

Supplementary

Obese individuals experience wheezing without asthma but not asthma without wheezing. A Mendelian randomization study of 85,437 adults from the Copenhagen General Population Study

Yunus Çolak, MD; Shoaib Afzal, MD, PhD; Peter Lange, MD, DMSc, and Børge G. Nordestgaard, MD, DMSc

Table S1. Potential confounders in the Copenhagen General Population Study according to the completeness of data.

	Complete	Incomplete	Imputed	Total
Age	85,437	0	0	85,437
Sex	85,437	0	0	85,437
Familial predisposition for asthma	85,437	0	0	85,437
Smoking status	85,168	269	269	85,437
Cumulative tobacco consumption (pack-years)	83,384	2,053	2,053	85,437
Education	85,182	255	255	85,437
Annual household income	84,389	1,048	1,048	85,437
Physical activity in leisure-time	84,761	676	676	85,437
Physical activity during work	84,676	761	761	85,437
Fast-food intake	85,437	0	0	85,437
Fruit intake	84,864	573	573	85,437
Vegetable intake	84,805	632	632	85,437

Table S2. Characteristics of participants in the Copenhagen General Population Study according to wheezing and asthma at examination.

	Wheezing			Any asthma		
	Yes (n=14,500)	No (n=70,937)	P*	Yes (n=5,406)	No (n=80,031)	P*
Age (years)	57 (48-67)	58 (48-67)	$1 \cdot 10^{-6}$	55 (46-65)	58 (48-67)	$2 \cdot 10^{-29}$
Men (%)	46	45	0.27	39	46	$9 \cdot 10^{-19}$
Familial predisposition for asthma (%)	26	16	$3 \cdot 10^{-202}$	37	16	$<1 \cdot 10^{-300}$
Ever smokers (%)	73	55	$<1 \cdot 10^{-300}$	52	59	$1 \cdot 10^{-21}$
Cumulative tobacco consumption (pack years)†	24 (11-39)	15 (5-29)	$<1 \cdot 10^{-300}$	14 (5-28)	16 (6-30)	$2 \cdot 10^{-9}$
Low level of education (%)	33	24	$2 \cdot 10^{-104}$	24	26	0.004
Low household income (%)	19	12	$6 \cdot 10^{-129}$	14	13	0.13
Low physical activity in leisure-time (%)	11	5	$7 \cdot 10^{-128}$	7	6	$3 \cdot 10^{-4}$
Low physical activity during work (%)	25	31	$5 \cdot 10^{-50}$	30	30	0.59
Low physical activity in leisure-time and during work (%)	32	27	$9 \cdot 10^{-32}$	28	28	0.91
Weekly fast-food intake (%)	29	24	$1 \cdot 10^{-33}$	26	25	0.008
Low intake of fruits (%)	37	27	$4 \cdot 10^{-139}$	27	28	0.11
Low intake of vegetables (%)	39	29	$6 \cdot 10^{-123}$	29	31	0.002
Low intake of fruits and vegetables (%)	23	15	$6 \cdot 10^{-133}$	15	16	0.02

Data are summarized as median with the 25th and 75th percentiles, or percent.

*P-values obtained with the Wilcoxon signed rank-sum test for continuous data and Pearson χ^2 -test for categorical data.

†Only current and former smokers were included.

Table S3. Characteristics of participants in the Copenhagen General Population Study according to allele score at examination.

	Allele score				P for trend*
	0-4 (n=23,937)	5 (n=23,351)	6 (n=21,338)	7-10 (n=16,811)	
Age (years)	58 (48-67)	58 (48-67)	58 (48-67)	58 (48-67)	0.98
Men (%)	45	45	45	46	0.91
Familial predisposition for asthma (%)	17	18	18	18	0.004‡
Ever smokers (%)	58	58	59	59	0.004‡
Cumulative tobacco consumption (pack years)†	16 (6-30)	16 (6-30)	16 (6-30)	17 (7-31)	0.03‡
Low level of education (%)	26	26	26	27	0.09
Low household income (%)	13	13	13	14	0.10
Low physical activity in leisure-time (%)	6	6	6	7	0.34
Low physical activity during work (%)	30	30	30	29	0.14
Low physical activity in leisure-time and during work (%)	29	28	28	28	0.74
Weekly fast-food intake (%)	24	25	25	25	0.95
Low intake of fruits (%)	29	28	28	28	0.08
Low intake of vegetables (%)	31	30	31	30	0.07
Low intake of fruits and vegetables (%)	17	16	17	16	0.03‡

Data are summarized as median with the 25th and 75th percentiles, or percent.

*P-values were calculated using Cuzicks non-parametric trend test across ordered groups.

†Only current and former smokers were included.

‡P-value non-significant when adjusted for number of individual trend analyses according to the Bonferroni method.

