MR Base.[26] Genetically determined WHR showed an effect on asthma in a paediatric study,[9] suggesting that there might be different aetiologies for asthma in children as opposed to adults. No reverse association between genetically determined asthma and risk of adiposity was observed in the current and previous studies.[9 27]

Overall, our study supported a causal effect of higher BMI on increased risk of asthma in particular non-atopic asthma, but there was little evidence to suggest different effects on the levels of asthma symptom control. This indicated that increased BMI might play a more important role in causing rather than worsening asthma. Several mechanisms have been proposed for the obesity–asthma association, including mechanical mechanisms resulted from reduced lung volume and airway diameter due to obesity, and inflammatory mechanisms resulted from cytokines, chemokines and hormones produced mainly by abdominal adipocytes.[28] Our study suggested that mechanical restriction to the lung and airways due to obesity might be a major underlying mechanism for the association in adults.[28] This is supported by (1) a previous MR study in adults showing that genetically predicted BMI was associated with reduced lung function,[10] and (2) we did not detect an effect of the central adiposity reflected by WHR.

Strengths and limitations
Our MR study has the following strengths. Apart from providing further evidence on a causal BMI–asthma association, we investigated the possibility of effect modification by sex in an adult population. We are the first to evaluate a potential causal association between WHR and asthma in adults. This is also the first attempt to investigate a potential causal effect of adiposity on asthma symptom control. In addition, our study is among the few to evaluate if reverse causation exists. Our study included a large homogenous population in which 97% were ethnic Norwegians,[14] which was favourable in terms of minimising population stratification bias.[23] We also included the largest number of BMI SNPs (73 vs 24–32) compared with the previous studies.[8–11]

We studied thoroughly the three assumptions of the 73 SNPs being instrumental variables for BMI: (1) the F statistic of the BMI GRS indicated these SNPs being valid instruments[29]; (2) the SNPs or GRS should not be associated with the measured confounders; and (3) there should be no horizontal pleiotropic effects of the BMI genetic variants on risk of asthma. To satisfy the second assumption, we first excluded two SNPs (rs13021737 and rs16951275) that were associated with smoking status, and further adjusted for family history of asthma and education when calculating the MR-derived ORs as they were associated with the BMI GRS. However, we cannot exclude the possibility that BMI SNPs or the GRS are associated with asthma through unknown confounders. Results from the MR-Egger method, which is relatively robust for horizontal pleiotropy, showed consistent associations and little evidence of pleiotropy with ever asthma and doctor-diagnosed asthma. In addition, the heterogeneity of the 73 BMI SNPs was relatively small.

Nevertheless, our study has several limitations. Weak instrument bias and lack of study power were possible, particularly in the evaluation of the WHR–asthma relationship. The MR-Egger intercept suggested a horizontal pleiotropic effect on doctor-diagnosed active asthma, which might be explained by the effect of BMI genetic variants on wheezing[11] as it was

part of the definition of doctor-diagnosed active asthma. In addition, the MR studies have similar weaknesses as observational studies in terms of selection and information bias. We only included 56 105 subjects (86% of the 65 227 participants) who had complete information on the BMI genetic variants, BMI and asthma. Besides, the participation rate in the HUNT2 Survey was moderate (70%). The excluded participants (n=9124) compared with the included participants (n=56 105) were relatively older, lower educated and more physically inactive, but the proportion of BMI ≥25 kg/m^2 (60.1% vs 60.0%) and the prevalence of ever asthma (9.4% vs 8.9%) were similar. Overall, selection bias might be possible, but it may not largely influence the causal association of BMI with asthma. Although it showed consistent results for the three asthma definitions, misclassification of asthma cannot be ruled out due to self-report, particularly among the obese individuals.[30] It was also possible that individuals with COPD reported having asthma. About 5% of the ever asthma adults reported having cough with phlegm for at least 3 months during each of the past 2 years and had FEV_1/FVC ratio <0.70. Anthropometric markers were objectively measured. While minor measurement errors are assumed for weight and height, we acknowledge larger measurement errors for waist and hip circumferences.[31] Evaluation of potential effects of other adiposity markers such as fat mass may therefore improve our understanding on the underlying mechanisms of the BMI–asthma association in adults. At last, although genetic assortments happen long before the onset of disease, which indicates a temporal order in an MR study, prospective data may provide additional information.

In conclusion, our study demonstrated evidence on a similar causal association between BMI and asthma risk in women and men. The causal association seemed stronger for non-atopic asthma, but it was similar for levels of asthma symptom control. The latter suggests that increased BMI might play a role in causing rather than worsening asthma. However, there was little evidence for an association between genetically determined WHR and asthma risk and for reverse causation between asthma and risk of adiposity in this adult population.

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