Accepted: 2 July 2017

DOI: 10.1111/all.13242

ORIGINAL ARTICLE

Epidemiology and Genetics

WILEY Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

Estimating the causal effect of body mass index on hay fever, asthma and lung function using Mendelian randomization

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Funding information
Købmand I Odense Johan og Hanne Weimann Født Seedorffs Legat; Aase og Ejnar Danielsens Fond, Grant/Award Number: 10-001490; Lundbeckfonden, Grant/Award Number: R165-2013-15410, R219-2016-471; Fonden til Lægevidenskabens Fremme, Grant/Award Number: 15-363; Harboefonden, Grant/Award Number: 16152

Edited by: Stephan Weidinger

Abstract

Background: Observational studies have shown that body mass index (BMI) is positively associated with asthma. However, observational data are prone to confounding and reverse causation. In Mendelian randomization, genetic variants are used as unconfounded markers of exposures to examine causal effects. We examined the causal effect of BMI on asthma, hay fever, allergic sensitization, serum total immunoglobulin E (IgE), forced expiratory volume in one-second (FEV1) and forced vital capacity (FVC).

Methods: We included 490 497 participants in the observational and 162 124 participants in the genetic analyses. A genetic risk score (GRS) was created using 26 BMI-associated single nucleotide polymorphisms (SNPs). Results were pooled in meta-analyses and expressed as odds ratios (ORs) or β-estimates with 95% confidence interval (CI).

Results: The GRS was significantly associated with asthma (OR=1.009; 95% CI: 1.004, 1.013), but not with hay fever (OR= 0.998; 95% CI: 0.994, 1.002) or allergic sensitization (OR=0.999; 95% CI: 0.986, 1.012) per BMI-increasing allele. The GRS was significantly associated with decrease in FEV1: β=−0.0012 (95% CI: −0.0019, −0.0006) and FVC: β=−0.0022 (95% CI: −0.0031, −0.0014) per BMI-increasing

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allele. Effect sizes estimated by instrumental variable analyses were OR=1.07 (95% CI: 1.03, 1.10) for asthma, a 9 ml decrease in FEV1 (95% CI: 2.0-15 mL decrease) and a 16 ml decrease in FVC (95% CI: 7.0-24 mL decrease) per 1 kg/m^2 higher BMI.

Conclusions: The results support the conclusion that increasing BMI is causally related to higher prevalence of asthma and decreased lung function, but not with hay fever or biomarkers of allergy.

KEYWORDS
allergic disease, allergic sensitization, asthma, hay fever, serum-specific IgE

1 | INTRODUCTION

Overweight and obesity are in reported observational studies consistently associated with increased prevalence of asthma and,[1] to some extent, decreased lung function,[2] while the association with hay fever and allergic sensitization is less clear.[3-5] Overweight and obesity may affect the lungs in several ways, for example, through inflammation that may predispose to asthma or through a mechanical effect on lung function. Mechanically, increased body mass index (BMI) may lead to decreased static lung volumes,[6] and breathing with smaller tidal volumes which may leave some of the cross-bridged myosin-actin in the airways unbroken,[7] thereby further narrowing the airways.[8] In addition, the overweight/obesity-related low-grade inflammation may affect lung function and the risk of asthma.[9] It is likely that other factors associated with overweight and obesity such as dyslipidaemia and increased mast cell activity are also implicated in the pathogenesis of asthma and decreased lung function. For example, an increased number of mast cells has been found in adipose tissue, and mast cells participate in asthma by degranulation in response to allergen challenge.[10] Upon activation, mast cells secrete peptidases such as tryptase.[11,12] Tryptase may increase inflammation and remodelling of airway smooth muscles, and tryptase inhibition has been found to reduce airway inflammation.

However, inferring a causal relationship, for example, between BMI and asthma, from such observational studies may be hampered by bias such as confounding and reverse causation. Mendelian randomization that is based on observational data is a method for making inferences about causal effects using genetic instrumental variables (IV). The idea is that if we can replace the actual measured values of an exposure (which may be correlated with confounders, etc.) by predicted values of the exposure (via the IV) that are related to the actual exposure but uncorrelated with confounders, we can get an unconfounded estimate. This has been used previously in a study of approximately 5000 children where a higher BMI was found to increase the risk of asthma.[13] However, this has not been examined in adults. Mendelian randomization takes advantage of the random allocation of alleles from parent to child and is a method for examining and estimating possible causal relationships where genetic IVs with well-known effects on an exposure are used as proxies for that exposure.[14] To be a valid instrument, the genetic variant must be associated with the exposure, it may only affect the outcome through the exposure, and it cannot be associated with any unmeasured confounders.

We used a genetically determined higher BMI to investigate and quantify the effect of adiposity on asthma, hay fever, biomarkers of allergy (IgE antibodies) and lung function in adults (≥16 years) according to the principles of Mendelian randomization. We included 26 SNPs, including the *FTO* rs9939609,[15] that are associated with BMI at genomewide significance levels in a number of genomewide association studies (GWAS)[16-28] previously validated in one of the included studies.[29,30]

2 | METHODS

2.1 | Study populations

We used data on 490 497 participants of European ancestry and aged ≥16 years of whom 162 124 had data on all or most of the relevant SNPs from the following seven population-based studies: the Danish Monitoring of trends and determinants in Cardiovascular Diseases (MONICA) study (the Monica10 study),[31] Health2006,[32] Health2008,[33] Inter99,[34] the Study of Health in Pomerania (SHIP),[35] SHIP TREND[36] and the UK Biobank (Supporting Material, incl. Table S1).[37] Each study was approved by local Ethics Committees, and the participants gave their informed consent.

