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Early View

Original research article

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SPIROMETRIC PHENOTYPES FROM EARLY CHILDHOOD TO YOUNG ADULTHOOD: A CADSET (CHRONIC AIRWAY DISEASE EARLY STRATIFICATION) STUDY

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Authors' contributions

EM, AMZ and JH conceived and designed the study with input from the CADSET management group (AA, RF, GCD, JAW, and EH). RG (ALSPAC), GW (BAMSE), AM (Generation R), AL (HUNT), MC (INMA together with GW), DC (IoW, MAAS, SEATON), RBK (LEAD), NO (Lifelines), HB (OLIN), JMV (PIAMA), and LML (SUS) conducted the cohort-specific analyses. GW meta-analyzed all results. GW, JH, AMZ and EM wrote the first draft of the manuscript. All authors (GW, JH, DC, MCS, RBK, AL, RG, JMV, AM, NO, LML, ER, AAb, AAg, SHA, AB, HMB, MKB, OB, ACB, AC, GD, GCD, AE, RF, FB, JGA, UG, SH, HB, JWH, GHK, AL, TLH, LL, SMM, CM, GR, LH, VS, TS, AS, JS, MT, ST, MVB, RCHV, SAAV, JAW, AMZ, and EM) read and critically revised subsequent drafts and approved the

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Take home message

Obstructive and restrictive phenotypes are present from childhood to adulthood but without age trends. Established risk factors for airway disease were associated with the obstructive phenotype, whereas low BMI was associated with the restrictive.

ABSTRACT

Background: The prevalences of obstructive and restrictive spirometric phenotypes, and their relation to early-life risk factors from childhood to young adulthood remain poorly understood. The aim was to explore these phenotypes and associations with well-known respiratory risk factors across ages and populations in European cohorts.

Methods: We studied 49,334 participants from 14 population-based cohorts in different age-groups (=<10, >10-15, >15-20, >20-25 years, and overall, 5-25 years). The obstructive phenotype was defined as FEV_1/FVC z-score <the lower limit of normal (LLN), whereas the restrictive as FEV_1/FVC z-score >=LLN, and FVC z-score <LLN.

Results: The prevalence of obstructive and restrictive phenotypes varied from 3.2-10.9% and 1.8-7.7%, respectively, without clear age trends. A diagnosis of asthma (adjusted odds ratio, aOR=2.55 [95% CI=2.14-3.04]), preterm birth (aOR=1.84 [1.27-2.66]), maternal smoking during pregnancy (aOR=1.16 [1.01-1.35]), and family history of asthma (aOR=1.44 [1.25-1.66]) were associated with a higher prevalence of obstructive, but not restrictive phenotype across ages (5-25 years). A higher current body mass index (BMI) was more often observed in those with the obstructive phenotype but less in those with the restrictive (aOR=1.05 [1.03-1.06] and aOR=0.81 [0.78-0.85], per kg/m^2 increase in BMI, respectively). Current smoking was associated with the obstructive phenotype in participants older than 10 years (aOR=1.24 [1.05-1.46]).

Conclusion: Obstructive and restrictive phenotypes were found to be relatively prevalent during childhood, which supports the early origins concept. Several well-known respiratory risk factors were associated with obstructive phenotype, whereas only low BMI was associated with the restrictive phenotype, suggesting different underlying pathobiology of these two phenotypes.

Key Words: Asthma, Lung function, Obstructive, Restrictive, Preterm, Smoking.

INTRODUCTION

Low peak lung function detected by spirometry in early adulthood relates to the increased incidence of respiratory, cardiovascular, and metabolic abnormalities, as well as premature death [1, 2]. Spirometry allows the identification and quantification of the severity of a ventilatory impairment, as well as the first step of classification into two main phenotypes, obstructive and restrictive patterns. The obstructive phenotype is defined by an lower than expected forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio, and the restrictive pattern by an abnormally low FVC with a normal FEV_1/FVC ratio (yet acknowledging that body plethysmography is needed to diagnose restrictive lung disease) [3]. Although both phenotypes are relatively common [4-10] and well-studied in adult cohorts [3, 9, 11, 12], to date, no large study has investigated their respective prevalence, age dependency, or associated risk factors in the period from childhood to young adulthood. The CADSET (Chronic Airway Disease Early Stratification) clinical research collaboration launched by the European Respiratory Society (ERS) in 2018 [13] offers a unique opportunity to combine individual data from multiple cohorts to increase the sample size required to explore these questions. In the current study, we collected data from almost 50,000 subjects across 14 population-based cohorts in Europe in order to report the age-specific prevalence, characteristics, and risk factors for spirometric phenotypes from early childhood to young adulthood (5 to 25 years of age), using the Global Lung Function Initiative (GLI) reference values [14].

METHODS

Study design and subjects

Fourteen European population-based cohorts from seven countries were included in the current meta-analysis. A total of 49,334 participants were included in the current study, and 18,430 of them (from seven cohorts) had repeated lung function

measurements from 4 to 25 years of age. Details about each cohort and the definition of covariates are provided in the online supplement.

Measurements and definitions of outcomes

Pre-bronchodilator lung function was tested in each cohort according to the ATS/ERS spirometry criteria [15]. FEV_1, FVC, and FEV_1/FVC were converted into z-scores according to the equations from the GLI [14] for each cohort separately. Although no disease selective cohorts were included, a high heterogeneity in GLI fit between age groups and between cohorts (see Results, "The fit of GLI z-scores" and Table 1) was observed, and we therefore applied a centering approach to make the cohorts more comparable. Centering was performed separately for each cohort and age group by subtracting the mean z-score (of FEV_1, FVC, and FEV_1/FVC, respectively) of non-smoking individuals without asthma (where a perfect fit would give a mean of 0 z-scores) from each individual z-score lung function variable.

The diagnostic algorithm of our spirometry phenotypes was based on the lower limit of normal (LLN) as the lower fifth percentile of distribution that corresponds to a z-score -1.645 (rounded to -1.65 if two decimals were used) and used as follows (Table E1): normal lung function was defined as the FEV_1/FVC ratio and FVC z-scores equal to or higher than LLN. The obstructive phenotype was defined as FEV_1/FVC ratio z-score lower than LLN, and severity defined according to Quanjer et al. as mild, moderate, and severe according to thresholds of FEV_1: z-score less than LLN but greater or equal than -2, less than -2 but greater or equal than -3, and less than -3, respectively [16]. In addition to these, a very mild group was added, defined as a FEV_1/FVC ratio z-score lower than LLN and FEV_1 z-score greater or equal than LLN. The restrictive phenotype ("Low FVC, non-obstructive") was defined as FEV_1/FVC ratio z-score equal to or higher than LLN, and FVC z-score lower than LLN. Severity was evaluated as mild, moderate, and severe according to

two thresholds of FVC: z-score less than LLN but greater or equal than -2, less than -2 but greater or equal than -3, and less than -3, respectively [16].

Statistical analysis

We performed cohort-specific analyses followed by meta-analysis. The associations between the cohort-specific prevalence of obstructive and restrictive phenotypes and age were tested by Pearson correlation. Comparisons of the prevalence of wheezing and asthma between obstructive and restrictive phenotypes and normal lung function groups were performed using the Wilcoxon Rank Sum test. Multivariable regression models were conducted to identify risk factors of obstructive and restrictive phenotypes, and FEV_1, FVC, and FEV_1/FVC ratio z-scores, respectively. We used two models to explore selected potential risk factors. In the first model, three well-known early-life respiratory risk factors (asthma family history, maternal smoking during pregnancy, and preterm birth (delivery before 37 completed weeks of gestation)), and two lifestyle factors (body mass index (BMI) and smoking status) were evaluated using logistic (for obstructive and restrictive phenotypes) and linear regressions (for z-scores). In the second model, current asthma was added as predictor to the models to specifically evaluate the influence of asthma since this is typically classified as an obstructive disease. In the meta-analysis of cohort-specific results, we combined data from each cohort in age- groups separately (=<10, >10-15, >15-20, >20-25 years), as well as overall across ages (5-25 years). For those cohorts that had repeated lung function measurements from multiple time points (i.e., data from several age groups), regression analysis for each time point was performed and included in the relevant age group. Where multiple time points existed for a cohort in an age group, only the largest age group was used in the meta-analyses (both age-bin specific and overall) to provide estimates from truly independent datasets. Heterogeneity was assessed with the Q and the I^2 statistic. The Q statistic was calculated according to the weighted sum of squared differences between

individual study effects and the pooled effect across studies and is distributed as a chi-square statistic with k (number of studies) minus 1 degrees of freedom [17]. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance [18, 19]. A random-effects model was used to pool data if substantial heterogeneity was observed ($I^2 > 50\%$ or $P < 0.1$ for Q statistic), otherwise we used a fixed-effects model. Meta-analyses were performed using the R software (version 4.0.4) with "meta" package (version 4.18.1).

RESULTS

Basic characteristics

Table 1 illustrates the basic characteristics of the cohorts. Of the fourteen included cohorts, seven (ALSPAC, BAMSE, Generation R, INMA, MAAS, PIAMA, SEATON) contributed repeated data from early childhood to young adulthood (age 4 to 25 years). Two, eight, eight, thirteen, and four cohorts contributed results in the 1-5, >5-10, >10-15, >15-20, >20-25 years age groups, respectively. As the 1-5 age bin only contained two cohorts (INMA and SEATON), the 1-5 and >5-10 age groups were combined into the <10 age bin in the meta-analysis. Although INMA contributed data at 4, 7 and 9 years, only the largest dataset (7 years) was included in the meta-analysis in the <10 age bin.