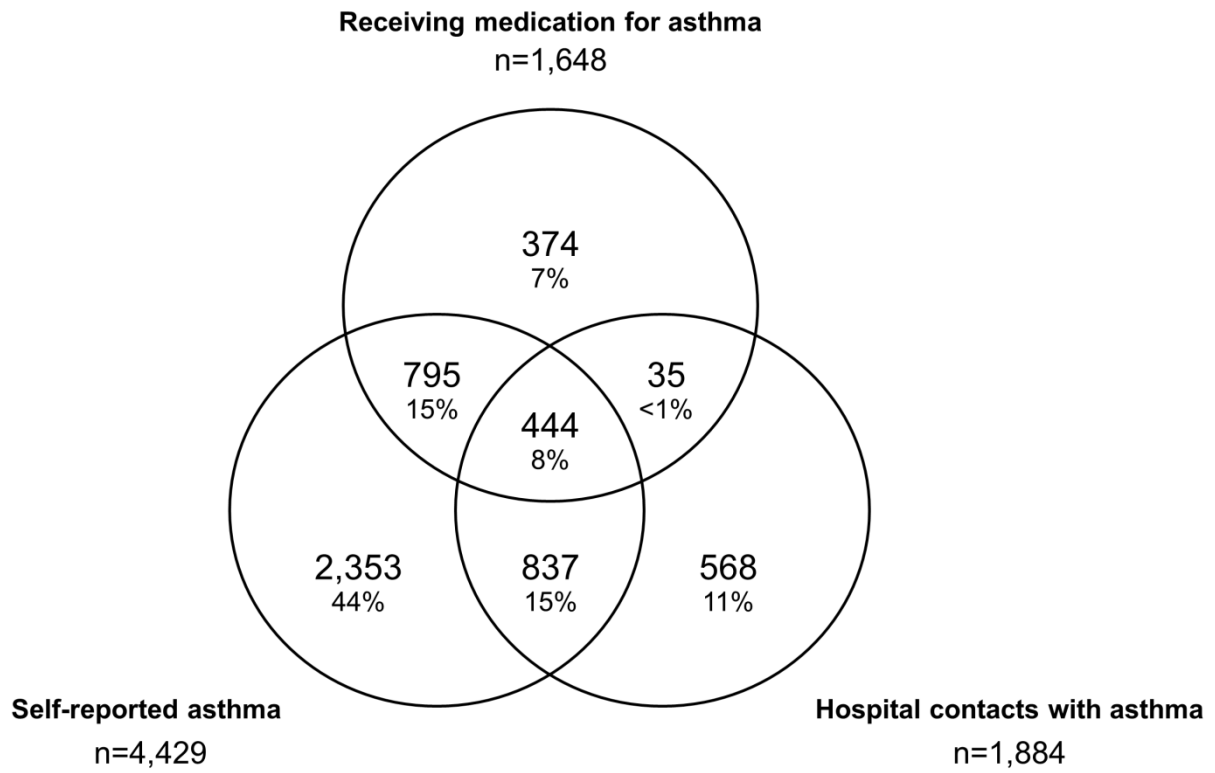


Figure S1. Distribution of participants according to the different asthma definitions.

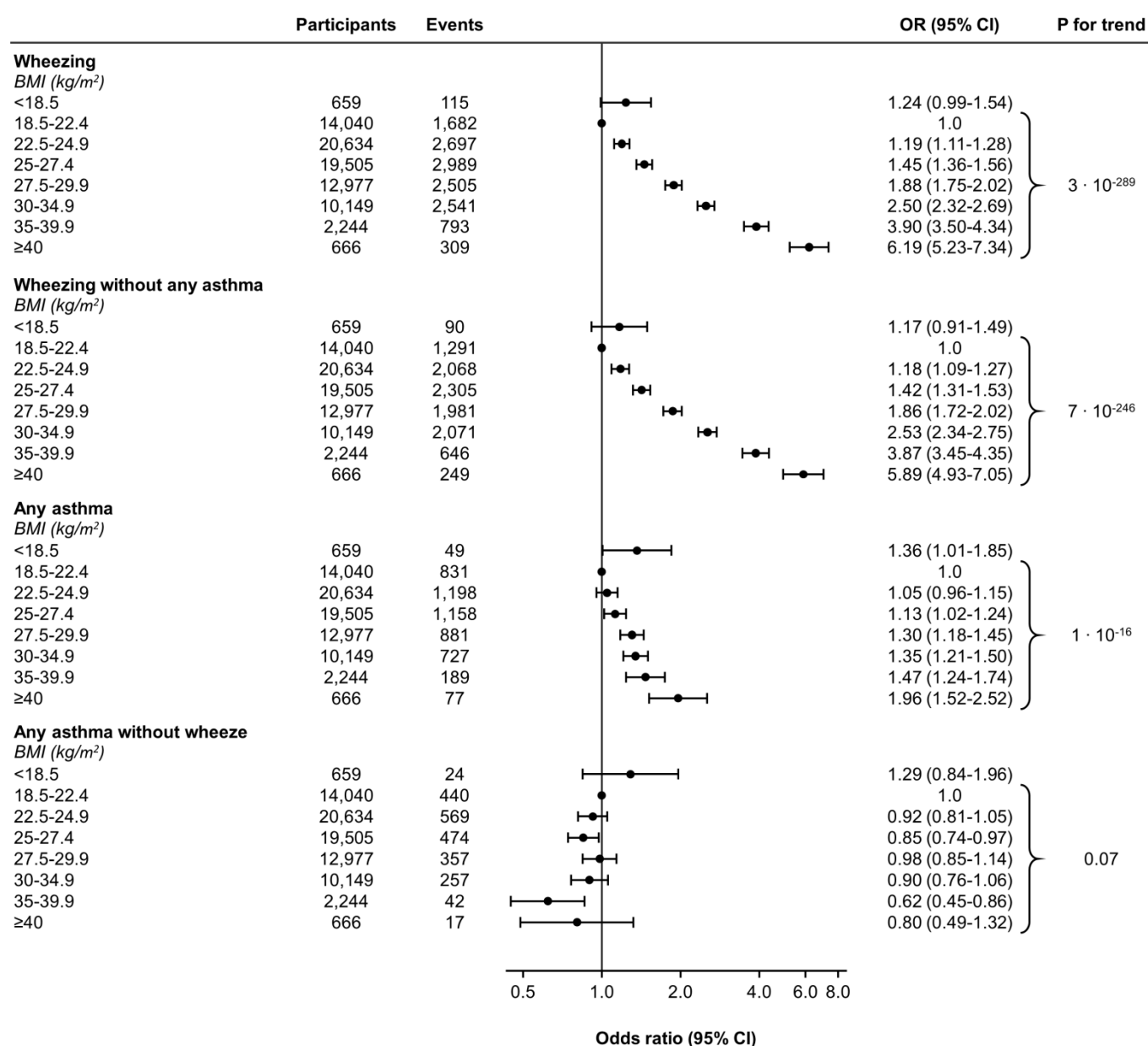


Figure S2. Association of BMI with wheezing and asthma without using imputation. Depicted results are from complete case analyses as opposed to Figure 2. Thus, individuals with missing values were excluded from the analyses. Odds ratios were multivariable adjusted for age, sex, familial predisposition for asthma, smoking status, cumulative tobacco consumption, education, annual household income, physical activity in leisure-time and during work, and dietary intakes, including fast-food, fruits, and vegetables. P-values for trend were across ordered groups excluding participants with BMI <18.5 kg/m².

BMI = body mass index; CI = confidence interval; OR = odds ratio.