2.2 | Genotype

We preselected 26 BMI-associated SNPs as listed in Table 1.[16-28] None of the cohorts used were in the discovery samples for these SNPs. Descriptions of the genotyping method within each study are provided in Supporting Material. Minor allele frequencies (MAF) and Hardy-Weinberg equilibrium *P*-values are shown in Table S2. Some SNPs were in one or a few studies not in Hardy-Weinberg equilibrium at the .05 significance level, but except for two SNPs in the UK Biobank, all SNPs were in Hardy-Weinberg equilibrium at the Bonferroni-adjusted significance level ($P<.00027$). Each SNP was

TABLE 1 BMI-associated SNPs[16-28]

SNP	Effect[a]/other	Effect size (kg/m^2)[a]
rs10838738	G/A	0.06
rs10938397	G/A	0.18
rs10968576	G/A	0.11
rs11847697	T/C	0.17
rs12444979	C/T	0.17
rs13107325	T/C	0.19
rs1424233	A/G	0.03[17]
rs1514175	T/C	0.07
rs1555543	C/A	0.06
rs17782313	C/T	0.23
rs1805081	A/G	0.039[17]
rs206936	G/A	0.06
rs2112347	T/G	0.10
rs2241423	G/A	0.13
rs2287019	C/T	0.15
rs2568958	A/G	0.13
rs29941	G/A	0.06
rs3810291	A/G	0.09
rs4929949	C/T	0.06
rs543874	G/A	0.22
rs713586	C/T	0.14
rs7647305	C/T	0.14
rs9939609	A/T	0.39
rs10146997	G/A	0.13
rs1121980	A/G	0.06[18]
rs7138803	A/G	0.12

[a]The effect allele is the allele associated with higher BMI.

classified according to the number of BMI-increasing alleles, that is 0, 1 or 2. A simple genetic risk score was calculated by adding the number of BMI-increasing alleles.[38] In secondary analyses, we used a weighted genetic risk score with weights derived from studies different from our own.[16-28] See individual weights in Table 1.

2.3 | BMI

Height and weight were measured, and BMI was calculated as weight divided by height squared, expressed in kg/m^2.

2.4 | Hay fever, asthma, allergic sensitization and serum total IgE, FEV1 and FVC

Information on hay fever and asthma was based on self-report (Supporting Material incl. Table S3). Our first choice was lifetime/ever diagnoses. Allergic sensitization was defined as serum-specific IgE positivity to at least one of a number of inhalant allergens (Supporting Material incl. Table S3). Serum total IgE levels were measured by the IMMULITE 2000 Allergy Immunoassay System in Inter99 Study and by the Latex IgE test on the BN II Nephelometer (Dade Behring Marburg GmbH, Marburg, Germany) in the SHIP Study.[39] FEV1 and FVC were measured with spirometry. More details are provided in the Supplementary Material. For additional analyses in UK Biobank data only, we created subgroups of persons who had both asthma and hay fever (as a measure of "atopic" asthma), asthma but not hay fever (as a measure of "nonatopic" asthma) and not asthma or hay fever.

2.5 | Statistical analyses

Statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA), STATA, version 13 (StataCorp, College Station, TX, USA) and R-statistical package, version 3.2.3 for Windows (http://www.r-project.org/). The *P*-values are two-tailed, and statistical significance was defined as $P<.05$, but the causality of associations was assessed by the strength of evidence rather than the size of the *P*-value only. For each of the studies, a data set was prepared in accordance with the study protocol, and the data were analysed by a preprepared Stata-script that was adapted to each study. To obtain a normal distribution, serum total IgE was transformed by the natural logarithm (log). Except for first stage analyses only (eg, Figure 3) where BMI was transformed to the logarithm of two, the reported data are according to BMI not log-transformed (incl. first stage estimates to be used in IV-analyses). The results from each study were meta-analysed with fixed effects analyses and heterogeneity assessed by the I^2 test. Effect estimates are presented as β-coefficients or odds ratios with 95% confidence intervals (95% CI).

2.6 | Observational analyses

Observational, that is, the BMI-outcome associations, analyses were performed using logistic and linear regression analyses that were adjusted for sex and age and in the FEV1 and FVC analyses also for height. We also compared results from observational analyses considering only those from UK Biobank that were included in the MR-analyses to the whole UK Biobank sample.

2.7 | Mendelian randomization analyses

The SNP data for each study is shown in Table S1. We created a SNP-score which is a single variable that summarizes multiple SNPs in a univariate score. Our primary analyses rely on a simple SNP-score that counts the number of BMI-increasing alleles, whereas in a weighted SNP-score, each SNP contributes a weight that reflects the effect of the SNP on BMI. The "F-value" is an analogue of the F-statistic for the joint significance of the SNP/SNP-score in the first stage regression. The F-value is an indicator of statistical power in the MR-analysis.[40] In the UK Biobank study, the F-value for the SNP-score was 1185 for BMI. The single-SNP F-values ranged from 1 to 397 in the UK Biobank data. The rs1424233 and rs11847697 SNPs had F-values below 10. Analyses excluding the three SNPs with signs of Hardy-Weinberg disequilibrium in the UK Biobank

Study were also performed. The requirement that the instrument is not associated with unmeasured confounders can only be falsified, but to substantiate the assumption, we assessed the associations between each single-SNP and age, sex, smoking status and alcohol status.

Mendelian randomization analyses (first stage: SNP-BMI, second stage: SNP outcome) were performed using logistic and linear regression analyses that were adjusted for sex and age and in the FEV1 and FVC analyses also for height. To obtain a normal distribution, serum total IgE was transformed by the natural logarithm (log).

IV-analyses were performed using the R packages "MendelianRandomization" and "ivpack," and graphs were made by the "rmeta" package in R. To obtain estimates expressed per 1 kg/m^2 higher BMI, we used the untransformed BMI in the first stage analysis. As the primary IV-analyses, we performed a one-sample analysis, where all relevant studies were included in both the first- and second-stage analysis. Secondarily, we performed two-sample IV-analyses where the first- and second-stage sample had no overlap: All studies except for the UK Biobank Study provided data for the first stage and UK Biobank alone provided data for the second stage analysis. To assess potential pleiotropy, we also performed MR Egger regression and median regression analyses.[41]

3 | RESULTS

3.1 | Observational analyses

Descriptive statistics for each study population are found in Table 2.