The fit of GLI z-scores

The fit of GLI z-scores is described for each cohort in non-asthmatic, asymptomatic lifelong non-smokers as mean and SD in Table 1. While the overall GLI fit was good in many age groups in the cohorts, a high heterogeneity was observed. For six, five, and three cohorts' GLI fit estimates for FEV_1, FVC, and FEV_1/FVC z-scores, respectively, were outside the suggested range using 0.4 as a cut-off [20] (Figure E1). Therefore, we proceeded with mean-centered z-scores (as described in the Methods)

for comparisons of prevalences across cohorts, and for the meta-analyses. While mean GLI z-score values varied by cohort and age, the SD was close to 1 in all groups.

Table 1. Characteristics and FEV_1, FVC, and FEV_1/FVC ratio z scores **of each cohort included in the age groups.**

Cohorts	Nations	Age groups	N	Age¶	FEV_1		FVC		FEV_1/FVC ratio	
					GLI fit¶	Mean-centered§	GLI fit¶	Mean-centered§	GLI fit¶	Mean-centered§
ALSPAC *	United Kingdom	>5-10	6804	8.7 (0.3)	0.04 (1.00)	-0.09 (1.02)	-0.06 (1.02)	-0.02 (1.04)	0.15 (1.02)	-0.10 (1.07)
		>15-20	4519	15.5 (0.3)	-0.68 (1.29)	-0.04 (1.26)	-1.02 (1.29)	0.04 (1.25)	0.61 (1.16)	-0.14 (1.21)
		>20-25	3731	24.5 (0.8)	-0.52 (1.01)	0.06 (1.00)	-0.37 (1.02)	0.13 (0.98)	-0.27 (0.94)	-0.1 (0.98)
BAMSE *	Sweden	>5-10	1832	8.3 (0.5)	0.47 (0.94)	-0.06 (0.94)	0.59 (0.90)	-0.00 (0.91)	-0.27 (0.87)	-0.07 (0.89)
		>15-20	2052	16.7 (0.4)	0.06 (0.92)	-0.11 (0.94)	0.16 (0.92)	-0.01 (0.92)	-0.19 (0.93)	-0.15 (0.96)
		>20-25	2032	22.5 (0.5)	-0.23 (0.85)	-0.03 (0.86)	-0.12 (0.85)	0.07 (0.85)	-0.20 (0.88)	-0.15 (0.90)
Generation R *	Netherlands	>5-10	4738	9.8 (0.3)	0.19 (0.93)	-0.04 (0.93)	0.21 (0.89)	0.02 (0.92)	-0.08 (0.90)	-0.01 (0.96)
		>10-15	3869	13.6 (0.4)	-0.15 (1.01)	-0.06 (0.93)	-0.09 (0.98)	0.04 (0.99)	-0.13 (0.92)	0.00 (1.02)
HUNT1	Norway	>10-15	2705	14.1 (0.6)	-0.23 (1.11)	-0.02 (1.11)	-0.19 (1.10)	0.01 (1.10)	-0.07 (1.03)	-0.05 (1.03)
		>15-20	5256	17.1 (1.3)	-0.12 (1.04)	-0.03 (1.04)	-0.09 (1.01)	0.02 (1.01)	-0.08 (0.98)	-0.08 (0.98)
HUNT3	Norway	>10-15	2792	14.1 (0.6)	0.01 (1.03)	-0.01 (1.03)	0.10 (1.05)	0.04 (1.05)	-0.15 (1.02)	-0.22 (1.02)
		>15-20	4363	16.9 (1.2)	0.09 (0.99)	-0.04 (0.99)	0.19 (1.01)	0.03 (1.01)	-0.19 (0.98)	-0.09 (0.97)
INMA *	Spain	1-5	704	4.5 (0.2)	-0.59 (1.20)	-0.01 (1.21)	-0.53 (1.23)	0.01 (1.25)	-0.03 (0.95)	-0.03 (0.97)
		>5-10	1277	7.4 (0.6)	0.21 (0.98)	-0.01 (0.99)	0.40 (0.95)	0.01 (0.96)	-0.34 (0.99)	-0.03 (1.00)
		>5-10	476	9.3 (0.9)	-0.02 (1.07)	-0.03 (1.05)	0.17 (1.04)	-0.00 (1.01)	-0.21 (0.98)	-0.06 (0.95)
		>10-15	988	11.2 (0.6)	-0.20 (1.00)	-0.01 (1.03)	-0.06 (1.03)	0.02 (1.04)	-0.25 (0.95)	-0.04 (1.01)
		>10-15	266	14.6 (0.2)	0.04 (0.94)	-0.04 (0.95)	-0.04 (0.98)	-0.02 (0.95)	0.13 (0.87)	-0.03 (0.90)
		>15-20	120	17.7 (0.3)	-0.34 (0.92)	-0.03 (0.89)	-0.32 (0.98)	0.07 (0.94)	-0.04 (0.99)	-0.15 (1.02)
IoW	United Kingdom	>5-10	980	9.9 (0.3)	0.37 (0.97)	-0.04 (0.99)	0.16 (0.88)	0.02 (0.88)	0.33 (0.96)	-0.09 (1.01)
		>15-20	836	17.8 (0.6)	0.30 (0.92)	-0.15 (0.99)	0.14 (0.85)	0.01 (0.93)	0.22 (1.07)	-0.21 (1.11)
LEAD	Austria	>5-10	451	8.4 (1.0)	0.46 (1.27)	-0.07 (0.99)	0.31 (1.26)	0.10 (0.92)	0.35 (1.17)	-0.31 (1.13)

		>10-15	526	12.3 (1.5)	0.01 (1.03)	-0.35 (1.02)	-0.19 (0.97)	-0.14 (0.98)	0.36 (0.95)	-0.39 (1.04)
		>15-20	540	17.4 (1.4)	-0.05 (1.07)	-0.36 (1.01)	-0.22 (1.08)	-0.11 (0.97)	0.30 (1.08)	-0.44 (1.12)
		>20-25	703	22.5 (1.4)	-0.13 (1.04)	-0.42 (0.92)	-0.31 (1.09)	-0.16 (0.92)	0.22 (0.99)	-0.46 (1.02)
Lifelines	Netherlands	>15-20	2556	18.9(0.8)	-0.42 (0.91)	-0.06 (0.92)	-0.34 (0.90)	0.03 (0.89)	-0.19 (0.98)	-0.14 (1.01)
		>20-25	5028	23.3(1.5)	-0.42 (0.90)	-0.06 (0.91)	-0.29 (0.89)	0.05 (0.87)	-0.23 (0.96)	-0.16 (0.96)
		>5-10	778	8.0 (0.2)	0.15 (0.93)	-0.07 (0.10)	0.26 (0.90)	0.00 (0.94)	-0.24 (0.89)	-0.11 (0.93)
MAAS *	United Kingdom	>10-15	778	11.5 (0.5)	-0.12 (0.95)	-0.05 (1.00)	-0.18 (1.12)	0.05 (1.12)	0.14 (1.03)	-0.15 (1.10)
		>15-20	566	16.0 (0.6)	-0.26 (0.95)	-0.06 (1.05)	-0.43 (0.90)	0.03 (0.96)	0.31 (1.02)	-0.16 (1.11)
		>15-20	504	19.4 (0.8)	-0.24 (0.87)	-0.04 (0.95)	-0.40 (0.90)	0.10 (0.90)	0.26 (0.97)	-0.24 (1.04)
OLIN	Sweden	>15-20	1470	18.2 (0.5)	-0.06 (1.01)	-0.04 (1.01)	0.08 (1.06)	0.01 (1.03)	-0.28 (0.93)	-0.07 (0.96)
		>5-10	1058	8.1 (0.3)	0.54 (0.88)	-0.05 (0.91)	0.29 (0.88)	0.00 (0.90)	0.42 (1.06)	-0.09 (1.09)
PIAMA *	Netherlands	>10-15	1267	12.7 (0.4)	-0.56 (0.84)	-0.04 (0.86)	-0.37 (0.85)	-0.01 (0.86)	-0.37 (0.87)	-0.04 (0.89)
		>15-20	720	16.4 (0.2)	-0.19 (0.86)	-0.07 (0.88)	0.02 (0.86)	-0.00 (0.82)	-0.40 (0.92)	-0.10 (0.94)
		1-5	446	4.9 (0.2)	0.17 (0.96)	-0.03 (0.95)	-0.13 (1.05)	-0.00 (1.05)	0.08 (0.93)	-0.04 (0.95)
SEATON *	United Kingdom	>10-15	430	10.3 (0.2)	-0.12 (1.10)	-0.06 (1.09)	-0.24 (1.04)	-0.01 (1.04)	0.15 (0.93)	-0.08 (0.96)
		>15-20	534	15.1 (0.3)	-0.36 (1.00)	-0.04 (1.00)	-0.77 (1.02)	0.01 (1.00)	0.83 (1.09)	-0.10 (1.13)
SUS	Denmark	>15-20	2294	18.9 (1.3)	-0.29 (0.90)	-0.01 (0.90)	-0.33 (0.88)	0.05 (0.88)	0.01 (1.00)	-0.09 (1.00)

Data was shown in mean (standard deviation).

*: They are longitudinal cohorts with repeated measurement at different age.

¶: Based on the whole group of participants.

§: Based on non-asthmatic, asymptomatic lifelong non-smokers.

Prevalence of spirometric phenotypes and association with respiratory symptoms

We used the mean-centred z-scores to explore the prevalence of spirometry impairment phenotypes across ages and cohorts. The prevalence of obstructive and restrictive phenotypes during early childhood and young adulthood ranged from 3.2 to 10.9% and 1.8 to 7.7%, respectively (Figure 1A and 1B). There was no overall association between age and the prevalence of obstructive and restrictive phenotypes ($r = 0.14$, $P = 0.39$ and $r = -0.14$, $P = 0.41$, respectively, Figure E2A and E2B). Most participants with the obstructive phenotype were classified as having a (very) mild impairment, while most participants with the restrictive phenotype were classified as having a mild to moderate impairment (Figure 1A and 1B).

