

# **Adiposity and asthma in adults: a bidirectional Mendelian randomization 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 randomization (MR) study using the Norwegian HUNT population including 56105 adults. 73 and 47 genetic variants were included as instrumental variables for body mass index (BMI) and waist-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 odds ratio (OR) was calculated with the Wald method.

**Results:** The ORs per 1 standard deviation (4.1 kg/m<sup>2</sup>) 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 to 1.72) appeared stronger than those for the atopic asthma (range 1.18 to 1.26), but they were similar for controlled vs. 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-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.

## Introduction

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

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

Two MR studies in children found genetically determined increase in BMI being associated with a higher risk of asthma <sup>8,9</sup>; 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-hip ratio (WHR) and asthma risk <sup>8,9</sup>. Two MR studies were performed in adults using the individual-level data <sup>10,11</sup>; one study reported a 7% increase in risk for asthma associated with 1 kg/m<sup>2</sup> increase in genetically predicted BMI <sup>10</sup>, while the other reported a marginal association <sup>11</sup>. None of the studies in adults has evaluated the potential effect modification by sex. Nor have they evaluated if waist-hip ratio, a marker for central adiposity, plays a causal role in asthma risk independently of BMI <sup>10,11</sup>. 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 <sup>12</sup>. This may be explained by less physical activity among adults with asthma <sup>13</sup>. An evaluation of the reverse causation, i.e. 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, 1995-97). HUNT2 included 65227 subjects 20 years or older living in Nord-Trøndelag in Norway (participation rate 70%)<sup>14</sup>. All participants completed two general questionnaires regarding health, lifestyle and socio-economic 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<sup>14</sup>. Genotyping was performed using Illumina HumanCoreExome arrays<sup>15</sup>. Seventy-seven single nucleotide polymorphisms (SNPs) were selected as instrumental variables for BMI based on a large genome-wide association study (GWAS) from the GIANT consortium<sup>16</sup>; 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<sup>16</sup>, 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 a  $p$  value  $< 5 \times 10^{-8}$ <sup>17</sup>; sex-specific instruments were suggested including 48 SNPs for women and 33 SNPs for men at a  $p$  value  $< 0.05$ . In HUNT2, data of 47, 46 and 32 SNPs were available and used to generate weighted WHR GRS for total, for women and for men respectively. None of these SNPs were

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<sup>17</sup>. 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<sup>18</sup>, levels of asthma symptom control were classified as controlled (0 of the above items) vs. partly controlled (1-4 items) in the doctor diagnosed active asthma individuals. The classification was adapted from the 2015 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention<sup>19</sup>.

In the HUNT2 Study, seven asthma-associated SNPs from the GABRIEL study ( $p < 5 \times 10^{-8}$  for asthma risk at all ages), a large GWAS on asthma in people with European ancestry<sup>20</sup>, 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)<sup>21</sup> 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 56105 participants who had complete information on the BMI SNPs, BMI and asthma. We performed one-sample MR analyses applying the Wald method<sup>22</sup>, with which MR-derived odds ratio (OR) and 95% confidence interval (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 (Table S1). The coefficient of the GRS-BMI association was derived after adjustment for sex, age and age-squared<sup>16</sup>. The MR-derived OR corresponded to an effect of 1 standard deviation (SD) increase in genetically determined BMI.

Second, we evaluated the potential causal WHR-asthma association in 55671 of the 56105 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<sup>17</sup>.

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-effect meta-analysis model<sup>23</sup>. Additionally, we tested for heterogeneity among the 73 BMI

SNPs by presenting the  $I^2$  value in the IVW method <sup>24</sup>. The MR-Egger method is relatively robust to horizontal pleiotropy <sup>25</sup>, by which we calculated the intercept and 95% CI of the MR-Egger regression line <sup>25</sup>. 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 <sup>26</sup>; summary-level statistics were extracted from the GIANT Consortium on WHR/WC <sup>17</sup> and the GABRIEL study on doctor diagnosed asthma <sup>20</sup>.

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 <sup>16 17 21</sup>. 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 <sup>26</sup>.

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,  $\geq$ 20.1 pack-years), current (0–10.0, 10.1–20.0,  $\geq$ 20.1 pack-years), and unknown], physical activity (inactive, low, moderate, high, and unknown), education (<10, 10–12,  $\geq$ 13 years, and unknown), and having economic difficulties (yes, no, and unknown).