In sex- and age-adjusted observational analyses (Figure 1), BMI was inversely and significantly associated with hay fever: OR=0.995 (95% CI: 0.994, 0.997, P<.001) per 1 kg/m^2 higher BMI and positively and significantly associated with asthma: OR=1.037 (95% CI: 1.035, 1.039, P<.001) per 1 kg/m^2 higher BMI. BMI was positively but nonsignificantly associated with allergic sensitization with OR=1.007 (95% CI: 0.998, 1.016, P=.131) per 1 kg/m^2 higher BMI. BMI was positively and significantly associated with log(IgE): β=0.02 (95% CI: 0.01, 0.03, P<.001) per 1 kg/m^2 higher BMI (Figure 2). In general, the heterogeneity was low to modest and ranged from 0.0%-53.2%. BMI was inversely associated with FEV1 and FVC with β=−0.012 (95% CI: −0.013, −0.012, P<.001) and β=−0.024 (95% CI: −0.025, −0.024, P<.001), respectively, per 1 kg/m^2 higher BMI (these analyses were further adjusted for height) in fixed effect meta-analyses (Figure 2). The heterogeneity was substantial (both I^2>90.0%). The study-specific estimates of observational analyses of the association between BMI, FEV1 and FVC are shown in Fig. S6. Random effect meta-analyses yielded for FEV1: β=−0.008 (95% CI:

TABLE 2 Descriptive statistics of the study populations

Monica10	Health2006	Inter99	Health2008	SHIP	SHIP trend	UK Biobank
Total, N[a]						
1833	3369	6404	783	4298	986	472 824
Males, % (N)						
49.7 (911)	44.88 (1512)	48.39 (3099)	43.81 (343)	49.12 (2111)	43.81 (432)	45.54 (215 309)
Hay fever, % (N)						
11.1 (203)	17.9 (603)	NA	21.2 (166)	7.91 (340)	14.30 (141)	22.95 (108 516)
Asthma, % (N)						
6.9 (127)	10.6 (357)	8.65 (535)	11.75 (92)	11.47 (488)	4.16 (41)	11.53 (54 503)
Allergic sensitization, % (N)						
17.9 (329)	23.18 (781)	34.55 (1962)	27.46 (215)	NA	NA	NA
Age, years, median (IQR)						
52 (42, 61)	50 (40, 60)	45 (40, 50)	46 (40, 53)	50 (36, 63)	50 (40, 61)	58 (50, 63)
BMI, kg/m^2 median (IQR)						
25.3 (23, 28.3)	25.2 (22.6, 28.2)	25.6 (23.1, 28.7)	25.1 (22.9, 28.3)	26.9 (23.8, 30.1)	27.0 (24.1, 30.1)	26.7 (24.1, 29.9)
FEV1, l, median (IQR)						
2.9 (2.4, 3.5)	3 (2.5, 3.6)	3.1 (2.7, 3.7)	3.2 (2.7, 3.9)	NA	NA	2.8 (2.3, 3.3)
Serum total IgE, IU/ml, median (IQR)						
NA	NA	28 (10.6, 76)	NA	36.5 (16.8, 103)	NA	NA
Height, cm, median (IQR)						
169 (162.5, 176)	171 (165, 178.6)	172 (165, 179)	172 (166.2, 180.3)	NA	NA	168 (162, 175)
FVC, l, median (IQR)						
3.7 (3.1, 4.5)	3.9 (3.3, 4.6)	4 (3.4, 4.8)	4 (3.4, 4.8)	NA	NA	3.6 (3, 4.4)

IgE, immunoglobulin E; IQR, interquartile range; Monica, Monitoring of trends and determinants in Cardiovascular Diseases; NA, not available; SHIP, Study of Health in Pomerania; UK Biobank, United Kingdom Biobank.

[a]The largest number included in the analyses.