Participants with the obstructive phenotype more frequently reported wheezing in the previous 12 months and having been diagnosed with asthma when compared to participants with normal lung function (Median=26.6%, interquartile range (IQR)=16.7 to 36.4% vs.12.5%, IQR=7.9 to 18.1%, $P < 0.001$, and 29.8%, IQR= 21.9 to 42.3% vs. 12.3%, IQR=7.1 to 22.5%, $P < 0.001$, respectively, Figure 2 and E3). However, no significant difference in respiratory symptoms between participants with the restrictive phenotype and normal lung function was observed (12.7%, IQR=7.6 to 18.1% vs.12.5%, IQR=7.9 to 18.1%, $P = 0.95$, and 10.1%, IQR=7.1 to 20.9% vs.12.3%, IQR=7.1 to 22.5%, $P = 0.57$, respectively, Figures 2 and E1). In the adjusted regression models, a current diagnosis of asthma was strongly associated with the obstructive phenotype (5-25 years age group adjusted odds ratio, aOR=2.55, 95% CI: 2.14 to 3.04, Figure 3, for other subgroups see Figure E4). No association between a current diagnosis of asthma and the restrictive phenotype (Figure E5) was observed.

Risk factors associated with impaired lung function

We explored the mutually adjusted associations of three well-known early-life respiratory risk factors (preterm birth, maternal smoking during pregnancy, and asthma family history), as well as the lifestyle factors at the time of lung function testing, BMI and smoking status (former and current smoker) and obstructive and restrictive phenotypes as well as FEV_1, FVC, and FEV_1/FVC ratio z-scores. The combined meta-analysis results are illustrated in Table 2 (for spirometry phenotypes) and Table E2 (for z-scores) and results additionally adjusted for asthma in Table 3 and Table E3.

Table 2. Meta-analysis results of obstructive and restrictive phenotypes in Model 1* in different age groups.

Variables	Age groups	Number of cohorts	I^2	P for Q statistic	OR	95% CI
Obstructive phenotype						
Preterm birth	<10	9	60.8	0.0089	1.82	1.08 to 3.06
	>10 - 15	5	17.6	0.30	2.73	1.67 to 4.46
	>15 - 20	8	6.7	0.38	1.61	1.13 to 2.29
	>20 - 25	4	0.0	0.63	1.37	0.88 to 2.12
	5 - 25	10	51.6	0.016	1.84	1.27 to 2.66
Maternal smoking during pregnancy	<10	9	0.0	0.61	1.11	0.94 to 1.30
	>10 - 15	6	0.0	0.98	1.20	0.90 to 1.59
	>15 - 20	10	9.1	0.36	1.43	1.14 to 1.78
	>20 - 25	3	0.0	0.41	1.43	1.07 to 1.93
	5 - 25	11	0.0	0.53	1.16	1.01 to 1.35
Asthma family history	<10	9	26.9	0.20	1.34	1.14 to 1.58
	>10 - 15	6	0.0	0.55	1.39	1.01 to 1.93
	>15 - 20	11	0.0	0.52	1.46	1.24 to 1.72
	>20 - 25	3	29.6	0.24	1.59	1.22 to 2.07
	5 - 25	12	0.0	0.83	1.44	1.25 to 1.66
BMI	<10	9	40.6	0.097	1.06	1.02 to 1.10
	>10 - 15	8	55.3	0.022	1.04	1.00 to 1.09
	>15 - 20	12	17.7	0.27	1.05	1.04 to 1.07
	>20 - 25	4	0.0	0.47	1.03	1.01 to 1.05
	5 - 25	13	44.7	0.019	1.05	1.03 to 1.06
Former smoker	>10 - 15	2	0.0	0.61	0.67	0.45 to 1.01
	>15 - 20	10	28.9	0.18	0.83	0.71 to 0.98
	>20 - 25	4	0.0	0.63	1.37	1.04 to 1.82
	10 - 25	11	41.3	0.048	0.93	0.75 to 1.16
Current smoker	>10 - 15	2	51.0	0.15	0.88	0.38 to 2.05
	>15 - 20	11	35.5	0.11	1.21	1.01 to 1.44
	>20 - 25	4	0.0	0.70	1.34	1.01 to 1.78
	10 - 25	11	29.8	0.13	1.24	1.05 to 1.46
Restrictive phenotype						
Preterm birth	<10	8	0.0	0.79	1.17	0.78 to 1.75
	>10 - 15	5	0.0	0.92	1.46	0.72 to 2.97
	>15 - 20	6	0.0	0.79	1.16	0.72 to 1.87
	>20 - 25	3	0.0	0.87	0.88	0.41 to 1.92
	5 - 25	9	0.0	0.98	1.20	0.84 to 1.70
Maternal smoking during pregnancy	<10	9	0.0	0.92	0.91	0.73 to 1.14
	>10 - 15	6	0.0	0.95	1.16	0.79 to 1.70
	>15 - 20	9	40.9	0.095	0.98	0.61 to 1.58
	>20 - 25	4	0.0	0.73	0.84	0.52 to 1.36
	5 - 25	11	0.0	0.66	1.00	0.82 to 1.22

Asthma family history	<10	9	3.8	0.40	0.92	0.74 to 1.15
	>10 - 15	6	0.0	0.97	0.91	0.58 to 1.44
	>15 - 20	10	13.4	0.32	0.89	0.71 to 1.12
	>20 - 25	4	0.0	0.64	0.97	0.66 to 1.42
	5 - 25	12	0.0	0.84	0.96	0.79 to 1.16
BMI	<10	9	69.3	0.001	0.88	0.80 to 0.96
	>10 - 15	8	51.6	0.035	0.80	0.75 to 0.85
	>15 - 20	12	78.8	<0.001	0.80	0.75 to 0.85
	>20 - 25	4	92.6	<0.001	0.84	0.70 to 1.00
	5 - 25	13	75.1	<0.001	0.81	0.78 to 0.85
Former smoker	>10 - 15	2	0.0	0.35	0.65	0.40 to 1.04
	>15 - 20	9	25.3	0.24	0.98	0.79 to 1.21
	>20 - 25	4	56.6	0.075	0.57	0.27 to 1.23
	10 - 25	11	35.9	0.10	0.93	0.76 to 1.12
Current smoker	>10 - 15	2	62.2	0.10	0.89	0.27 to 2.97
	>15 - 20	11	27.3	0.18	0.80	0.60 to 1.05
	>20 - 25	4	0.0	0.54	0.72	0.48 to 1.06
	10 - 25	11	19.6	0.23	0.85	0.67 to 1.08

* Model 1 was adjusted for asthma family history, maternal smoking during pregnancy, preterm birth, body mass index (BMI) and smoking status.

Table 3. Meta-analysis results of obstructive and restrictive phenotypes in Model 2* in different age groups.

Variables	Age groups	Number of cohorts	I^2	P for Q statistic	OR	95% CI
Obstructive phenotype						
Preterm birth	<10	8	53.1	0.037	2.04	1.24 to 3.34
	>10 - 15	6	21.0	0.28	2.83	1.73 to 4.46
	>15 - 20	8	7.1	0.38	1.53	1.06 to 2.22
	>20 - 25	4	0.0	0.47	1.49	0.94 to 2.36
	5 - 25	10	40.1	0.06	1.83	1.31 to 2.57
Maternal smoking during pregnancy	<10	9	0.0	0.70	1.06	0.89 to 1.28
	>10 - 15	6	0.0	0.97	1.28	0.95 to 1.73
	>15 - 20	10	17.0	0.29	1.48	1.20 to 1.82
	>20 - 25	3	0.0	0.79	1.23	0.86 to 1.75
	5 - 25	11	0.0	0.58	1.13	0.97 to 1.33
Asthma family history	<10	9	21.9	0.25	1.09	0.90 to 1.32
	>10 - 15	6	0.0	0.63	1.17	0.82 to 1.67
	>15 - 20	11	0.0	0.84	1.28	1.07 to 1.52
	>20 - 25	3	69.6	0.037	1.33	0.74 to 2.40
	5 - 25	12	0.0	0.67	1.21	1.04 to 1.41
BMI	<10	9	53.7	0.027	1.05	1.00 to 1.11
	>10 - 15	8	0.0	0.50	1.06	1.04 to 1.09
	>15 - 20	12	16.5	0.28	1.04	1.03 to 1.06
	>20 - 25	4	0.0	0.88	1.04	1.01 to 1.07
	5 - 25	13	34.4	0.071	1.04	1.03 to 1.06
Former smoker	>10 - 15	2	0.0	0.72	0.67	0.45 to 1.01
	>15 - 20	10	20.8	0.25	0.83	0.70 to 0.97
	>20 - 25	4	0.0	0.59	1.55	1.14 to 2.11
	10 - 25	11	47.0	0.023	0.96	0.76 to 1.22
Current smoker	>10 - 15	2	54.1	0.14	0.89	0.37 to 2.15
	>15 - 20	11	45.1	0.052	1.18	0.90 to 1.54
	>20 - 25	4	0.0	0.67	1.28	0.92 to 1.79
	10 - 25	11	37.6	0.07	1.18	0.93 to 1.49
Restrictive phenotype						
Preterm birth	<10	8	0.0	0.70	1.08	0.68 to 1.73
	>10 - 15	5	0.0	0.85	1.80	0.88 to 3.71
	>15 - 20	6	0.0	0.83	1.17	0.72 to 1.92
	>20 - 25	3	0.0	0.95	0.76	0.30 to 1.92
	5 - 25	9	0.0	0.97	1.13	0.77 to 1.68
Maternal smoking during pregnancy	<10	9	0.0	0.71	0.95	0.75 to 1.22
	>10 - 15	6	0.0	0.98	1.19	0.78 to 1.79
	>15 - 20	9	43.8	0.076	0.98	0.59 to 1.62
	>20 - 25	4	0.0	0.99	1.01	0.61 to 1.69
	5 - 25	11	0.0	0.59	1.06	0.86 to 1.32