All statistical analyses were performed in R (version 3.5.1) or STATA/MP 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 effect of BMI than the observational estimates, i.e. 36%-49% vs. 15%-17% higher ORs for asthma by the three definitions per 1 SD (4.1 kg/m<sup>2</sup>) increase in BMI (Table 2). Although the ORs per 1 SD (4.1 kg/m<sup>2</sup>) in men were generally lower than those in women in the MR analyses, statistical tests showed little evidence of effect modification by sex ( $p>0.30$  for all).

The proportion of atopic vs. 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 vs. 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 (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 ( $p>0.27$  for all).

Results from the IVW method were comparable with those from the Wald method (Table S4). The  $I^2$  values showed relatively low heterogeneity among the 73 BMI genetic variants.

Results from the MR-Egger method showed consistent evidence for ever asthma and doctor diagnosed asthma (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 (Table S5) or WC (Table S6) with doctor diagnosed asthma.

Regarding the reverse asthma-adiposity relationship, genetically determined asthma was not associated with BMI (Table 5) or WHR (Table S7) in the HUNT2 Study. In two-sample MR of asthma on BMI/WHR we found similar results (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<sup>8-11</sup>. A most recent two-sample MR study using publicly available summary data further confirmed this causal direction in adults<sup>27</sup>. The similar association between genetically determined BMI and asthma in women and men in the current study was supported by prospective cohort studies<sup>1,3</sup>. However, it was not supported by the paediatric MR studies in which one reported a stronger causal association in girls<sup>8</sup> and the other reported a stronger association in boys<sup>9</sup>. Regarding a stronger effect of BMI on non-atopic asthma, our finding was supported by the paediatric studies<sup>8,9</sup>, but not by an adult MR study that seemed to report a stronger effect on atopic asthma<sup>10</sup>. Misclassification of atopic status was possible in the latter study as it was defined by reported allergic rhinitis only<sup>10</sup>, 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<sup>26</sup>. Genetically determined WHR showed

an effect on asthma in a paediatric study <sup>9</sup>, 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 <sup>9 27</sup>.

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 <sup>28</sup>. 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 <sup>28</sup>. This is supported by 1) a previous MR study in adults showing that genetically predicted BMI was associated with reduced lung function <sup>10</sup> 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 <sup>14</sup>, which was favourable in terms of minimizing population stratification bias <sup>23</sup>. We also included the largest number of BMI SNPs (73 vs. 24-32) compared with the previous studies <sup>8-11</sup>.

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<sup>29</sup>; 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 horizontal pleiotropic effect on doctor diagnosed active asthma, which might be explained by the effect of BMI genetic variants on wheezing<sup>11</sup> 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 56105 subjects (86% of the 65227 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 (n=9124) compared with the included participants (n=56105) were relatively older, lower educated, and more physically inactive, but the proportion of BMI  $\geq 25$  kg/m<sup>2</sup> (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<sup>30</sup>. It was also possible that individuals with chronic obstructive pulmonary disease (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 two years and had FEV<sub>1</sub>/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<sup>31</sup>. 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 adiposity in this adult population.



## **Contributors**

YQS, BMB, AL, YC, KK and XMM contributed to the study design. YQS conducted statistical analyses. YQS and XMM wrote the initial draft of the manuscript. AL is the leader of the HUNT Lung Study and contributed to data collection. All authors participated in the data interpretation and contributed to the final draft of manuscript with intellectual importance.

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## **Competing interests**

There are no competing interests provided for any authors.

## **Ethics approval**

All participants gave their informed consent for participation in HUNT. The current study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics.

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**Table 1.** Description of the HUNT2 cohort, 1995–1997

	Total	Women	Men
No. of subjects	56105	29678	26427
Age (years)*	49.6±16.6	49.5±16.8	49.6±16.3
Body mass index (kg/m <sup>2</sup> )*	26.3±4.1	26.2±4.6	26.5±3.5
Waist-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