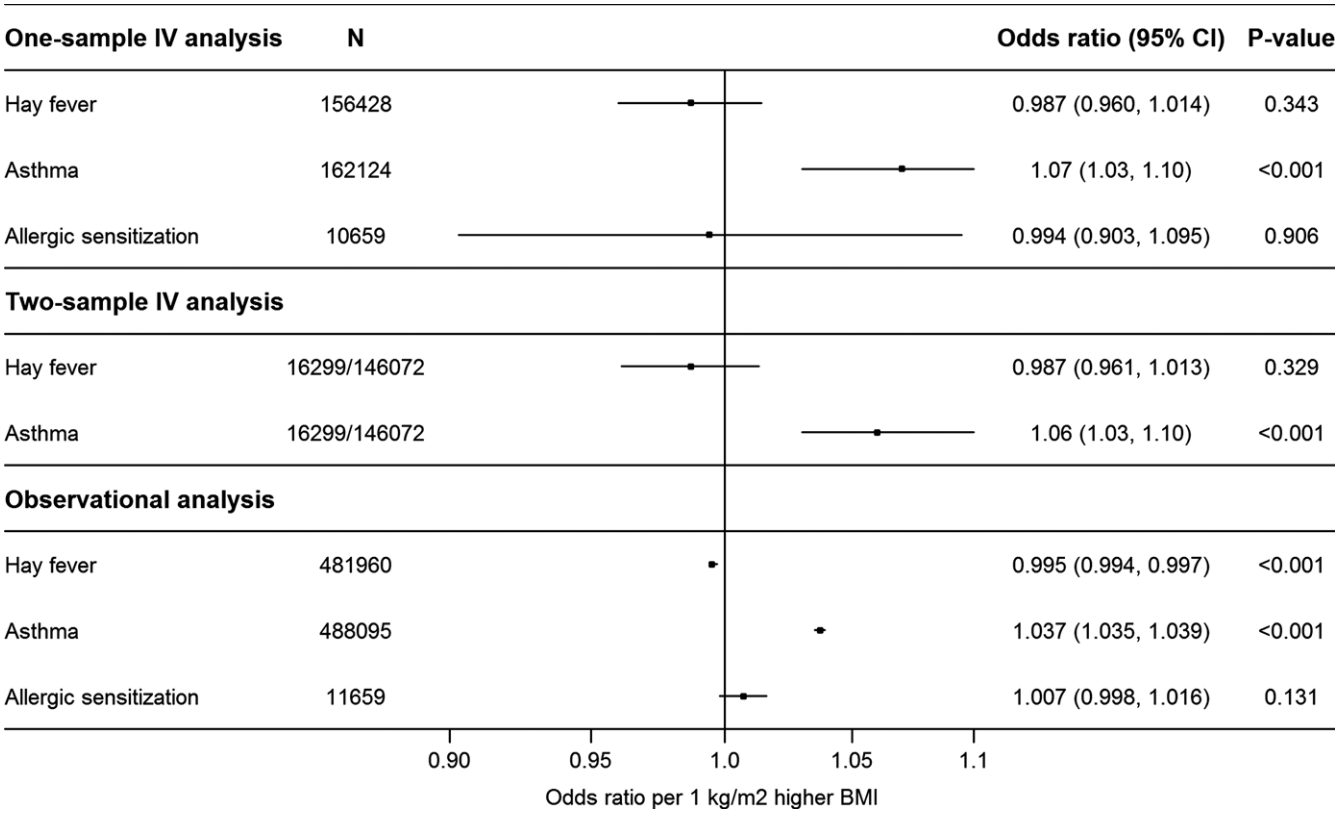

FIGURE 1 One- and two-sample IV-analysis and fixed effects meta-analysis of the observational estimates of age- and sex-adjusted associations between BMI and hay fever, asthma and allergic sensitization, respectively. The numbers of persons included in the two-sample IV-analysis are shown as "number in first stage analysis"/"number in second stage analysis." CI, confidence interval; BMI, body mass index; IV, instrumental variable

−0.012, −0.004, *P*=.0002) and FVC: β=−0.019 (95% CI: −0.023, −0.014, *P*<.0001). Applying a Bonferroni correction (six outcomes, *P*=.05/6=.0083) did not change the statistical significance in the observational analyses. The observational results considering only those from UK Biobank that were included in the MR-analyses below compared to the whole UK Biobank sample showed similar results. The results of observational analyses excluding UK Biobank were largely similar (Figs. S2 and S4).

3.2 | Mendelian randomization analyses

Figure 3 shows the associations of each SNP with the log2-transformed BMI and substantiates their use as valid instruments. Fixed-effect meta-analyses of the age- and sex-adjusted association of the BMI-associated SNP-score and BMI showed significantly higher log2 (BMI): β=0.007 (95% CI: 0.007, 0.008, *P*<.0001) per BMI-increasing allele. However, there was substantial heterogeneity (I^2=95.3%) and random effects meta-analysis showed β=0.007 (95% CI: 0.006, 0.009, *P*<.0001) per BMI-increasing allele. To justify the assumption that the instruments are not associated with unmeasured confounders,[33,42] we assessed the associations between each single-SNP and the available possible confounders age (all *P*>.007 in Kruskal-Wallis test), sex (all *P*>.021 in the chi-square test), smoking status (all *P*>.0009 in the chi-square test) and alcohol status (all *P*>.016 in the chi-square test). No associations were statistically significant at the Bonferroni-adjusted significance level (*P*=.05/(4*26)=.00048), however.

In the primary, one-sample sex- and age-adjusted Mendelian randomization analyses (Figure 1), the SNP-score was positively and significantly associated with asthma: OR=1.009 (95% CI: 1.004, 1.013, *P*<.001, I^2=51.1%) per BMI-increasing allele. The results of MR-analyses excluding UK Biobank were largely similar (Figs. S1 and S3). Using a weighted SNP-score in the UK Biobank alone, we found for asthma: OR=1.068 (95% CI: 1.034, 1.104, *P*<.001) per BMI-increasing allele. There was a high degree of consistency in the predicted effect of each single-SNP on asthma (Fig. S5). IV-analysis yielded an OR=1.07 (95% CI: 1.03, 1.10) of asthma per 1 kg/m^2 higher BMI. There was no clear evidence that the SNP-score was associated with hay fever: OR=0.998 (95% CI: 0.994, 1.002, *P*=.333, I^2=0.0%) per BMI-increasing allele. Likewise, using a weighted SNP-score in the UK Biobank alone, we found for hay fever: OR=0.995 (95% CI: 0.969, 1.022, *P*=.711) per BMI-increasing allele. Alternative definitions of hay fever in UK Biobank data (See Supporting information) showed for those taking medication for hay fever at baseline: OR=1.006 (95% CI: 0.994, 1.018, *P*=.316, N=146 072), with self-reported hay fever as serious illness at baseline: OR=1.000 (95% CI: 0.992, 1.009, *P*=.908, N=146 072), or persons with self-reported hay fever or allergic rhinitis at follow-up in 2015: OR=0.998 (95% CI:

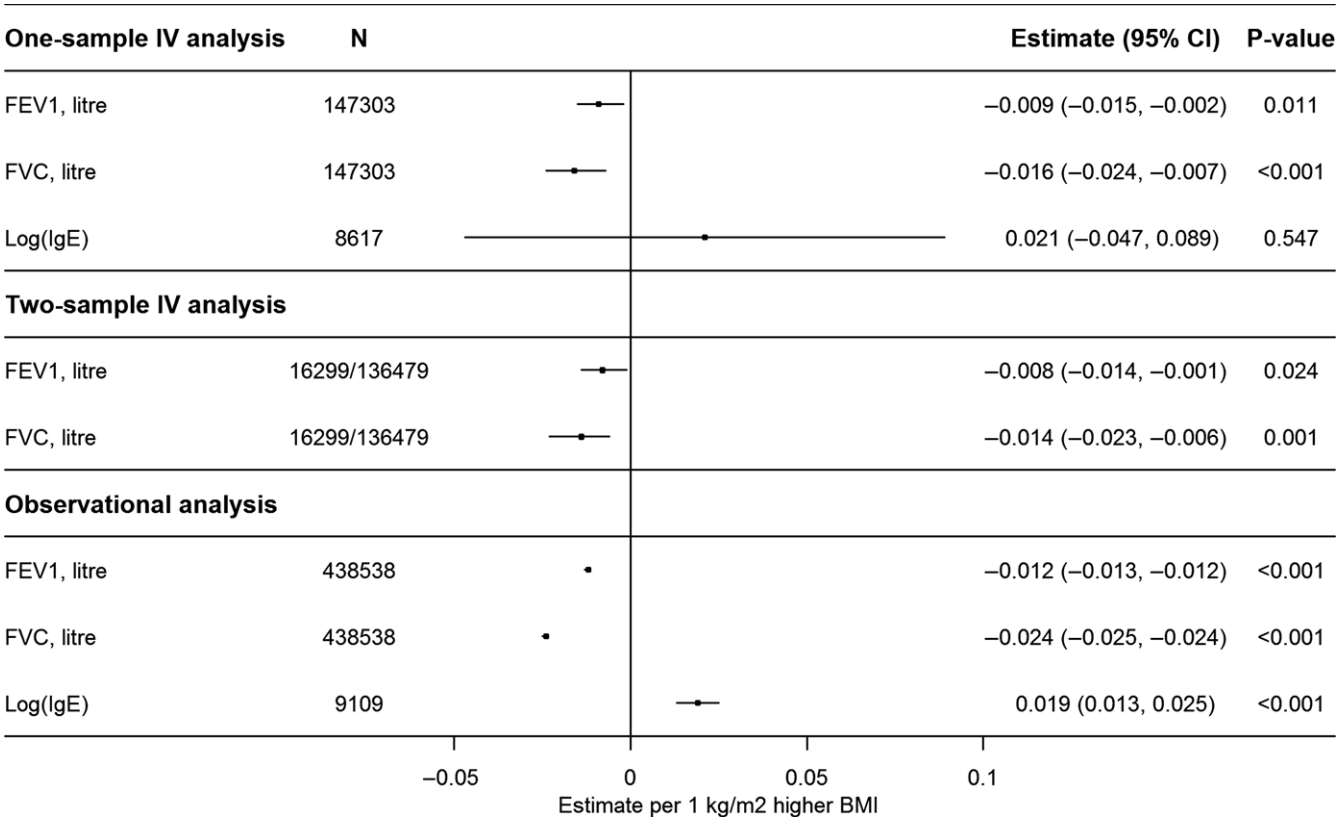

FIGURE 2 One- and two-sample IV-analysis and fixed effects meta-analysis of the observational estimates of BMI (kg/m^2) with FEV1 (litre), FVC (litre) and log(IgE). The IV estimates are generated from unadjusted first and second stage analyses. Units are noted in parentheses. The numbers of persons included in the two-sample IV-analysis are shown as "number in first stage analysis"/"number in second stage analysis." CI, confidence interval; BMI, body mass index; IV, instrumental variable

0.990, 1.006, *P*=.655, N=34 556) for hay fever per BMI-increasing allele compared with the rest, respectively. The SNP-score was non-significantly associated with allergic sensitization with OR=0.999 (95% CI: 0.986, 1.012, *P*=.906, I^2=0.0%) per BMI-increasing allele.

The BMI-increasing SNP-score was inversely associated with FEV1 and FVC with β=−0.0012 L (95% CI: −0.0019, −0.0006, *P*=.011) and β=−0.0022 L (95% CI: −0.0031, −0.0014, *P*<.001), respectively, per BMI-increasing allele in age-, sex- and height-adjusted analyses. Correspondingly, using a weighted SNP-score in the UK Biobank only, we found for FEV1: β=−0.0089 L (95% CI: −0.0155, −0.0023, *P*=.008) and for FVC: β=−0.0164 L (95% CI: −0.0249, −0.0078, *P*<.001) per BMI-increasing allele. IV-analyses showed a 9 mL decrease in FEV1 (95% CI: 2.0-15 mL decrease) and a 16 ml decrease in FVC (95% CI: 7.0-24 mL decrease) per 1 kg/m^2 higher BMI. The heterogeneity was low (all I^2 <26.9%) in the analyses of the SNP-score vs FEV1 and FVC, respectively. Fixed-effects meta-analysis showed a nonsignificantly β=0.003 (95% CI: −0.006, 0.012, *P*=.547) higher log(IgE) per BMI-increasing allele with low heterogeneity (I^2=0.0%). Except for the association between the SNP-score and FEV1, applying a Bonferroni correction (6 outcomes, *P*=.05/6=.0083) did not change the statistical significance in the main IV-analyses. Two-sample Mendelian randomization analyses of hay fever, asthma, FEV1 and FVC supported the one-sample results (Figure 1-2). We found little evidence of pleiotropy for the BMI-associated SNPs on asthma, as indicated by the MR Egger intercept test (*P*=.069) and the Egger regression analysis showed an odds ratio of asthma: OR=1.09 (95% CI: 1.03, 1.15, *P*=.002) per 1 kg/m^2 higher BMI.[43] Likewise, median regression yielded an odds ratio of asthma: OR=1.05 (95% CI: 1.01, 1.09, *P*=.007) per 1 kg/m^2 higher BMI.

Analyses excluding the three SNPs with signs of Hardy-Weinberg disequilibrium in the UK Biobank Study showed for hay fever: OR=0.999 (95% CI: 0.995, 1.003, *P*=.544), asthma: OR=1.011 (95% CI: 1.006, 1.016, *P*=.00003) and FEV1: β=−0.001 (95% CI: −0.002, −0.0004, *P*=.004) and FVC: β=−0.003 (95% CI: −0.004, −0.001, *P*=.0001) litre per BMI-increasing allele. In additional analyses of the association between the genetic risk score and hay fever, we performed the analyses with and without the SHIP TREND Study. The estimate and confidence intervals were equal to the third decimal place. Also, we found that persons with both asthma and hay fever ("atopic" asthma) vs persons with neither asthma nor hay fever had largely the same odds ratio per BMI-increasing allele as in the primary analyses where we compared those with asthma to those without asthma regardless of hay fever status. In comparison, persons who had asthma but not hay fever ("nonatopic" asthma) vs persons with neither asthma nor hay fever had a slightly lower odds ratio per BMI-increasing allele that was not statistically significant.