Asthma family history	<10	9	3.8	0.40	0.99	0.77 to 1.27
	>10 - 15	5	0.0	0.88	0.89	0.54 to 1.46
	>15 - 20	10	25.9	0.21	0.88	0.69 to 1.12
	>20 - 25	4	0.0	0.61	0.99	0.63 to 1.56
	5 - 25	12	0.0	0.84	1.02	0.83 to 1.25
BMI	<10	9	75.0	<0.001	0.86	0.77 to 0.95
	>10 - 15	8	50.8	0.039	0.79	0.74 to 0.84
	>15 - 20	12	75.9	<0.001	0.80	0.75 to 0.85
	>20 - 25	4	92.2	<0.001	0.84	0.70 to 1.01
	5 - 25	13	76.9	<0.001	0.81	0.77 to 0.85
Former smoker	>10 - 15	2	0.0	0.35	0.64	0.40 to 1.04
	>15 - 20	9	40.3	0.12	0.96	0.77 to 1.20
	>20 - 25	4	46.7	0.13	0.69	0.43 to 1.08
	10 - 25	11	35.2	0.11	0.91	0.75 to 1.11
Current smoker	>10 - 15	2	62.8	0.10	0.89	0.26 to 3.07
	>15 - 20	11	41.8	0.07	0.74	0.49 to 1.13
	>20 - 25	4	0.0	0.56	0.73	0.47 to 1.15
	10 - 25	11	19.2	0.24	0.87	0.68 to 1.13

* Model 2 was adjusted for asthma family history, maternal smoking during pregnancy, preterm birth, body mass index (BMI) and smoking status, as well as for current asthma.

Preterm birth was associated with a higher likelihood of having the obstructive phenotype in the <10, >10-15, >15-20, and the overall 5-25 years age groups (aOR=1.82, 95% CI: 1.08 to 3.06, aOR=2.73, 95% CI: 1.67 to 4.46; aOR=1.61, 95% CI: 1.13 to 2.29 and aOR=1.84, 95% CI: 1.27 to 2.66, Table 2), and effect estimates remained similar when current asthma was included in the model (Table 3). Maternal smoking during pregnancy was also associated with a higher risk of the obstructive phenotype in several age groups, including the overall 5-25 years group (aOR=1.16, 95% CI: 1.01 to 1.35), but the effect estimates somewhat attenuated when current asthma was adjusted for in the model (Table 3). Asthma family history was associated with the obstructive phenotype in model 1, but the effect estimates attenuated with additional adjustment for current asthma in model 2 (aOR decreased from 1.44 to 1.21). No association between these risk factors and the restrictive phenotype was observed. Using spirometry indices as continuous trait outcomes, preterm birth was negatively associated with FEV_1, FVC, and FEV_1/FVC ratio z-scores (Table E2). Maternal smoking during pregnancy was negatively associated with FEV_1 and FEV_1/FVC ratio. Asthma family history was negatively associated with FEV_1 and FEV_1/FVC ratio z-scores, but not with FVC z-scores.

BMI was positively associated with the obstructive phenotype in all age groups in both models (from aOR=1.03, 95% CI: 1.01 to 1.05 to aOR=1.06, 95% CI: 1.04 to 1.09 per kg/m^2 increase, Table 2 and Table 3). In contrast, BMI was negatively associated with the restrictive phenotype in all age groups in both models (from aOR=0.79, 95% CI: 0.74 to 0.84 to aOR=0.88, 95% CI: 0.80 to 0.96 per kg/m^2 increase, Table 2, Table 3, and Figure 4) except in the >20-25 age bin (Figure E6). In addition, a higher BMI was associated with higher FEV_1 and FVC but lower FEV_1/FVC ratio z-scores (Table E2).

Current smoking was positively associated with the obstructive phenotype in the >15-20, >20-25 and >10-25 years age groups in model 1, but the association somewhat attenuated when current asthma was adjusted for in the model (Table 3). No clear associations between former smoking and an obstructive phenotype were observed in the current study because former making both positively and negatively associated with obstructive phenotype. No association between participants' smoking status and the restrictive phenotype was observed. In addition, both former and current smoking were associated with higher FVC but lower FEV_1/FVC ratio z-scores (Table E2).

DISCUSSION

The main observations in the current study using data from 14 population-based cohorts are that: *(1)* the obstructive and restrictive phenotypes are present at any age from childhood to early adulthood without an apparent age trend; and, *(2)* a diagnosis of asthma, family history of asthma, maternal smoking during pregnancy, preterm birth, a higher BMI, and current smoking were risk factors for the obstructive phenotype, while a lower BMI was the only factor associated with a restrictive phenotype in this age range.

Previous studies

Previous studies have reported that the prevalence of an obstructive spirometric phenotype in young adults is between 5 and 7% [21-23]. Our current results extend these previous findings by demonstrating that an obstructive phenotype widely exists in the general population from childhood to early adulthood. The prevalence of the restrictive phenotype during early childhood to young adulthood ranged from 1.8 to 7.7% in our study. These figures are lower than in population-based studies of adults 40 years or older, where prevalence range from around 7 to 20% [5-10]. Most participants with obstructive and restrictive phenotypes in our study were classified

as having mild impairments, and interestingly, no difference in respiratory symptoms between participants with the restrictive phenotype and normal lung function was observed. As such, they may be at the early stage of the impairment and indicate a potential window of opportunity for early interventions to conserve or improve their lung function [24].

Interpretation of key findings

Several early life potential risk factors, including asthma family history, maternal smoking during pregnancy, and preterm birth, were associated with the obstructive phenotype. Preterm birth is associated with several respiratory sequelae during early childhood, such as bronchopulmonary dysplasia and higher risk of lower-respiratory-tract/respiratory syncytial virus infections [25]. Further, preterm birth has been associated with substantial impairments in airflow later during childhood and adolescence [26, 27]. In the current study, preterm birth was related to a higher risk of having an obstructive phenotype and a lower FEV_1 z-score up to early adulthood. Despite recent substantial advances in neonatal care, with more babies surviving after preterm birth (including extreme prematurity, defined as <28 weeks gestation), the underlying pathophysiological mechanisms related to future respiratory health in these patients need further investigation [28].

Maternal smoking during pregnancy is a well-known *in utero* exposure that is negatively associated with fetal lung development and respiratory function in new-born infants [29] and with a higher risk of recurrent wheezing throughout childhood [30, 31]. Our results support these findings by demonstrating that maternal smoking during pregnancy is associated with a higher risk of the obstructive phenotype and impaired lung function development assessed as FEV_1 and FEV_1/FVC ratio z-scores in offspring.

Further, asthma and smoking are other well-known factors associated with airway obstruction [32], and children with persistent asthma are at higher risk for fixed airflow obstruction and possibly COPD in early adulthood [33, 34]. As expected, current asthma was strongly associated with the obstructive phenotype (more than 2 fold) and lung function impairment (lower FEV_1 and FEV_1/FVC z-scores) in our study. Current smoking of the participants was also associated with a higher likelihood of the obstructive phenotype (almost 20%). However, the association between current smoking and the obstructive phenotype was attenuated somewhat when a current diagnosis of asthma was taken into consideration, and the same trend was also observed for asthma family history and maternal smoking during pregnancy, suggesting that involved mechanisms partly overlap with asthma pathophysiology. It should be noted that we did not consider asthma as a confounder in the regression model (Model 2), since asthma and airway obstruction may represent the same disease entity, but rather to explore shared risk factors between asthma and our spirometry outcomes. However, we acknowledge that not all individuals classified as having asthma necessarily have clinical asthma, as the criteria for asthma in young children are typically based on symptoms only and not any objective tests. Future studies may explore more specific characteristics of asthma, such as airway hyperresponsiveness or airway inflammation, in relation to lower lung function development.

We did not identify any association between explored risk factors and the restrictive phenotype, except for BMI, where we found a lower BMI to be associated with the restrictive phenotype, indicating different underlying metabolic pathobiology between the obstructive and restrictive phenotypes. Although restrictive spirometry outcomes and lung disease are receiving increased attention in respiratory research lately, most studies to date were designed to explore health consequences of restrictive disease [9, 10, 12], while origins and risk factors remain poorly studied. In adults, early life circumstances, such as low birth weight and intrauterine growth restriction [35, 36], pneumonia before school age [37], smoking [38], abdominal adiposity [38], and dust

exposure [39] have been associated with lower FVC levels. In our study, smoking status was not associated with the restrictive phenotype, possibly because of the low cigarette load among adolescents and young adults. However, we observed a two-way relationship between BMI and lung function in our study. On the one hand, a lower BMI was associated with increased likelihood of restrictive phenotype and BMI correlated negatively with FVC z-scores from childhood to adolescence. On the other hand, a higher BMI was associated with increased likelihood of obstructive phenotype and correlated negatively with FEV_1/FVC ratio z-scores from childhood to young adulthood. In children, faster weight growth is associated with higher FVC and FEV_1 values [40]. BMI gain during early childhood has, however, greater influence on lung volume than airway growth, which may lead to airway dysanapsis [41, 42]. This is a phenomenon where the growth of the lung parenchyma is beyond the caliber of the airways leading to a higher FVC than FEV_1, and a lower than expected FEV_1/FVC ratio [43]. Of high clinical relevance is the observation that among obese children with asthma, dysanapsis has been associated with severe disease exacerbations [41]. Lower BMI during early childhood has in other studies been associated with lower FVC [42] and restrictive spirometric phenotype [44]. Those results indicate that maintenance of normal BMI during childhood to early adulthood may lead to improved respiratory health. In addition, the influence of BMI on lung function could differ depending on the proportion of different body components (i.e., fat mass and lean mass) [45, 46]. Due to lack of body composition data in our study, we cannot explore these mechanisms further.

