

**Table S1.** Associations of the externally weighted BMI genetic risk score (GRS) with BMI values and potential confounders in the HUNT2 Study (n=56105)

Baseline variables	Coefficient *	95% CI	P value
BMI (kg/m <sup>2</sup> )	3.74	(3.53 to 3.96)	6.5x10 <sup>-251</sup>
Sex (men vs. women)	-0.06	(-0.17 to 0.05)	0.29
Age (difference in years)	0.55	(-0.36 to 1.47)	0.23
Family history of asthma (yes vs. no)	0.25	(0.10 to 0.41)	0.001 <sup>†</sup>
Pack-years of active smoking (difference)	0.16	(0.03 to 0.28)	0.01
Physical activity (active vs. inactive)	-0.07	(-0.21 to 0.08)	0.37
Education (years) (≥10 vs. <10)	-0.18	(-0.30 to -0.07)	0.002 <sup>†</sup>
Economic difficulties (yes vs. no)	0.14	(-0.00 to 0.28)	0.06

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

\*Coefficient was derived from linear regression for continuous variables and from logistic regression for categorical variables corresponding to 1 unit increase in GRS

<sup>†</sup>Regarded as significant when P value <0.007 (Bonferroni correction 0.05/7=0.007)

The externally 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>1</sup>, and summing across the 73 variants.

**Table S2.** Association between BMI and atopic/non-atopic asthma in women and men respectively in the HUNT2 Study

	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
Women (n=29678)									
Ever asthma	1063/1525	1.22	(1.16 to 1.29)	1.20	(1.15 to 1.26)	1.41	(0.93 to 2.13)	1.51	(1.07 to 2.13)
Doctor diagnosed asthma	833/791	1.21	(1.14 to 1.28)	1.19	(1.12 to 1.26)	1.44	(0.90 to 2.29)	1.87	(1.16 to 3.00)
Doctor diagnosed active asthma	598/536	1.21	(1.13 to 1.30)	1.22	(1.14 to 1.31)	1.24	(0.72 to 2.14)	1.57	(0.88 to 2.78)
Men (n=26427)									
Ever asthma	775/1624	1.09	(1.00 to 1.19)	1.13	(1.06 to 1.20)	1.04	(0.58 to 1.86)	1.34	(0.89 to 2.02)
Doctor diagnosed asthma	607/830	1.07	(0.97 to 1.17)	1.07	(0.99 to 1.17)	1.01	(0.52 to 1.95)	1.59	(0.91 to 2.76)
Doctor diagnosed active asthma	403/546	1.05	(0.93 to 1.18)	1.11	(1.01 to 1.23)	1.06	(0.48 to 2.37)	1.78	(0.89 to 3.54)

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 age, family history of asthma, pack-years of active smoking, physical activity, education and economic difficulties

†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>1</sup>, and summing across the 73 variants.

**Table S3.** Association between BMI and asthma symptom control in women and men respectively in the HUNT2 Study

	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
Women (n=29664)									
Doctor diagnosed active asthma	305/815	1.28	(1.16 to 1.40)	1.20	(1.13 to 1.27)	1.38	(0.65 to 2.94)	1.48	(0.92 to 2.36)
Men (n=26419)									
Doctor diagnosed active asthma	256/685	1.06	(0.92 to 1.23)	1.10	(1.00 to 1.20)	1.50	(0.55 to 4.05)	1.40	(0.76 to 2.61)

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 age, family history of asthma, pack-years of active smoking, physical activity, education and economic difficulties

†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>1</sup>, and summing across the 73 variants.

**Table S4.** Mendelian randomization estimates based on summary statistics of the associations between BMI and ever asthma, doctor diagnosed asthma, and doctor diagnosed active asthma in the HUNT2 Study

	IVW method			MR-Egger method			
	OR* (95% CI)	P value	I <sup>2</sup> (95% CI)	OR* (95% CI)	P value	Intercept (95% CI)	P value of intercept
Ever asthma	1.43 (1.14 to 1.80)	0.002	0.31 (0.07 to 0.48)	1.22 (0.83 to 1.80)	0.32	0.006 (-0.005 to 0.017)	0.31
Doctor diagnosed asthma	1.46 (1.13 to 1.88)	0.004	0.13 (0.00 to 0.35)	1.09 (0.71 to 1.67)	0.70	0.010 (-0.002 to 0.023)	0.10
Doctor diagnosed active asthma	1.38 (1.04 to 1.85)	0.027	0.00 (0.00 to 0.12)	0.91 (0.56 to 1.48)	0.69	0.015 (0.001 to 0.029)	0.04

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

\*Per standard deviation increase in genetically determined BMI.