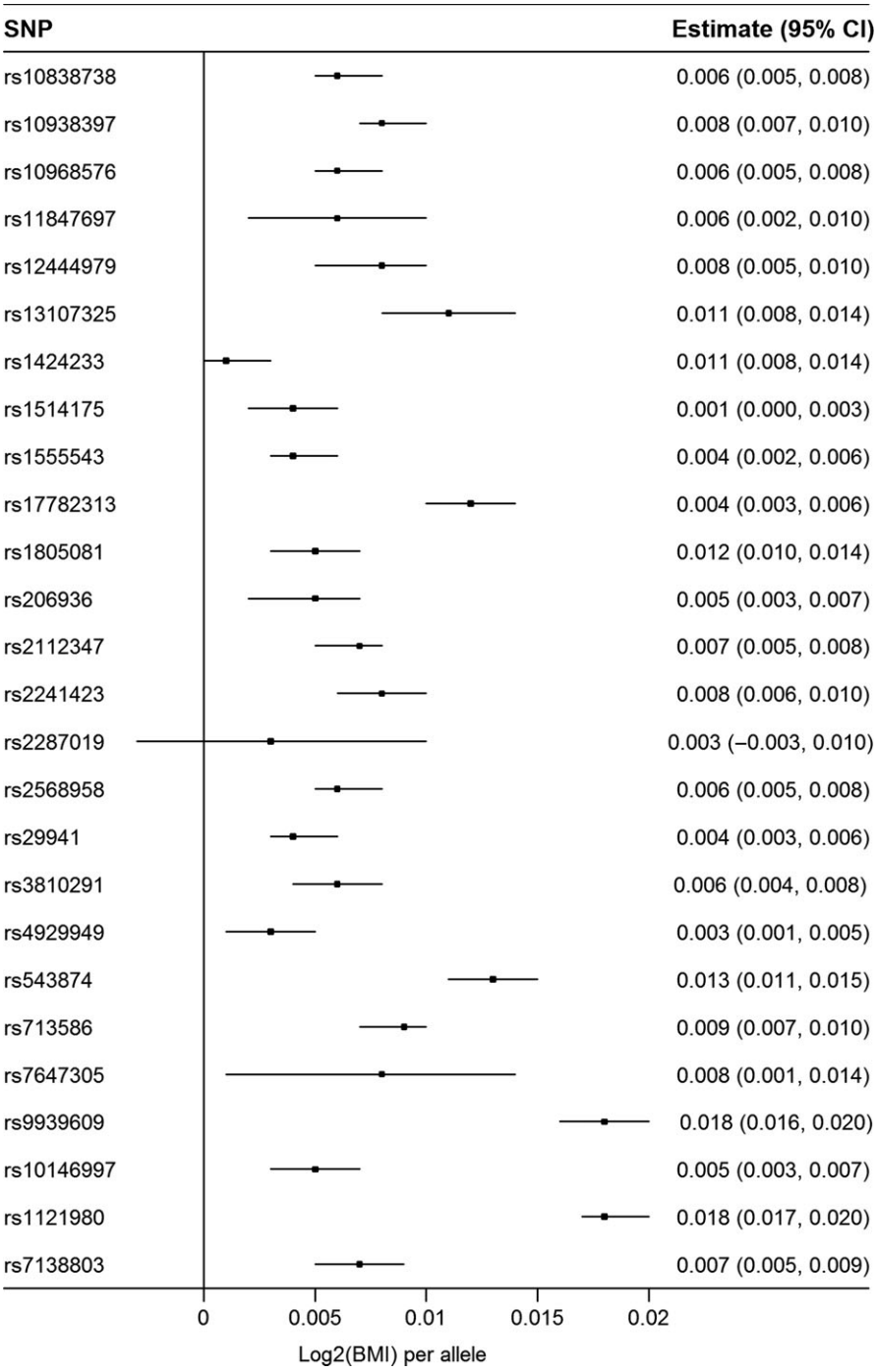

FIGURE 3 Age- and sex-adjusted associations of each BMI-associated SNP and the log2-transformed BMI

4 | DISCUSSION

In a Mendelian randomization meta-analysis, we found that a genetically determined higher BMI was associated with a significantly higher prevalence of asthma and lower lung function (both FEV1 and FVC), but not with hay fever and allergy biomarkers. The observed positive association between BMI and asthma is in line with the results from the majority of previous studies (Table 3),[44-53] including a Mendelian Randomization study of close to 5000 children where a higher BMI increased the risk of asthma in mid-childhood.[13] A review by Baumann et al.[54] concluded that the association between obesity and asthma was particularly seen for non-atopic asthma. However, our analysis in the UK Biobank sample using presence/absence of hay fever to define atopic/nonatopic asthma could not fully corroborate that. A number of studies found no statistically significant associations between BMI and asthma.[55-57]

The observed negative association between BMI and lung function is in line with a study by Ciprandi et al.[58] comprising 268

TABLE 3 Observational studies of the association between BMI and asthma (incl. two meta-analyses)