Strengths and Limitations

Using data from 14 population-based cohorts in Europe, we provide robust estimates on the prevalence of obstructive and restrictive phenotypes from childhood to young adulthood. However, some limitations of the current study should be noted. Firstly, our current study is exploratory. Although three well-known early life risk factors and lifestyle factors were taken into account, residual confounding, by e.g., diet or physical activity, and unexplored risk factors may still be an issue. Besides, the

definition of restrictive phenotype in the current study was based on spirometry, which is commonly used in population-based studies [9, 10] but was not confirmed by residual volume and/or total lung capacity data. While the obstructive disease has received much attention in recent years, less is known about factors associated with restrictive outcomes. Future studies may explore the association between a restrictive phenotype and other early life factors, such as additional perinatal factors (including extreme prematurity), growth trajectories, air pollution exposure, respiratory insults, and diet [47, 48]. In addition, we did not have the possibility to explore potential influence of allergic comorbidities such as atopy, atopic dermatitis or allergic rhinitis, as earlier studies have indicated [49, 50]. Secondly, our study included almost 50,000 participants from 14 population-based cohorts from Europe, which provides high study power and external validity of the results, but also introduces some heterogeneity according to the fit of the GLI equation. In order to make the results comparable between cohorts, we centered the z-scores in each cohort according to the mean values of non-asthmatic, asymptomatic lifelong non-smokers [14]. Thirdly, not all cohorts contributed data on all the risk factors, but we included all available variables in the regression analysis. In addition, definitions in some risk factors slightly differed between cohorts as appears in the appendix.

Conclusions

Both obstructive and restrictive phenotypes do indeed occur during childhood and early adulthood but without a clear age trend. Participants with the obstructive phenotype more often reported asthma and wheezing symptoms. In addition, several well-known risk factors for airway disease in adults were associated with the obstructive phenotype across ages, including asthma family history, preterm birth, smoking, and higher BMI, while the only identified factor related to the restrictive phenotype was lower BMI, pointing to other reasons for this phenotype in children compared to adults. Further studies on the mechanisms of these functional abnormalities are warranted.

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REFERENCES

1. Vasquez MM, Zhou M, Hu C, Martinez FD, Guerra S. Low Lung Function in Young Adult Life Is Associated with Early Mortality. *Am J Respir Crit Care Med* 2017: 195(10): 1399-1401.
2. Agustí A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *Lancet Respir Med* 2017: 5(12): 935-945.
3. Vaz Fragoso CA, McAvay G, Van Ness PH, Casaburi R, Jensen RL, MacIntyre N, Klar Yaggi H, Gill TM, Concato J. Phenotype of spirometric impairment in an aging population. *Am J Respir Crit Care Med* 2016: 193(7): 727-735.
4. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, Nair H, Gasevic D, Sridhar D, Campbell H, Chan KY, Sheikh A, Rudan I. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. *J Glob Health* 2015: 5(2): 020415.
5. Jankowich M, Elston B, Liu Q, Abbasi S, Wu W-C, Blackshear C, Godfrey M, Choudhary G. Restrictive Spirometry Pattern, Cardiac Structure and Function, and Incident Heart Failure in African Americans. The Jackson Heart Study. *Annals of the American Thoracic Society* 2018: 15(10): 1186-1196.
6. Honda Y, Watanabe T, Shibata Y, Otaki Y, Kadowaki S, Narumi T, Takahashi T, Kinoshita D, Yokoyama M, Nishiyama S, Takahashi H, Arimoto T, Shishido T, Inoue S, Miyamoto T, Konta T, Kawasaki R, Daimon M, Kato T, Ueno Y, Kayama T, Kubota I. Impact of restrictive lung disorder on cardiovascular mortality in a general population: The Yamagata (Takahata) study. *Int J Cardiol* 2017: 241: 395-400.
7. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and functional limitation: data from the Third National Health and Nutrition Examination. *J Intern Med* 2003: 254(6): 540-547.
8. Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax* 2003: 58(5): 388-393.
9. Wijnant SRA, De Roos E, Kavousi M, Stricker BH, Terzikhan N, Lahousse L, Brusselle GG. Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam Study. *Eur Respir J* 2020: 55(1).
10. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Morbidity and mortality associated with the restrictive spirometric pattern: a longitudinal study. *Thorax* 2010: 65(6): 499-504.
11. Agustí A, Hogg JC. Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2019: 381(13): 1248-1256.
12. Wan ES, Fortis S, Regan EA, Hokanson J, Han MK, Casaburi R, Make BJ, Crapo JD, DeMeo DL, Silverman EK. Longitudinal Phenotypes and Mortality in Preserved Ratio Impaired Spirometry in the COPDGene Study. *Am J Respir Crit Care Med* 2018: 198(11): 1397-1405.
13. Agusti A, Faner R, Donaldson G, Heuvelin E, Breyer-Kohansal R, Melén E, Maitland-van der Zee AH, Vestbo J, Allinson JP, Vanfleteren LEGW, van den Berge M, Adcock IM, Lahousse L, Brusselle G, Wedzicha JA. Chronic Airway Diseases Early Stratification (CADSET): a new ERS Clinical Research Collaboration. *Eur Respir J* 2019: 53(3).

14. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MSM, Zheng J, Stocks J. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012: 40(6): 1324-1343.
15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005: 26(2): 319-338.
16. Quanjer PH, Pretto JJ, Brazzale DJ, Boros PW. Grading the severity of airways obstruction: new wine in new bottles. *Eur Respir J* 2014: 43(2): 505-512.
17. Gavaghan DJ, Moore AR, McQuay HJ. An evaluation of homogeneity tests in meta-analyses in pain using simulations of individual patient data. *Pain* 2000: 85(3): 415-424.
18. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed)* 2003: 327(7414): 557-560.
19. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002: 21(11): 1539-1558.
20. Quanjer PH, Stocks J, Cole TJ, Hall GL, Stanojevic S. Influence of secular trends and sample size on reference equations for lung function tests. *Eur Respir J* 2011: 37(3): 658-664.
21. Wang G, Kull I, Bergström A, Hallberg J, Bergström PU, Guerra S, Pershagen G, Gruzieva O, van Hage M, Georgelis A, Janson C, Lindén A, Melén E. Early-life risk factors for reversible and irreversible airflow limitation in young adults: findings from the BAMSE birth cohort. *Thorax* 2020.
22. Çolak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Prevalence, Characteristics, and Prognosis of Early Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. *Am J Respir Crit Care Med* 2020: 201(6): 671-680.
23. Backman H, Eriksson B, Hedman L, Stridsman C, Jansson S-A, Sovijärvi A, Lindberg A, Rönmark E, Lundbäck B. Restrictive spirometric pattern in the general adult population: Methods of defining the condition and consequences on prevalence. *Respir Med* 2016: 120: 116-123.
24. Agusti A, Breyer-Kohansal R, Faner R. Transitioning from infancy to adulthood: a black box full of opportunities. *Eur Respir J* 2021: 57(3).
25. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet (London, England)* 2008: 371(9608): 261-269.
26. den Dekker HT, Sonnenschein-van der Voort AMM, de Jongste JC, Anessi-Maesano I, Arshad SH, Barros H, Beardsmore CS, Bisgaard H, Phar SC, Craig L, Devereux G, van der Ent CK, Esplugues A, Fantini MP, Flexeder C, Frey U, Forastiere F, Gehring U, Gori D, van der Gugten AC, Henderson AJ, Heude B, Ibarluzea J, Inskip HM, Keil T, Kogevinas M, Kreiner-Møller E, Kuehni CE, Lau S, Mélen E, Mommers M, Morales E, Penders J, Pike KC, Porta D, Reiss IK, Roberts G, Schmidt A, Schultz ES, Schulz H, Sunyer J, Torrent M, Vassilaki M, Wijga AH, Zabaleta C, Jaddoe VWV, Duijts L. Early growth characteristics and the risk of reduced lung function and asthma: A meta-analysis of 25,000 children. *J Allergy Clin Immunol* 2016: 137(4): 1026-1035.