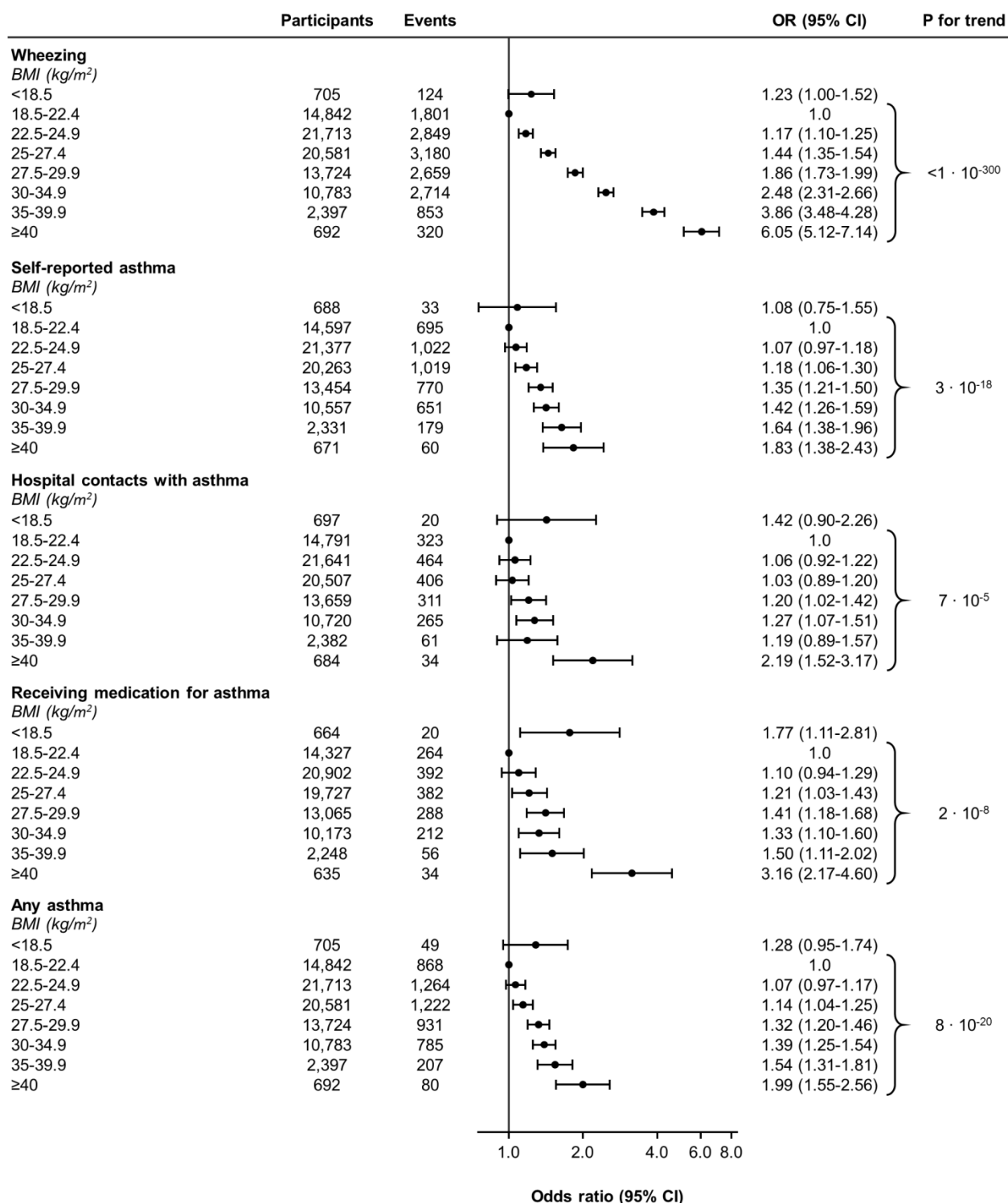


Figure S3. Association of BMI with wheezing and different asthma definitions. Odds ratios were multivariable adjusted for age, sex, familial predisposition for asthma, smoking status, cumulative tobacco consumption, education, annual household income, physical activity in leisure-time and during work, and dietary intakes, including fast-food, fruits, and vegetables. P-values for trend were across ordered groups excluding participants with BMI <18.5 kg/m². Number of individuals for the different outcomes differs slightly due to availability of data. BMI = body mass index; CI = confidence interval; OR = odds ratio.