Study characteristics	Exposure[a]	Effect size[b] (95% CI)	Outcome
Rönmark, 2016[49] 1172 adults and adolescent, 16-75 y, Sweden, cross-sectional	BMI normal if 20-25 kg/m^2, overweight 25-30 kg/m^2, obese >30 kg/m^2	Overweight: OR=1.04 (0.65-1.67) Obese: OR=1.95 (1.13-3.36)	Self-reported current asthma
Sybilski, 2015[51] 2133 adults, 20-44 y, Poland, cross-sectional	Normal weight: BMI=18.5-24.9 kg/m^2 Overweight: BMI=25.0-29.9 kg/m^2 Obese: BMI≥30.0 kg/m^2	Females: Overweight: OR=0.96 (0.58, 1.61). Obese: OR=1.50 (0.76, 2.95) Males: Overweight: OR=1.05 (0.64, 1.72). Obese: OR=0.54 (0.22, 1.31)	Clinically diagnosed asthma
Konno, 2012[52] 22819 adults 20-79 y, cross-sectional, Japan	Self-reported height and weight BMI: normal 18.50-24.99, overweight 25.00-29.99, obese ≥30.00 kg/m^2	20-44 y: Overweight: OR=1.05 (0.63, 1.76). Obese: OR=2.01 (0.98, 4.10) 45-79 years: Overweight: OR=1.44 (1.04, 1.99). Obese: OR=2.31 (1.15, 4.64)	Self-reported asthma without rhinitis
Yao, 2011[53] 5351 children aged 4-18 y, cross-sectional, Taiwan	Obesity and overweight defined according to the age- and gender-specific cut-off values	Overweight: OR=1.19 (0.95, 1.49) Obese: OR=1.52 (1.13, 2.06)	Self-reported asthma
Luo, 2013[55] 266 atopics and 532 matched healthy controls, >18 y, cross-sectional, China	BMI≥ 28.0 kg/m^2 were considered as obese	Obese: OR[c]=7.1 (0.8, 62.4)	Doctor-diagnosed atopic asthma
Kreissl, 2014[56] 1794 adolescents, 9-11 y (16-18 y at follow-up), longitudinal, Germany	Overweight: BMI in at least the 90th percentile according to German age- and sex-specific reference values	Change from normal weight to overweight during follow-up: OR=1.4 (0.8, 2.3)	Incident asthma
Katebi, 2015[57] 3466 adolescents, 14-16 y, cross-sectional, UK	Self-reported BMI	No association (no estimate available)	Self-reported wheezing in last 12 months
Visness 2010[47] 16074 children and adolescents, 2-19 y, cross-sectional, United States	Overweight: ≥ 85th percentile of BMI-for-age. Obese ≥ 95th percentile of BMI-for-age	Overweight: OR=1.32 (1.08, 1.60) Obese: OR=1.68 (1.33, 2.12)	Self-reported current asthma
Beuther, 2004[1] 333102 adults, meta-analysis, 7 longitudinal studies, United States, Canada and Europe	Normal weight (BMI <25), overweight (BMI: 25-29.9) and obese (BMI ≥30)	Overweight: OR=1.38 (1.17, 1.62) Obese: OR=1.92 (1.43, 2.59)	Incident self-reported asthma
Fra Flaherman 2006[45] ≈40000 persons, 0-31 y, meta-analysis, 12 studies, pro- or retrospective, Europe, New Zeeland, United States	High body weight: BMI ≥85th centile, ponderal index ≥2.5 g/cm^3 or ≥27 kg/m^3 and birthweight ≥3.8 kg	High birthweight: pooled RR=1.2 (1.1, 1.3). High body weight in childhood: pooled RR=1.5 (1.2, 1.8)	Incident asthma

BMI, body mass index; CI, confidence interval; OR, odds ratio; RR, risk ratio; y, years.
[a]Measured anthropometrics and calculated BMI unless otherwise stated.
[b]Compared to persons with normal BMI.
[c]For cases vs controls.

individuals who found that lung function was significantly impaired in overweight and obese asthmatic patients, for example, overweight patients, had double (OR=1.89) and obese patients had triple the risk (OR=3.17) of a pathological FEV1 compared to normal weight patients. Fenger et al.[2] found in a study of 2308 adults that increasing adiposity was associated with decreasing lung function over a five-year period in longitudinal study of 2308 adults. A one standard deviation increase in BMI corresponded to a −78.5 mL and −113.6 mL five-year change in FEV1 and FVC, respectively, in men, and a −25.5 mL and −32.6 mL five-year change in FEV1 and FVC, in women, respectively.

The results from previous studies on BMI and hay fever are inconsistent (Table 4). The observed lack of association in the current study is in line with the conclusions from two research studies of 3047 adults and 3466 adolescents, respectively,[57,59] and a review including 50 086 individuals.[54] However, several studies have found

TABLE 4 Observational studies of the association between BMI and hay fever

First author	Characteristics	Findings	Effect
Abramson[59]	3047 adults, cross-sectional, Switzerland, 2016	No associations between obesity and allergic- or nonallergic rhinitis	0
Katebi[57]	3466 adolescents, 14-16 y, cross-sectional, UK, 2015	No associations between self-reported BMI and symptoms of hay fever	0
Baumann[54]	34 studies, review, 2013	No clear association between obesity and prevalent allergic rhinitis	0
Han[60]	2358 children, 6-17 y, cross-sectional, USA, 2016	Central obesity was associated with lower odds of allergic rhinitis	–
Kimura[61]	4076 nonsmokers, 18-25 y, cross-sectional, Japan, 2015	Allergic rhinitis inversely associated with BMI	–
Ciprandi[58]	286 asthmatics, cross-sectional, 2014	Lower risk of allergic rhinitis in overweight and obese	–
Konno[52]	22819 adults, 20-79 y, cross-sectional, Japan, 2012	Obesity inversely associated with rhinitis without asthma, particularly in the 20- to 44-year-olds	–
Sybilski[51]	10 000 adults, 20-44 y, cross-sectional, Poland, 2015	Overweight/obesity inversely associated with allergic rhinitis in men	–
Ronmark[49]	1172 adults, 16-75 y, cross-sectional, Sweden, 2016	Obesity a risk factor for rhinitis	+
Ciprandi[62]	155 allergic rhinitis patients, 155 controls, cross-sectional, 2013	BMI significantly higher in allergic rhinitis patients than controls	+
Kreissl[56]	1794 adolescents, 16-18 y, prospective, Germany, 2014	BMI positively associated with incident rhinitis	+
Bhattacharyya[63]	46 617 adults, cross-sectional, USA, 2013	BMI positively associated with allergic rhinitis	+
Luo[55]	266 atopics, 532 controls, cross-sectional, China, 2013	Obesity associated with atopic rhinitis	+
Han[60]	4906 adults, ≥18 y, cross-sectional, USA, 2016	Obesity positively associated with nonallergic (not allergic) rhinitis, particularly men	+