27. Um-Bergström P, Hallberg J, Thunqvist P, Berggren-Broström E, Anderson M, Adenfelt G, Lilja G, Ferrara G, Sköld CM, Melén E. Lung function development after preterm birth in relation to severity of Bronchopulmonary dysplasia. *BMC pulmonary medicine* 2017: 17(1): 97.
28. Simpson SJ, Hallberg J. The PELICAN (Prematurity's Effect on the Lungs In Children and Adults Network) ERS Clinical Research Collaboration: understanding the impact of preterm birth on lung health throughout life. *Eur Respir J* 2021: 57(4).
29. Stick SM, Burton PR, Gurrin L, Sly PD, LeSouëf PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet (London, England)* 1996: 348(9034): 1060-1064.
30. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2001: 163(2): 429-436.
31. Neuman Å, Hohmann C, Orsini N, Pershagen G, Eller E, Kjaer HF, Gehring U, Granell R, Henderson J, Heinrich J, Lau S, Nieuwenhuijsen M, Sunyer J, Tischer C, Torrent M, Wahn U, Wijga AH, Wickman M, Keil T, Bergström A. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. *Am J Respir Crit Care Med* 2012: 186(10): 1037-1043.
32. Ulrik CS. Outcome of asthma: longitudinal changes in lung function. *Eur Respir J* 1999: 13(4): 904-918.
33. McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, Wise RA, Szefler SJ, Sharma S, Kho AT, Cho MH, Croteau-Chonka DC, Castaldi PJ, Jain G, Sanyal A, Zhan Y, Lajoie BR, Dekker J, Stamatoyannopoulos J, Covar RA, Zeiger RS, Adkinson NF, Williams PV, Kelly HW, Grasemann H, Vonk JM, Koppelman GH, Postma DS, Raby BA, Houston I, Lu Q, Fuhlbrigge AL, Tantisira KG, Silverman EK, Tonascia J, Weiss ST, Strunk RC. Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma. *N Engl J Med* 2016: 374(19): 1842-1852.
34. Melén E, Guerra S, Hallberg J, Jarvis D, Stanojevic S. Linking COPD epidemiology with pediatric asthma care: Implications for the patient and the physician. *Pediatr Allergy Immunol* 2019: 30(6): 589-597.
35. Hancox RJ, Poulton R, Greene JM, McLachlan CR, Pearce MS, Sears MR. Associations between birth weight, early childhood weight gain and adult lung function. *Thorax* 2009: 64(3): 228-232.
36. Pei L, Chen G, Mi J, Zhang T, Song X, Chen J, Ji Y, Li C, Zheng X. Low birth weight and lung function in adulthood: retrospective cohort study in China, 1948-1996. *Pediatrics* 2010: 125(4): e899-e905.
37. Johnston ID, Strachan DP, Anderson HR. Effect of pneumonia and whooping cough in childhood on adult lung function. *N Engl J Med* 1998: 338(9): 581-587.
38. Vatrella A, Calabrese C, Mattiello A, Panico C, Costigliola A, Chiodini P, Panico S. Abdominal adiposity is an early marker of pulmonary function impairment: Findings from a Mediterranean Italian female cohort. *Nutr Metab Cardiovasc Dis* 2016: 26(7): 643-648.
39. Berger KI, Reibman J, Oppenheimer BW, Vlahos I, Harrison D, Goldring RM. Lessons from the World Trade Center disaster: airway disease presenting as restrictive dysfunction. *Chest* 2013: 144(1): 249-257.

40. Sonnenschein-van der Voort AMM, Howe LD, Granell R, Duijts L, Sterne JAC, Tilling K, Henderson AJ. Influence of childhood growth on asthma and lung function in adolescence. *J Allergy Clin Immunol* 2015: 135(6).
41. Forno E, Weiner DJ, Mullen J, Sawicki G, Kurland G, Han YY, Cloutier MM, Canino G, Weiss ST, Litonjua AA, Celedón JC. Obesity and Airway Dysanapsis in Children with and without Asthma. *Am J Respir Crit Care Med* 2017: 195(3): 314-323.
42. Peralta GP, Abellan A, Montazeri P, Basterrechea M, Esplugues A, González-Palacios S, Roda C, Santa-Marina L, Sunyer J, Vrijheid M, Casas M, Garcia-Aymerich J. Early childhood growth is associated with lung function at 7 years: a prospective population-based study. *Eur Respir J* 2020: 56(6).
43. Mead J. Dysanapsis in normal lungs assessed by the relationship between maximal flow, static recoil, and vital capacity. *Am Rev Respir Dis* 1980: 121(2): 339-342.
44. Ali GB, Bui DS, Lodge CJ, Waidyatillake NT, Perret JL, Sun C, Walters EH, Abramson MJ, Lowe AJ, Chandrika Dharmage S. Infant Body Mass Index Trajectories, and Asthma & Lung Function. *J Allergy Clin Immunol* 2021.
45. Mensink-Bout SM, Santos S, van Meel ER, Oei EHG, de Jongste JC, Jaddoe VWV, Duijts L. General and Organ Fat Assessed by Magnetic Resonance Imaging and Respiratory Outcomes in Childhood. *Am J Respir Crit Care Med* 2020: 201(3): 348-355.
46. Peralta GP, Fuertes E, Granell R, Mahmoud O, Roda C, Serra I, Jarvis D, Henderson J, Garcia-Aymerich J. Childhood Body Composition Trajectories and Adolescent Lung Function. Findings from the ALSPAC study. *Am J Respir Crit Care Med* 2019: 200(1): 75-83.
47. Breyer-Kohansal R, Faner R, Breyer M-K, Ofenheimer A, Schrott A, Studnicka M, Wouters EFM, Burghuber OC, Hartl S, Agusti A. Factors Associated with Low Lung Function in Different Age Bins in the General Population. *Am J Respir Crit Care Med* 2020: 202(2): 292-296.
48. Agier L, Basagaña X, Maitre L, Granum B, Bird PK, Casas M, Oftedal B, Wright J, Andrusaityte S, de Castro M, Cequier E, Chatzi L, Donaire-Gonzalez D, Grazuleviciene R, Haug LS, Sakhi AK, Leventakou V, McEachan R, Nieuwenhuijsen M, Petraviciene I, Robinson O, Roumeliotaki T, Sunyer J, Tamayo-Uria I, Thomsen C, Urquiza J, Valentin A, Slama R, Vrijheid M, Siroux V. Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort. *Lancet Planet Health* 2019: 3(2): e81-e92.
49. Hallberg J, Ballardini N, Almqvist C, Westman M, van Hage M, Lilja G, Bergström A, Kull I, Melén E. Impact of IgE sensitization and rhinitis on inflammatory biomarkers and lung function in adolescents with and without asthma. *Pediatric Allergy and Immunology* 2019: 30(1): 74-80.
50. Lødrup Carlsen KC, Mowinckel P, Hovland V, Håland G, Riiser A, Carlsen K-H. Lung function trajectories from birth through puberty reflect asthma phenotypes with allergic comorbidity. *J Allergy Clin Immunol* 2014: 134(4).

FIGURE LEGENDS

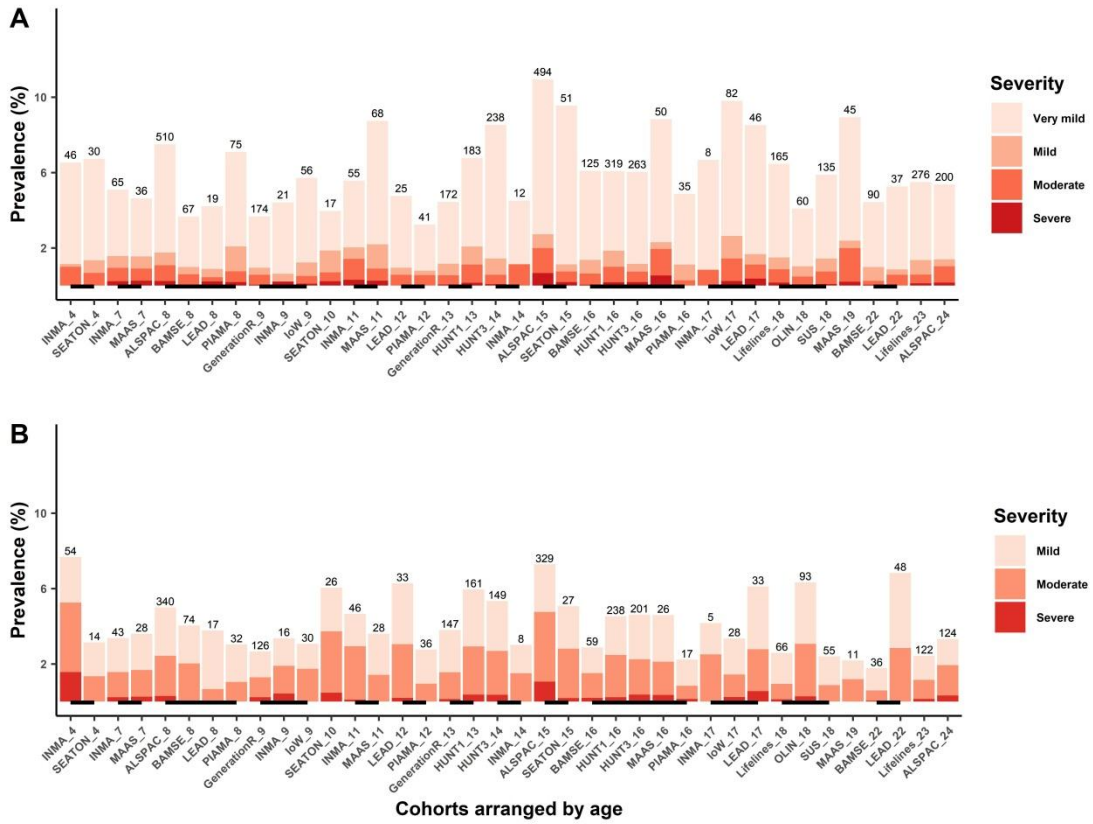

Figure 1. Prevalence of the obstructive (A) and restrictive phenotypes (B) from early childhood to young adulthood. The numbers above each bar represent the number of cases in the respective study. Cohorts linked by lines had the same mean age (in years).