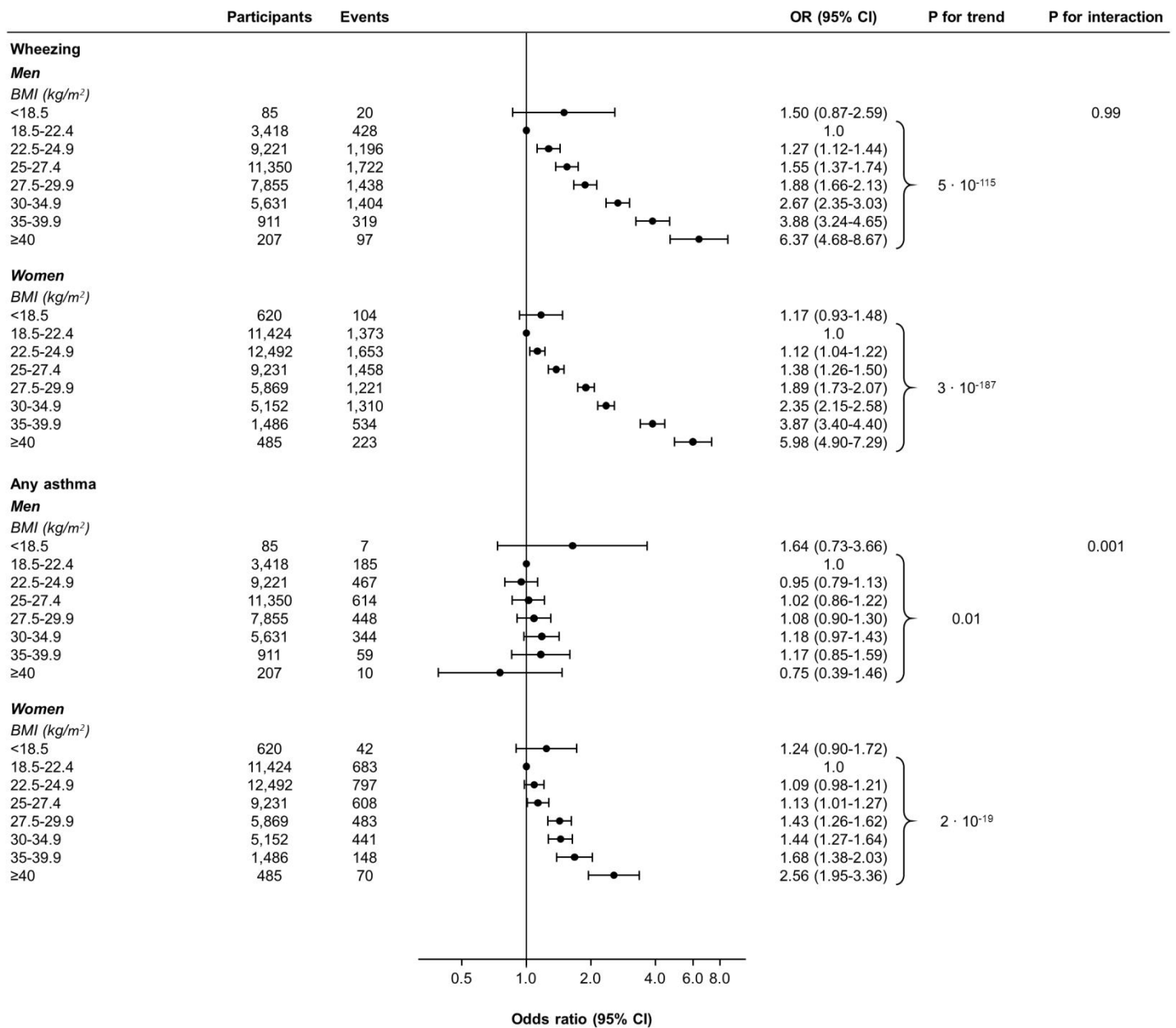


Figure S4. Association of BMI with wheezing and asthma according to sex. Odds ratios were multivariable adjusted for age, familial predisposition for asthma, smoking status, cumulative tobacco consumption, education, annual household income, physical activity in leisure-time and during work, and dietary intakes, including fast-food, fruits, and vegetables. P-values for trend were across ordered groups excluding participants with BMI <18.5 kg/m². P-values for interaction of sex and BMI on risk of wheezing and any asthma were assessed using the Wald test. BMI = body mass index; CI = confidence interval; OR = odds ratio.

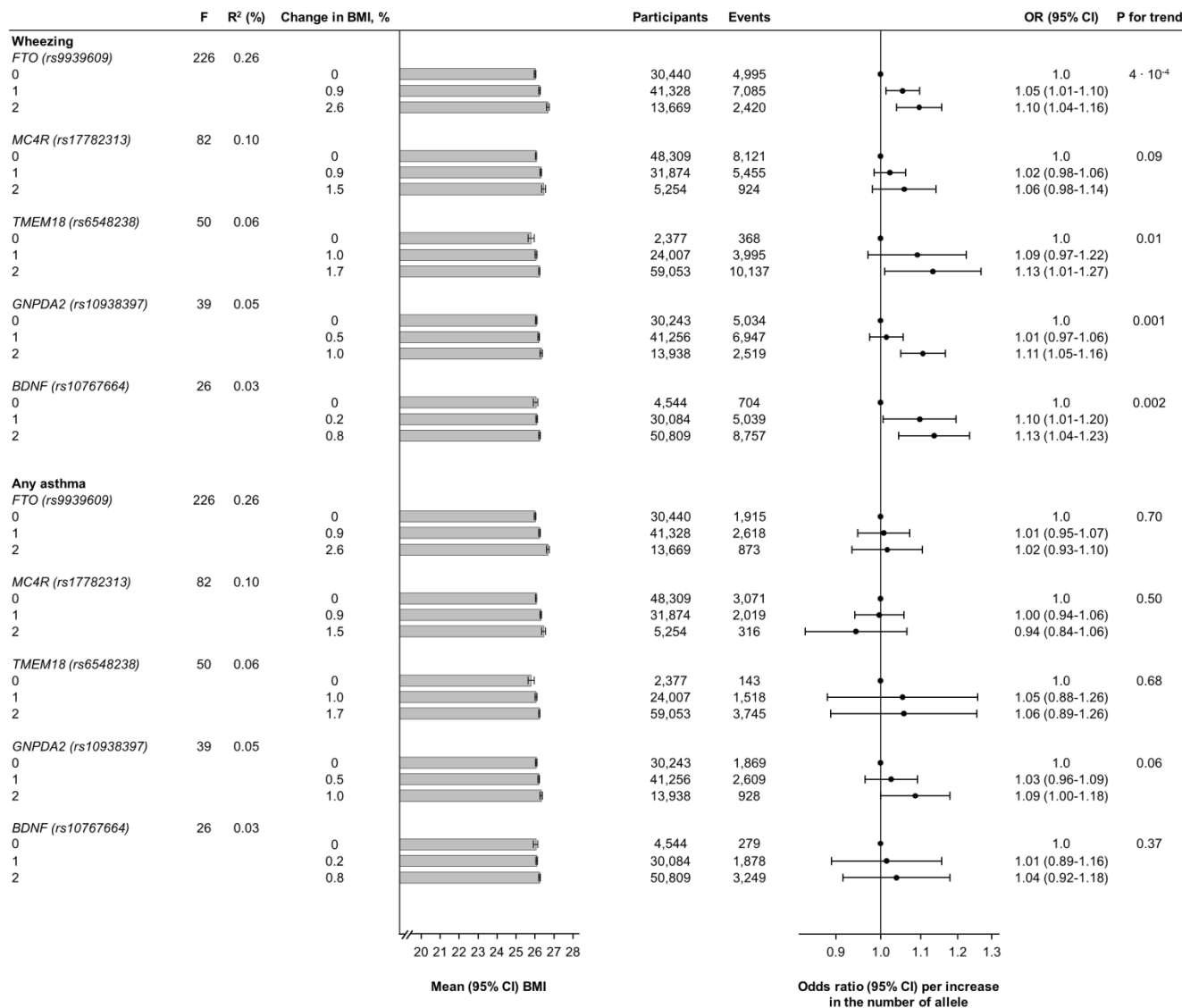


Figure S5. Association of individual genotypes with BMI and wheezing and asthma. Association between genotypes and BMI was adjusted for age and sex. Odds ratios were adjusted for age and sex.

BMI = body mass index; CI = confidence interval; F = statistical strength of the genotype as an instrument for BMI; OR = odds ratio; R² = measure of explained variation in BMI by the genotype.