HUNT2: The Nord-Trøndelag Health Study Survey 2

\*Data are given as mean ± standard deviation

†Data are available for 55671 adults including 29291 women and 26380 men

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

	Number of asthma/ no asthma	Observational estimates		MR estimates	
		OR*	95% CI	OR <sup>†</sup>	95% CI
Total (n=56105)					
Ever asthma	4987/51118	1.17	(1.14 to 1.21)	1.36	(1.10 to 1.68)
Doctor diagnosed asthma	3061/53044	1.15	(1.11 to 1.19)	1.49	(1.14 to 1.94)
Doctor diagnosed active asthma	2083/54022	1.17	(1.12 to 1.22)	1.40	(1.02 to 1.93)
Women (n=29678)					
Ever asthma	2588/27090	1.21	(1.17 to 1.25)	1.47	(1.12 to 1.93)
Doctor diagnosed asthma	1624/28054	1.20	(1.15 to 1.25)	1.64	(1.17 to 2.30)
Doctor diagnosed active asthma	1134/28544	1.21	(1.15 to 1.28)	1.39	(0.93 to 2.07)
Men (n=26427)					
Ever asthma	2399/24028	1.12	(1.06 to 1.17)	1.24	(0.88 to 1.74)
Doctor diagnosed asthma	1437/24990	1.07	(1.00 to 1.14)	1.31	(0.85 to 2.03)
Doctor diagnosed active asthma	949/25478	1.08	(1.00 to 1.17)	1.43	(0.84 to 2.43)

BMI: body mass index; CI: confidence interval; HUNT2: The Nord-Trøndelag Health Study Survey 2; MR: Mendelian randomization; OR: odds ratio

\*Per standard deviation (4.1 kg/m<sup>2</sup>) increase in BMI. Model was adjusted for sex, age, family history of asthma, pack-years of active smoking, physical activity, education and economic difficulties

<sup>†</sup>Per standard deviation (4.1 kg/m<sup>2</sup>) 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 GIANT study <sup>16</sup>, and summing across the 73 variants.



**Table 3.** Associations of BMI with atopic/non-atopic asthma and with asthma symptom control in the HUNT2 Study (n=56105)

	Number of atopic/non-atopic asthma	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)

  

	Number of controlled/partly controlled asthma	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 <sup>#</sup>	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)

BMI: body mass index; CI: confidence interval; HUNT2: The Nord-Trøndelag Health Study Survey 2; MR: Mendelian randomization; OR: odds ratio

\*Per standard deviation 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 standard deviation 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 GIANT study<sup>16</sup>, and summing across the 73 variants.

<sup>#</sup>22 individuals with doctor diagnosed active asthma were excluded due to missing of the asthma symptom control variables

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

	Number of asthma/no asthma	Observational estimates		MR estimates	
		OR*	95% CI	OR†	95% CI
Total (n=55671)					
Ever asthma	4954/50717	1.24	(1.18 to 1.30)	1.00	(0.61 to 1.63)
Doctor diagnosed asthma	3042/52629	1.23	(1.16 to 1.30)	1.01	(0.55 to 1.86)
Doctor diagnosed active asthma	2073/53598	1.26	(1.18 to 1.34)	1.17	(0.56 to 2.44)
Women (n=29291)					
Ever asthma	2562/26729	1.18	(1.11 to 1.25)	1.11	(0.70 to 1.78)
Doctor diagnosed asthma	1607/27684	1.12	(1.04 to 1.21)	0.95	(0.53 to 1.70)
Doctor diagnosed active asthma	1125/28166	1.18	(1.08 to 1.29)	1.22	(0.61 to 2.43)
Men (n=26380)					
Ever asthma	2392/23988	1.35	(1.26 to 1.45)	0.48	(0.14 to 1.61)
Doctor diagnosed asthma	1435/24945	1.42	(1.30 to 1.55)	0.73	(0.16 to 3.37)
Doctor diagnosed active asthma	948/25432	1.40	(1.26 to 1.56)	0.61	(0.09 to 3.96)

CI: confidence interval; HUNT2: The Nord-Trøndelag Health Study Survey 2; MR: Mendelian randomization; OR: odds ratio; WHR: waist-hip ratio

\*Per standard deviation 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 standard deviation 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.*<sup>17</sup>, and summing across the 47, 46, 32 variants in total, women, and men respectively

**Table 5.** MR estimates of association between asthma and BMI in the HUNT2 Study (n=56105)

Exposure	BMI (kg/m <sup>2</sup> )		<i>P</i> value
	Coefficient*	95% CI	
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

BMI: body mass index; CI: confidence interval; HUNT2: The Nord-Trøndelag Health Study Survey 2; MR: Mendelian randomization

\*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 study<sup>20</sup>, and summing across the 7 variants.