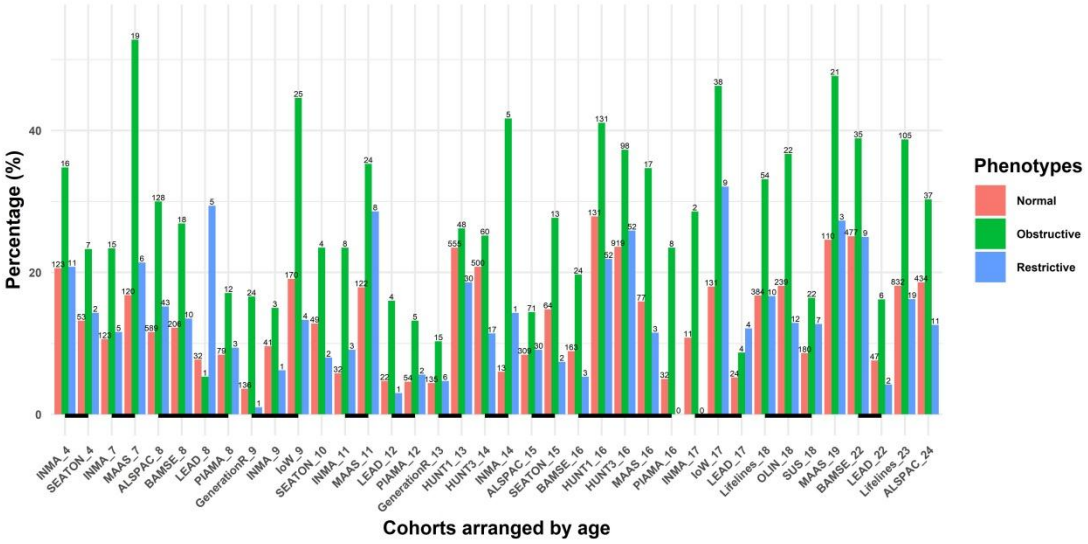

Figure 2. Prevalence of any wheezing in participants with obstructive or restrictive phenotypes, or normal lung function. The numbers above each bar represent the number of cases in the respective study. Cohorts linked by lines had the same mean age (in years).

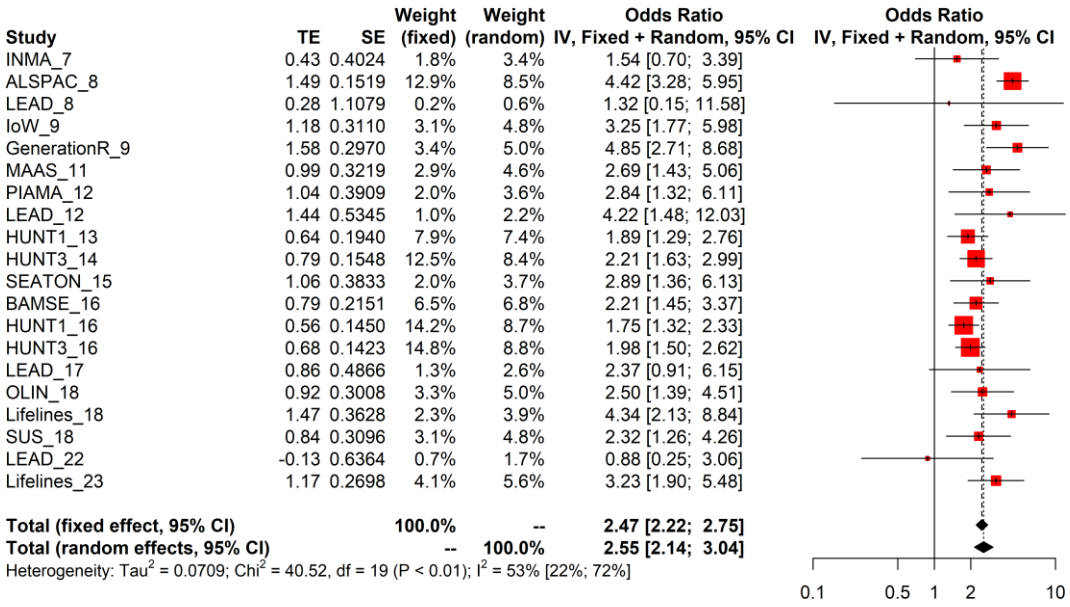

Figure 3. Meta-analysis results of association between asthma and obstructive phenotype in 5-25 years subgroup.

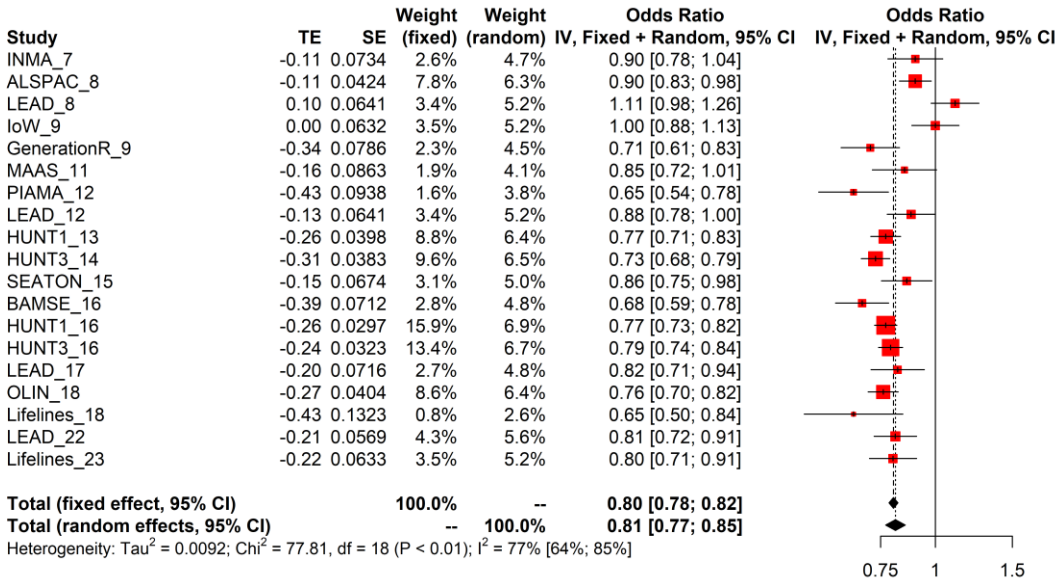

Figure 4. Meta-analysis results of association between body mass index and restrictive phenotype in Model 2 in 5-25 years age group.

Online Data Supplement

"Spirometric phenotypes from early childhood to young adulthood – A CADSET (Chronic Airway Disease Early Stratification) study"

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Supplementary Content

Cohort-specific methods (alphabetical order)

Avon Longitudinal Study of Parents and Children (ALSPAC)

Design and study population

Pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992 were invited to take part in the study [1-3]. The initial number of pregnancies enrolled is 14,541 (for these at least one questionnaire has been returned or a "Children in Focus" clinic had been attended by 19/07/99). Of these initial pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age.

When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 24 is 913 (456, 262 and 195 recruited during Phases II, III and IV respectively), resulting in an additional 913 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper and its update. The total sample size for analyses using any data collected after the age of seven is therefore 15,454 pregnancies, resulting in 15,589 fetuses. Of these 14,901 were alive at 1 year of age.

A 10% sample of the ALSPAC cohort, known as the Children in Focus (CiF) group, attended clinics at the University of Bristol at various time intervals between 4 to 61 months of age. The CiF group were chosen at random from the last 6 months of ALSPAC births (1432 families attended at least one clinic). Excluded were those mothers who had moved out of the area or were lost to follow-up, and those partaking in another study of infant development in Avon.

Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool" and reference the following webpage: http://www.bristol.ac.uk/alspac/researchers/our-data/

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via

questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

Definitions of potential confounders and covariates

Premature birth was defined as babies who were delivered before 37 completed weeks of gestation.

Maternal smoking during pregnancy was defined as self-reported active tobacco smoking during any trimester of pregnancy.

Asthma family history was defined as combined self-reported maternal and paternal asthma ever.

Smoking exposure during childhood at 8 years was defined as mother reported child in a smoky room during weekdays/weekends. Smoking status at 15 and 24 years were defined as self-reported active smoking from questionnaires and clinics.

Asthma at 8 (mother reported), 15 (self-reported) and 24 (self-reported) years was defined as doctor diagnosis ever.

Asthma in the last 12 months at 8 (mother reported), 15 (self-reported) and 24 (self-reported) years was defined as doctor diagnosis ever and (current symptoms or medication).

Current wheeze at 8 (mother reported), 15 (self-reported) and 24 (self-reported) was defined as wheezing in the last 12 months.

Data at 24 years was collected and managed using REDCap electronic data capture tools [4] hosted at University of Bristol. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies.

Children (Barn), Allergy, Milieu, Stockholm, Epidemiology (BAMSE)

Design and study population

BAMSE (Children, Allergy, Milieu, Stockholm, Epidemiology in Swedish) is a prospective population-based cohort study of children recruited at birth and followed during childhood and early adulthood. Details of the study design, inclusion criteria, enrolment and data collection are described elsewhere [5]. Between February 1994 and November 1996, 4089 infants from inner-city, urban and suburban districts of Stockholm were included in the cohort.

Data on background characteristics, respiratory health, and exposure factors were obtained from parental questionnaires administered at age of 2 months. Follow-up questionnaires were repeatedly answered by parents at age of 1, 2, 4, 8, 12, and 16 years. The response rates were 96%, 94%, 91%, 84%, 82% and 78%, respectively. At the 24-year follow-up, questionnaires focusing on respiratory symptoms and key exposures such as smoking habits were answered by the participants themselves. Details about the definitions of health outcomes and covariates are provided in the online supplement.

Definitions of potential confounders and covariates

Premature birth was defined as babies who were delivered before 37 completed weeks of gestation.

Maternal smoking during pregnancy was defined as the mother smoked at least one cigarette per day at any point in time during pregnancy.

Asthma family history was defined as any parent with a doctor's diagnosis of asthma and asthma medication of mother or father at the time of questionnaire 0.

Parental smoking during childhood was defined as any of the parents smoking ≥1 cigarette per day at each visit time point.

Smoking status were defined as positive answers to the question related to smoke: 1) Yes, sometimes or 2) Yes, every day.

Asthma was defined as ever been diagnosed asthma by a doctor at all follow-up time (8, 16 and 24 years).