BMI, body mass index; y, years.

both inverse[51,52,58,60,61] and positive associations between BMI/overweight/obesity and hay fever.[49,55,56,60,62,63]

Likewise, previous studies examining the association between obesity and allergic sensitization in adults have shown conflicting results.[44] There are studies supporting a positive association[4,64,65] and studies reporting no or an inverse association between BMI and allergic sensitization.[66-68] The observed nonsignificantly higher odds ratio of allergic sensitization for a higher BMI is in line with a study by Sybilski et al.[51] who in almost 10 000 adults found that obesity and overweight were not associated with the frequency of sensitization to aeroallergens. Likewise, Yao et al.[53] found a statistically nonsignificant higher prevalence of allergic sensitization in 5351 Taiwanese children. Somewhat in contrast, a study by Byberg et al.[48] involving 617 study participants found BMI in early childhood to be positively associated with atopic sensitization in later childhood. Also, in a study of 139 individuals, Lokaj-Berisha et al.[50] found high BMI to be associated with atopy.

Strengths of the current study include the fact that the SNPs were preselected from GWAS studies of populations different from our own but of the same ethnicity. As most of the SNPs had small individual effects, we constructed a genetic risk score where the multidimensional genetic data were collapsed into one variable. Risk scores—as opposed to the individual variants—may be stronger instruments.[69] Each SNP in the SNP-score had to fulfil the requirements for an IV in order for the score to be a valid instrument.[69] All but two of the SNPs had F-values above 10 in the UK Biobank data, and the F-value was 2000 for the SNP-score.

Limitations of the study include the low power in the analyses of allergic sensitization and serum total IgE compared with the power in the analyses of asthma, hay fever and lung function. The hay fever variable in the UK Biobank included eczema which is a less specific variable for hay fever than most of the other studies. However, we assessed three additional hay fever variables from the UK Biobank with similar results which indicate that the misclassification did not seriously bias our results. The main weaknesses of the three additional hay fever variables were the fact that the first was measured at follow-up in 2015 in a subgroup only; the second only included participants who would classify their hay fever as a serious illness or disability; and the third additional hay fever variable was based on self-reported medication rather than doctor-diagnosed hay

fever. In addition, the definition of hay fever in the SHIP TREND Study differs. However, the estimate and confidence intervals of the association between the genetic risk score and hay fever were equal to the third decimal place which means that this potential misclassification did not seriously bias our results.

Causal inference may be distorted by a number of violators of the Mendelian randomization assumptions, for example, pleiotropy where the genetic marker has diverse biological functions. This assumption may be more plausible for specific proteins or serum markers than for a general phenotype such as BMI. However, MR Egger and median regressions showed little sign of pleiotropy in the BMI-associated SNPs and asthma. There was also a high degree of consistency in the predicted effect of each single-SNP on asthma (Fig. S5). Also, we found little evidence of associations between the included SNPs and the possible confounders, age, sex, smoking and alcohol intake in the UK Biobank data. There were no obvious trends or consistencies regarding the SNPs with signs of Hardy-Weinberg disequilibrium, neither relating to the SNPs nor the studies, and we consider these chance findings. This was corroborated by analyses excluding the three SNPs in Hardy-Weinberg disequilibrium in the UK Biobank Study as listed in the results. Weak instrument bias is a particular concern in small studies when using genetic variants that explain only little variation in the risk factor.[70] Weak instrument bias can be introduced in one-sample MR studies because the associations of the SNPs with the risk factor and outcome are correlated. The causal estimate will be biased in the direction of the observational association contrary to a two-sample Mendelian randomization analysis where any weak instrument bias is in the direction of the null. Even so, in support of using an overlapping sample in the current study, the SNP-score was constructed from SNPs not discovered in the included studies, the SNP-score did not use (internal) weights, and it had a high F-value. The current study included the very large UK Biobank Study that had acceptable F-values for the large majority of the SNPs. The estimates in UK Biobank data were similar to the meta-analysis estimates for asthma, hay fever and lung function. In addition, results from two-sample Mendelian randomization analyses of hay fever, asthma, FEV1 and FVC were almost identical to the one-sample analyses which means that weak instrument bias does not seriously bias our results. The results from using a weighted genetic risk score supported our findings from using a simple genetic risk score.

In conclusion, we found that genetically determined higher BMI was associated with a higher prevalence of asthma and lower lung function. Taken together with the traditional observational results and the existing evidence, the results are supportive of a positive causal relation between BMI and asthma and an inverse relation with FEV1 and FVC.

ACKNOWLEDGMENTS

Tea Skaaby was supported by a grant from the Lundbeck Foundation (Grant number R165-2013-15410 and R219-2016-471), the Harboe Foundation (Grant number 16152), the A.P. Møller Foundation for the Advancement of Medical Science (Grant number 15-363), Aase and Einar Danielson's Foundation (Grant number 10-001490) and the Weimann's grant. This research has been conducted using the UK Biobank Resource. The Novo Nordisk Foundation Center for Basic Metabolic Research is an independent Research Center at the University of Copenhagen partially funded by an unrestricted donation from the Novo Nordisk Foundation (www.metabol.ku.dk).

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of the study or the collection and processing of samples. TS conducted data analyses and wrote the initial manuscript. All authors were involved in critical appraisal and revision of the manuscript, and all authors approved the final version.

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SUPPORTING INFORMATION

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How to cite this article: Skaaby T, Taylor AE, Thuesen BH, et al. Estimating the causal effect of body mass index on hay fever, asthma and lung function using Mendelian randomization. *Allergy*. 2018;73:153–164. https://doi.org/10.1111/all.13242