**Table S5.** Two-sample MR estimates of the association between WHR and doctor diagnosed asthma

Method	Coefficient <sup>*</sup>	95% CI	P value
Inverse variance weighted	-0.15	(-0.47 to 0.16)	0.35
MR Egger	0.94	(-0.33 to 2.20)	0.16
Weighted median	-0.08	(-0.49 to 0.33)	0.71
Robust adjusted profile score (RAPS)	-0.11	(-0.45 to 0.24)	0.54

CI: confidence interval; MR: Mendelian randomization; WHR: waist-hip ratio

<sup>\*</sup>Estimates were calculated in MR Base <sup>2</sup>. Summary statistics of association between SNPs and WHR were from the GIANT Consortium <sup>3</sup>. Summary statistics of association between SNPs and asthma were from the GABRIEL Consortium <sup>4</sup>. 35 of 47 SNPs were used as instrumental variables for WHR due to data availability in the GABRIEL Consortium

**Table S6.** Two-sample MR estimates of the association between WC and doctor diagnosed asthma

Method	Coefficient <sup>*</sup>	95% CI	P value
Inverse variance weighted	-0.04	(-0.30 to 0.23)	0.79
MR Egger	0.03	(-1.14 to 1.20)	0.96
Weighted median	-0.09	(-0.44 to 0.25)	0.59
Robust adjusted profile score (RAPS)	-0.03	(-0.31 to 0.25)	0.83

CI: confidence interval; MR: Mendelian randomization; WC: waist circumference

<sup>\*</sup>Estimates were calculated in MR Base <sup>2</sup>. Summary statistics of association between SNPs and WC adjusted for BMI were from the GIANT Consortium <sup>3</sup>. Summary statistics of association between SNPs and asthma were from the GABRIEL Consortium <sup>4</sup>. 51 of 53 SNPs were used as instrumental variables for WC due to data availability in the GABRIEL Consortium

**Table S7.** MR estimates of association between asthma and WHR in the HUNT2 Study (n=55671)

Exposure	WHR		<i>P</i> value
	Coefficient*	95% CI	
Ever asthma	-0.002	(-0.002 to 0.006)	0.37
Doctor diagnosed asthma	-0.002	(-0.002 to 0.006)	0.37
Doctor diagnosed active asthma	-0.002	(-0.002 to 0.006)	0.37

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

\*Per unit increase of ln (OR) in genetically determined asthma. Wald method was applied for calculating MR estimates using externally weighted asthma genetic risk score (GRS). The weighted asthma GRS 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>4</sup>, and summing across the 7 variants.

**Table S8.** Two-sample MR estimates of the associations between asthma and BMI/WHR

Outcome	BMI			WHR		
Method	Coefficient*	95% CI	P value	Coefficient*	95% CI	P value
Inverse variance weighted	0.00	(-0.03 to 0.02)	0.76	-0.02	(-0.05 to 0.01)	0.26
MR Egger	0.08	(-0.02 to 0.19)	0.14	-0.05	(-0.18 to 0.08)	0.44
Weighted median	0.00	(-0.04 to 0.03)	0.86	-0.02	(-0.06 to 0.02)	0.39
Robust adjusted profile score (RAPS)	0.00	(-0.02 to 0.03)	0.96	-0.01	(-0.04 to 0.02)	0.65

BMI: body mass index; CI: confidence interval; MR: Mendelian randomization; WHR: waist-hip ratio

\*Estimates were calculated in MR Base <sup>2</sup>. Summary statistics of association between SNPs and asthma were from the study by Ferreira *et al.* <sup>5</sup>. Summary statistics of association between SNPs and BMI/WHR (adjusted for BMI) were from the GIANT Consortium <sup>1 3</sup>. 26 of 34 SNPs were used as instrumental variables for asthma due to data availability in the GIANT studies.

**References**

1. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015;518(7538):197-206. doi: 10.1038/nature14177 [published Online First: 2015/02/13]

2. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. *eLife* 2018;7 doi: 10.7554/eLife.34408 [published Online First: 2018/05/31]

3. Shungin D, Winkler TW, Croteau-Chonka DC, et al. New genetic loci link adipose and insulin biology to body fat distribution. *Nature* 2015;518(7538):187-96. doi: 10.1038/nature14132 [published Online First: 2015/02/13]

4. Moffatt MF, Gut IG, Demenais F, et al. A large-scale, consortium-based genomewide association study of asthma. *The New England journal of medicine* 2010;363(13):1211-21. doi: 10.1056/NEJMoa0906312 [published Online First: 2010/09/24]

5. Ferreira MAR, Mathur R, Vonk JM, et al. Genetic Architectures of Childhood- and Adult-Onset Asthma Are Partly Distinct. *American journal of human genetics* 2019;104(4):665-84. doi: 10.1016/j.ajhg.2019.02.022 [published Online First: 2019/04/02]