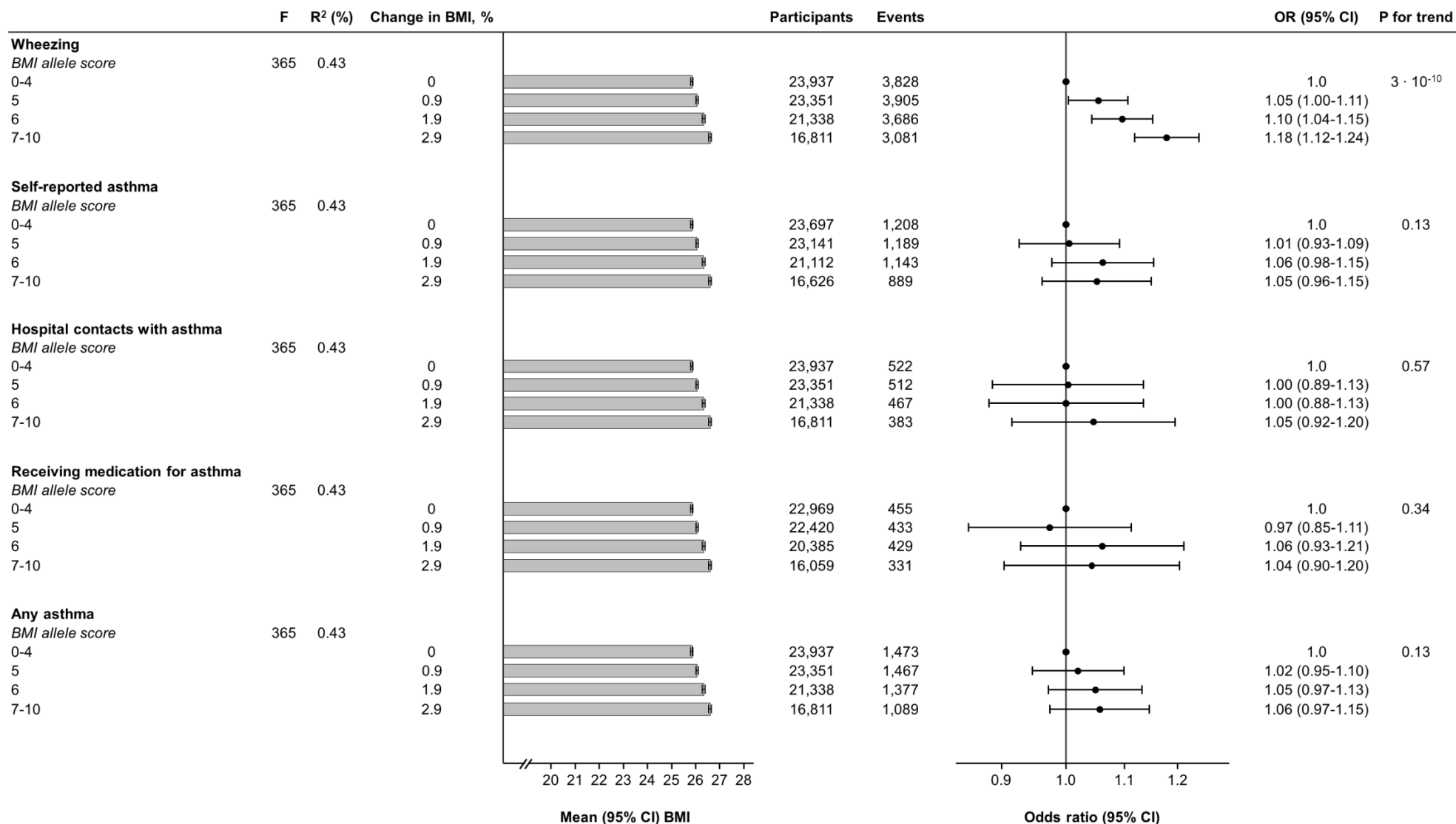


Figure S6. Association of BMI allele score with BMI and with wheezing and different asthma definitions. BMI allele score was created using the genotypes *FTO* (rs9939609), *MC4R* (rs17782313), *TMEM18* (rs6548238), *GNPDA2* (rs10938397), and *BDNF* (rs10767664). Association between BMI allele score and BMI was adjusted for age and sex. Odds ratios were adjusted for age and sex. Number of individuals for the different outcomes differs slightly due to availability of data. BMI = body mass index; CI = confidence interval; F = statistical strength of BMI allele score as an instrument for BMI; OR = odds ratio; R² = measure of explained variation in BMI by BMI allele score.

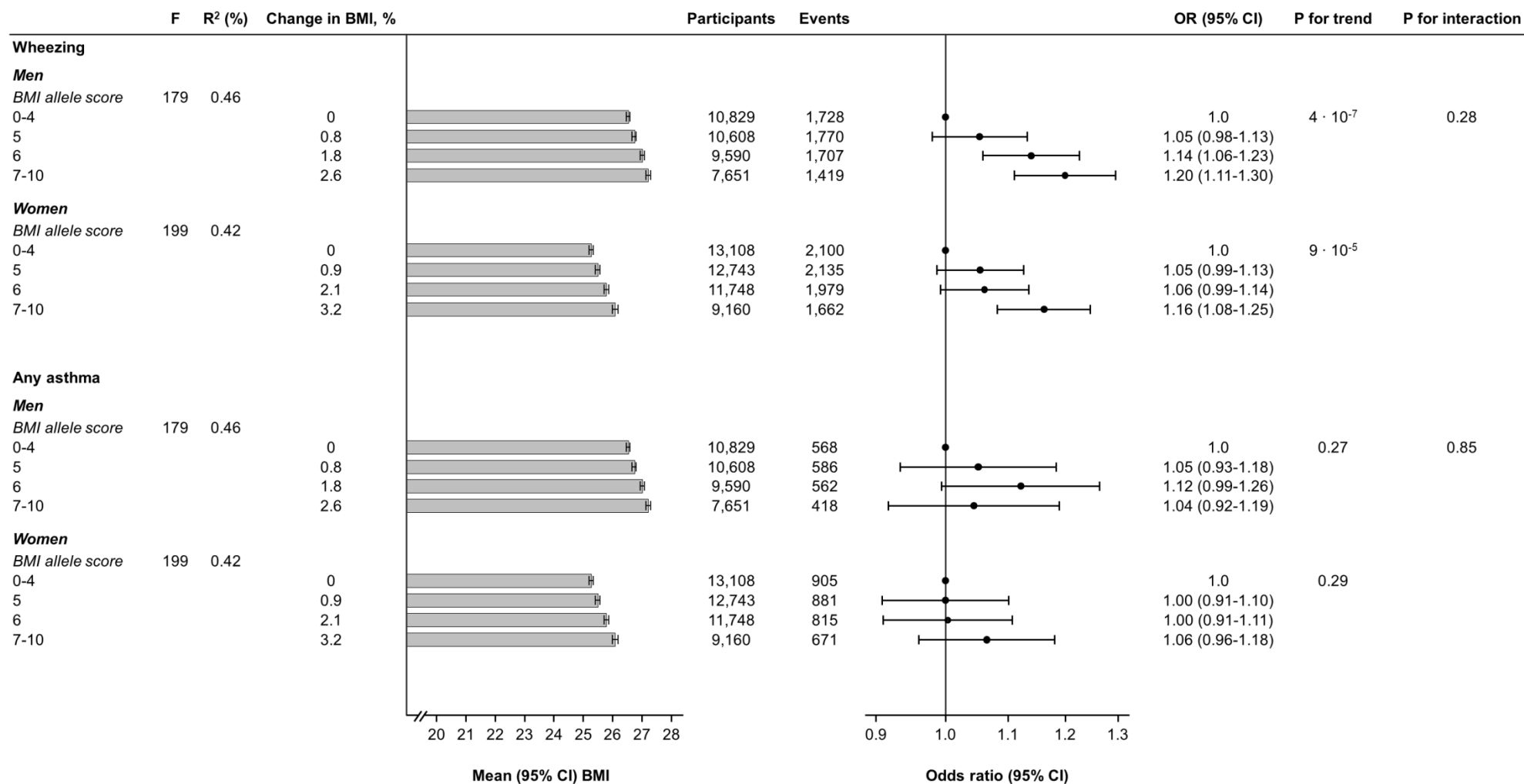


Figure S7. Association of BMI allele score with BMI and with wheezing and asthma according to sex. BMI allele score was created using the genotypes: *FTO* (rs9939609), *MC4R* (rs17782313), *TMEM18* (rs6548238), *GNPDA2* (rs10938397), and *BDNF* (rs10767664). Association between BMI allele score and BMI was adjusted for age and sex. Odds ratios were adjusted for age. P-values for interaction of sex and BMI allele score on risk of wheezing and any asthma were assessed using the Wald test. BMI = body mass index; CI = confidence interval; F = statistical strength of BMI allele score as an instrument for BMI; OR = odds ratio; R² = measure of explained variation in BMI by BMI allele score.

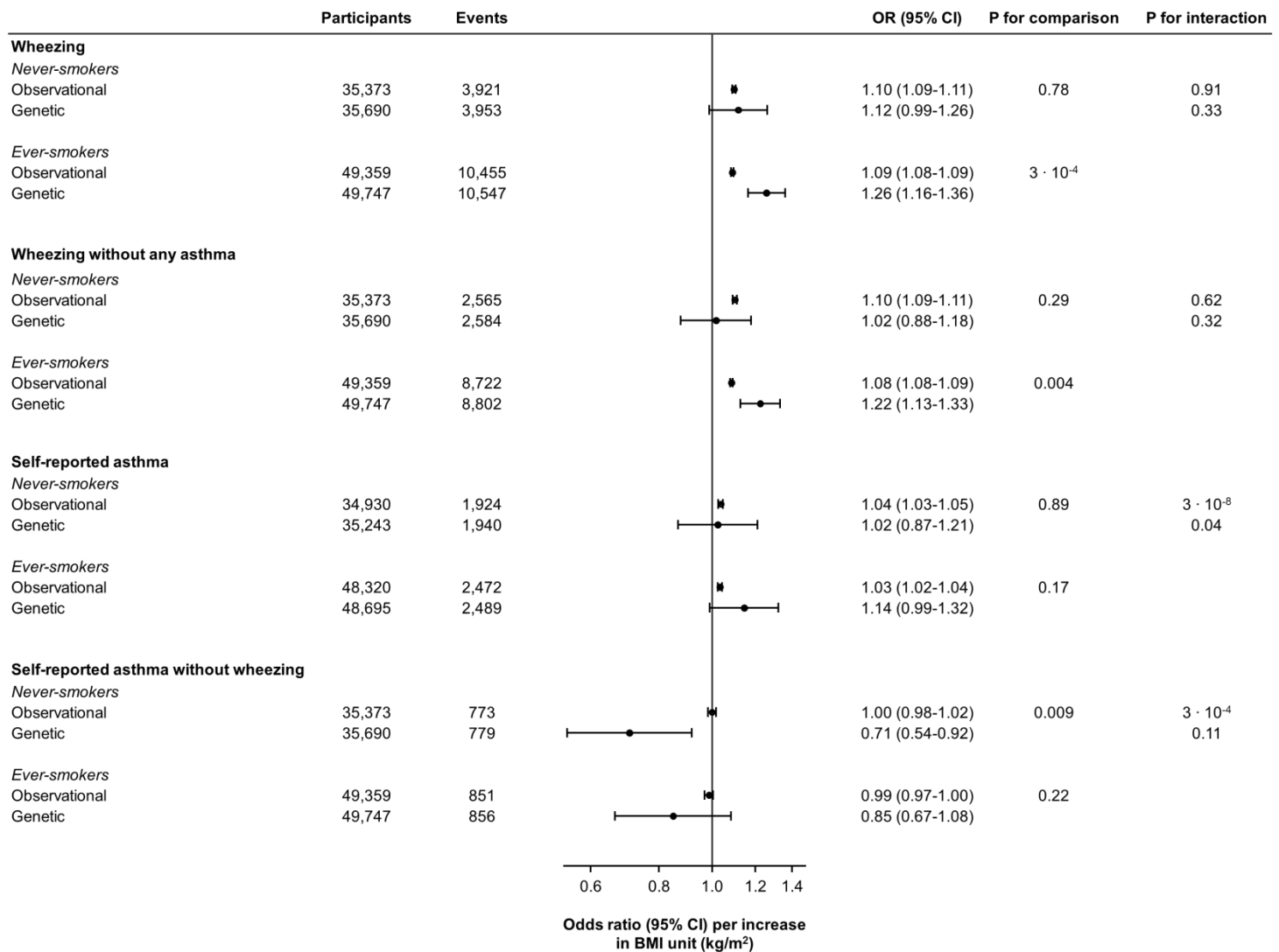


Figure S8. Association of genetic and observational determined BMI with wheezing and self-reported asthma according to smoking status. Odds ratios from the observational estimates included only participants with BMI ≥ 18.5 kg/m², and were multivariable adjusted for age, sex, familial predisposition for asthma, education, annual household income, physical activity in leisure-time and during work, and dietary intakes, including fast-food, fruits, and vegetables. However, in the analyses regarding ever-smokers, additional adjustment with smoking status and cumulative tobacco consumption was included. Odds ratios for genetic analyses were obtained from the instrumental variable analyses. P-values for comparison were obtained with the Durbin form of the Hausman specification test. P-values for interaction of smoking status (never-smokers versus ever-smokers) and BMI, both determined observationally and genetically, were obtained from the Wald tests. Number of individuals for the different outcomes differs slightly due to availability of data. BMI = body mass index; CI = confidence interval; OR = odds ratio.

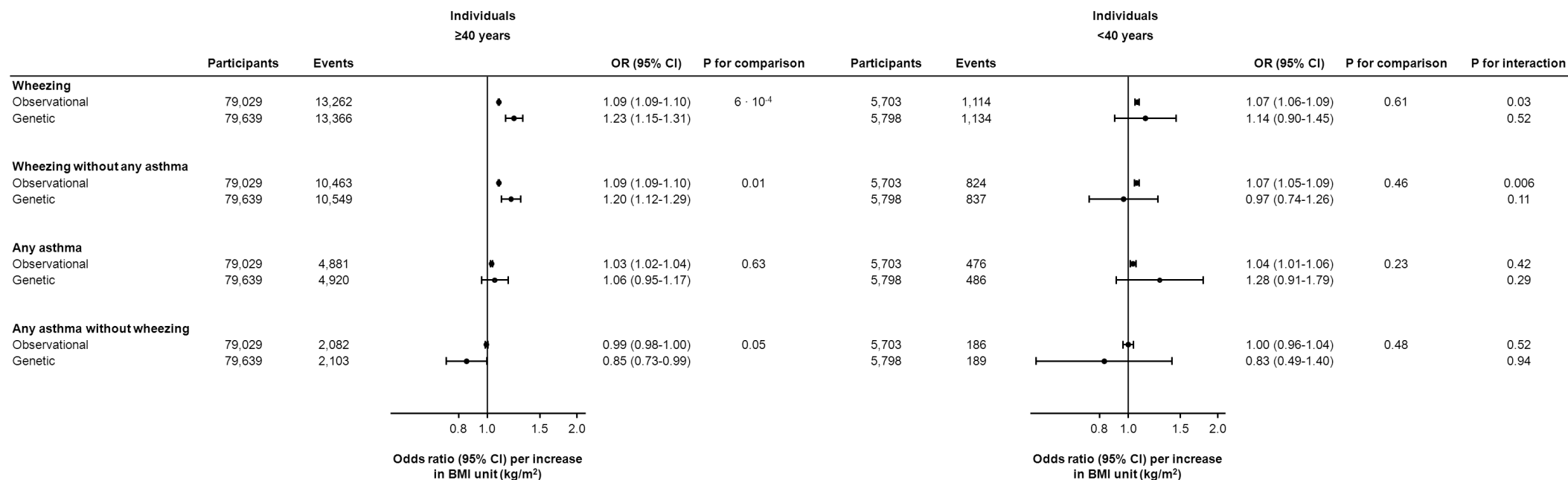


Figure S9. Association of genetic and observational determined BMI with wheezing and asthma according to age. Odds ratios from the observational estimates included only participants with BMI ≥ 18.5 kg/m², and were multivariable adjusted for age, sex, familial predisposition for asthma, education, annual household income, physical activity in leisure-time and during work, and dietary intakes, including fast-food, fruits, and vegetables. Odds ratios for genetic analyses were obtained from the instrumental variable analyses. P-values for comparison were obtained with the Hausman specification test. P-values for interaction of age (≥ 40 years versus < 40 years) and BMI, both determined observationally and genetically, were obtained from the Wald tests. BMI = body mass index; CI = confidence interval; OR = odds ratio.

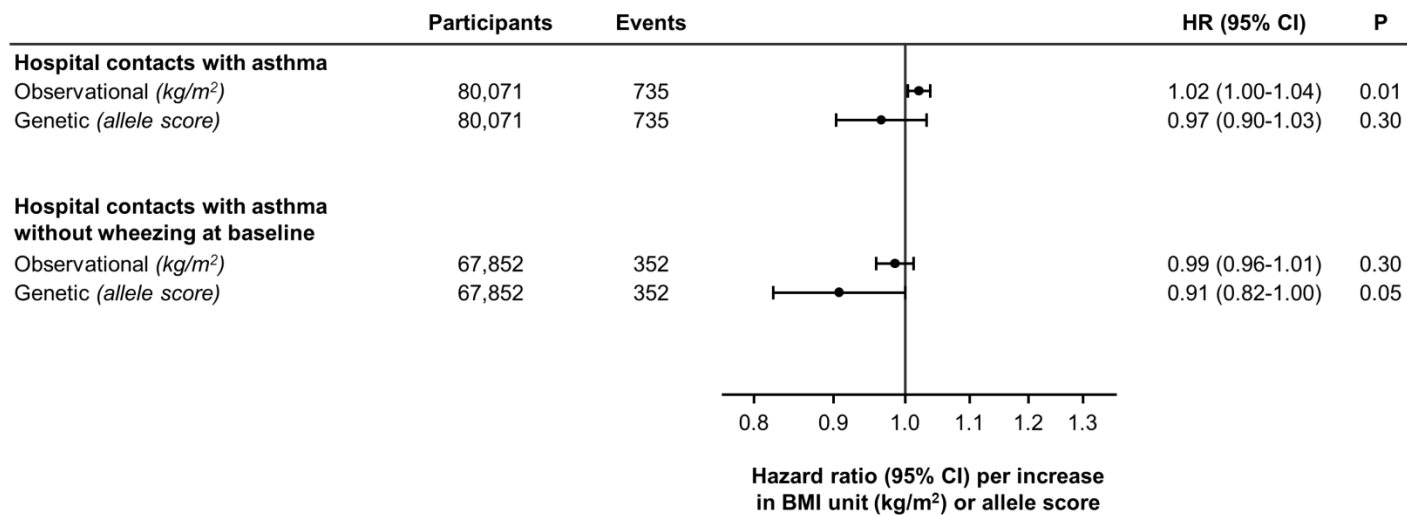


Figure S10. Association of genetic and observational determined BMI with asthma with and without wheezing at baseline. Hazard ratios for the observational analyses were multivariable adjusted for age, sex, familial predisposition with for asthma, smoking status, cumulative tobacco consumption, education, annual household income, physical activity in leisure-time and during work, and dietary intakes, including fast-food, fruits, and vegetables. Hazard ratios for the genetic analyses were adjusted for age and sex. Number of individuals differs slightly due to availability of data and/or exclusion of participants with the outcome at baseline. BMI = body mass index; CI = confidence interval; HR = hazard ratio.

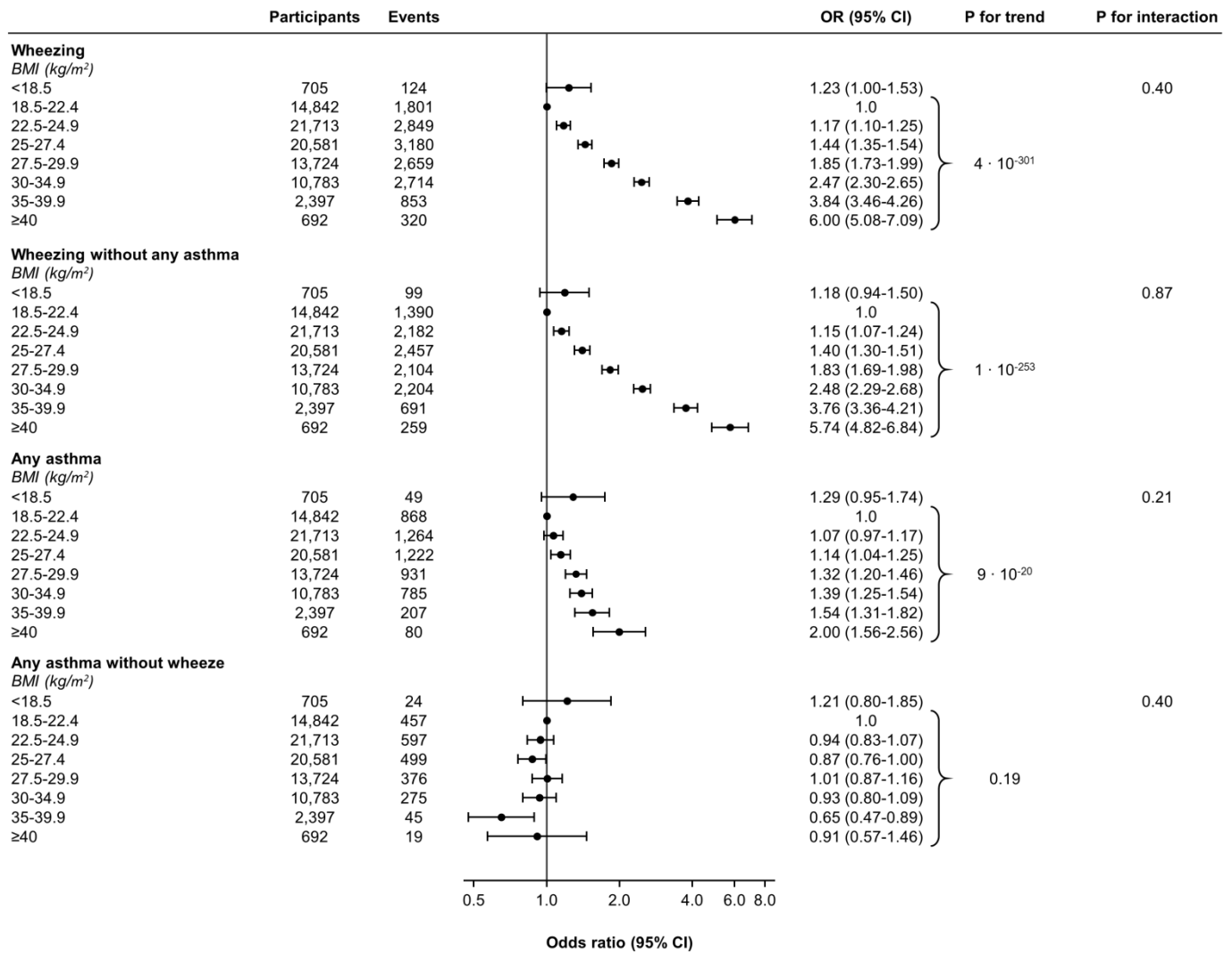


Figure S11. Association of BMI and BMI allele score with wheezing and asthma. Models were multivariable adjusted for age, sex, familial predisposition for asthma, smoking status, cumulative tobacco consumption, education, annual household income, physical activity in leisure-time and during work, dietary intakes, including fast-food, fruits, and vegetables, and BMI allele score. P-values for trend were across ordered groups excluding participants with BMI <18.5 kg/m². P-values for interaction of BMI and BMI allele score were obtained from the likelihood-ratio test. BMI = body mass index; CI = confidence interval; OR = odds ratio.

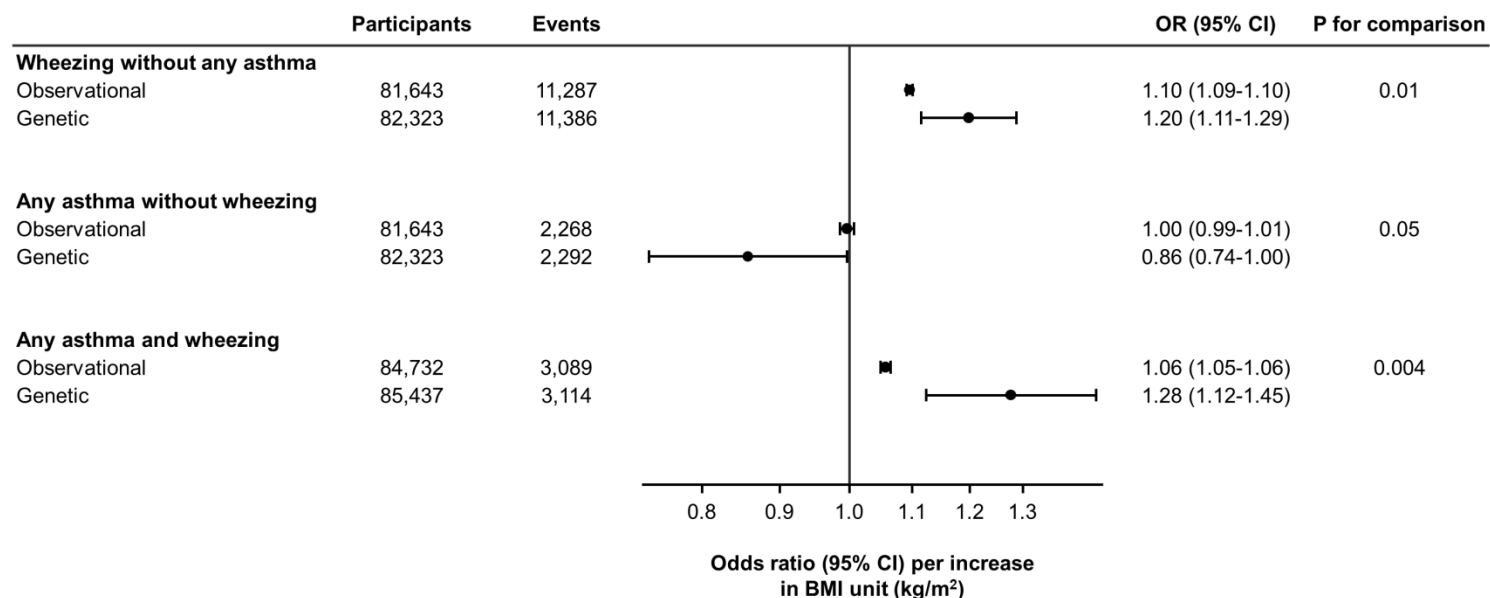


Figure S12. Association of genetic and observational determined BMI with wheezing and asthma separately and combined. Odds ratios from the observational estimates included only participants with BMI ≥ 18.5 kg/m², and were multivariable adjusted for age, sex, familial predisposition with for asthma, smoking status, cumulative tobacco consumption, education, annual household income, physical activity in leisure-time and during work, and dietary intakes, including fast-food, fruits, and vegetables. Odds ratios for genetic analyses were obtained from the instrumental variable analyses. In both the observational and genetic analyses with regard to risk of wheezing without any asthma and any asthma without wheezing, individuals having both wheezing and any asthma were excluded. P-values for comparison were obtained with the Hausman specification test.

BMI = body mass index; CI = confidence interval; OR = odds ratio.