Asthma in the last 12 months was defined if at least two of the following three criteria were fulfilled: doctor's diagnosis of asthma ever; wheezing in the last 12 months; and/or use of asthma medication during the last 12 months.

Any wheeze was defined as at least 1 episode of wheeze in the last 12 months prior to the visit data.

Generation R

Design and study population

The Generation R Study is a population-based prospective cohort study from fetal life until adulthood conducted in the Netherlands, Rotterdam [6]. The study is designed to identify early environmental and genetic causes, and causal pathways leading to normal and abnormal growth, development and health from fetal life, childhood and young adulthood. In total, 9,778 mothers with a delivery date from April 2002 until January 2006 were enrolled. Of these mothers 9,749 gave birth to live born children. Response at baseline was 61%, and general follow-up rates until the age of 13 years were around 80%. Data collection in children and their parents includes questionnaires, interviews, detailed physical and ultrasound examinations, behavioral observations, lung function, Magnetic Resonance Imaging and biological sampling. For the current project, the total number of subjects was 4,738 and 3,869 at age 9 and 13 years, respectively. Information on maternal ethnicity, preterm birth, maternal smoking during pregnancy, and parental asthma was obtained by self-reported questionnaires during pregnancy, and midwife or hospital registries. Child height and weight were measured without shoes and heavy clothing, and in standing position at the research center. Information on wheezing and asthma of the child was obtained by questions adapted from the International Study on Asthma and Allergy in Childhood (ISAAC) questionnaires. Lung function at the ages of 9 and 13 years of the child was measured by spirometry according to ATS/ERS guidelines.

Definitions of potential confounders and covariates

Categories of ethnicity were created based on country of births of parents according to Statistics Netherlands into the Global Lung Function Initiative categories of ethnicity.

Premature birth was defined as birth before 37 weeks of gestational age.

Maternal smoking during pregnancy was defined as ever maternal smoking in pregnancy.

Parental asthma was defined as maternal or paternal history of asthma.

Body mass index (BMI) was calculated based on measured height and weight

Ever asthma was categorized based on the question: “Has your child ever had asthma diagnosed by a doctor? (no; yes)”

Current asthma was defined by means of the MeDALL criteria: 2 out of 3 of the following questions: Has your child ever been diagnosed with asthma by a doctor? or/and Has your child suffered from a wheezing chest in these past 12 months? or/and Has your child received prescribed medication for asthma symptoms in the past 12 months?

Any wheeze in the last 12 months was categorized based on the question: "Has your child suffered from attacks of wheezing in the chest in the past 12 months? (no; yes)"

More than 3 episodes of wheeze in the last 12 months were categorized based on the question: "Has your child suffered from attacks of wheezing in the chest in the past 12 months?" (No/Yes, less than 4 attacks/Yes, 4 or more attacks)

Current maternal smoking during childhood at age 9 years categorized based on the question: "Have you ever smoked? (No; yes, but stopped; yes, I still do) "

Trøndelag Health Study (HUNT)

Design and study population

The Trøndelag Health Study (HUNT) is a population-based study having invited all inhabitants aged 13- 104 years living in the Nord-Trøndelag region to participate in questionnaires, interviews and clinical measurement in four data collections from 1984 to 2019. In 2019 questionnaire data also were collected from the Sør-Trøndelag region, including 104.000 participants (40% of invited) [7].

In Nord-Trøndelag, HUNT invited persons aged 20 + in 1984-86 (HUNT1), 1995-97 (HUNT2), 2006-08 (HUNT3) and 2017-19 (HUNT4), while corresponding data collections from adolescents aged 13-19 years were performed in Young-HUNT1 (1995-97), Young-HUNT3 (2006-08) and YoungHUNT4 (2017-19). The adults were invited to field stations located in all municipalities, while Young-HUNT performed data collection at schools. In the four HUNT studies number of participants (% of invited) have been, 77,000 (89%), 65,000 (69%), 51,000 (54%) and 56,000 (54%) in HUNT1, 2, 3 and 4, respectively. In Young-HUNT 9000 (88%), 8200 (78%), and 8000 (76%) participated in Young-HUNT 1,3 and 4, respectively. Among all participants in YoungHUNT1 and 3, and samples of participants in the adult part of HUNT (11-15000 persons) were included in spirometry[8].

Definitions of potential confounders and covariates

Smoking status was defined based on answers to question on: never-smoking, previous smoking, current daily or occasional smoking.

Asthma was defined as ever been diagnosed asthma by a doctor.

Any wheeze was defined as: any wheeze or dyspnoea in the last 12 months prior to the visit data.

INfancia y Medio Ambiente – Environment and Childhood (INMA)

Design and study population

INMA (INfancia y Medio Ambiente – Environment and Childhood; http://www.proyectoinma.org) is a prospective population-based birth cohort study in several regions of Spain: Gipuzkoa, Menorca, Sabadell, and Valencia. This project aims to study the associations between pre- and postnatal environmental exposures and growth, health, and development from early fetal life until adolescence and has been described previously in detail [9]. Pregnant women recruitment took place between 1997 and 1998 in Menorca and between 2003 and 2008 in Gipuzkoa, Sabadell, and Valencia. Inclusion criteria were as follows: to be at least 16 years old, to have intention to deliver in the reference hospital, to have a singleton pregnancy, not have any assisted conception, and not have any communication problems. Children have been followed from birth until 12 years in Gipuzkoa, Sabadell, and Valencia and until 18 years in Menorca. Data on sociodemographic characteristics, lifestyle factors, and respiratory symptoms was obtained from mothers during pregnancy and in each follow-up of the child. Informed consent was obtained from all participants and the study was approved by the Hospital Ethics Committees in each participating region.

Definitions of potential confounders and covariates

Premature birth was defined as less than 37 weeks of gestational age.

Maternal smoking during pregnancy …

Asthma family history was defined as maternal history of allergic asthma, allergic rhinitis or eczema.

Parental smoking during childhood was defined …

Smoking status…

Asthma was defined as ever been diagnosed asthma by a doctor at all follow-up times.

Any wheeze was defined as at least 1 episode of wheeze in the last 12 months prior to the visit data. …

Isle of Wight (IoW)

Design and study population

IOW is an unselected birth cohort study established in 1989 on the Isle of Wight, UK [10-12]. After the exclusion of adoptions, perinatal deaths, and refusal for follow-up, written informed consent was obtained from parents to enrol 1,456 newborns born between 1st January 1989 and 28th February 1990. Follow-up assessments were conducted to 26 years of age to prospectively study the development of asthma and allergic diseases. At each follow-up, validated questionnaires were completed by the parents. Additionally, the Skin Prick Test (SPT) was performed on 980, 1036 and 853 participants at 4, 10 and 18 years of age to check allergic reactions to common allergens. At 10, 18, and 26 years, spirometry and methacholine challenge tests were performed to diagnose lung problems. Ethics approvals were obtained from the Isle of Wight Local Research Ethics Committee (now named the National Research Ethics Service, NRES Committee South Central – Southampton B) at recruitment and for the subsequent follow-ups.

Definitions of potential confounders and covariates

Asthma was defined as "yes" to "have you ever had asthma?"

Asthma in the last 12 months was defined as "yes" to "have you ever had asthma?" and either of "have you had wheezing in the last 12 months"? or "have you had current asthma treatment?".

Any wheeze was defined as at least 1 episode of wheeze in the last 12 months. Number of wheeze attacks was defined as 1-3, 4-12, >12 wheeze attacks in the last 12 months.

Asthma family history was defined as any parent with diagnosis of asthma of mother or father at the time of questionnaire.

Premature birth was defined as babies who were delivered before 37 completed weeks of gestation.

Maternal smoking during pregnancy was defined as the mother smoking at least one cigarette per day at the time of recruitment (i.e. a few days after giving birth while inpatient).

Smoking status was defined as positive answer to the question "Do you currently smoke".

Parental smoking during childhood was defined as any of the parents smoking ≥1 cigarette per day inside the house at each follow-up.

Lung, hEart, sociAl, boDy (LEAD)

Design and study population

The Austrian (Lung, hEart, sociAl, boDy) LEAD Study (NCT01727518) is a single-centered, longitudinal, observational, population-based cohort study aiming to investigate the relationship between genetic, environmental, social, developmental and ageing factors influencing respiratory health and co-morbidities through life. In total, 11,423 male and female, aged 6–80 years have been recruited randomly from the national inhabitants register stratified by age, gender and residential area from Vienna (urban population) and Lower Austria (rural population). Study population participated and completed their first visit from 2012-2016 including main measurements and questionnaires described in detail elsewhere [13].

Definitions of potential confounders and covariates

Asthma was a current "doctor`s diagnosis of Asthma" .

Wheezing was defined as "wheezing in sudden attacks and/or wheezing without cold".

Asthma family history was defined as any parent with doctor`s diagnosis of asthma of mother and/or father ever.

Premature birth was defined as birth <260 days of gestation and/or birth weight or <2500g .

Maternal smoking during pregnancy was defined as the mother smoking regularly during pregnancy.

Parental smoking during childhood was defined as any of the parents smoked regularly during childhood.

Current smoking was defined as reported smoking regularly.

Lifelines

Design and study population

LifeLines [14], population base study Since all inhabitants in The Netherlands are registered with a general practitioner (GP), eligible participants were invited to participate in the LifeLines Cohort Study through their GP. A large number of GPs within the northern three provinces of The Netherlands (Friesland, Groningen and Drenthe) were involved and invited all their patients between the ages of 25 and 50 years, unless the participating GP considered the patient not eligible based on the following criteria: severe psychiatric or physical illness;

limited life expectancy (<5 years); insufficient knowledge of the Dutch language to complete a Dutch questionnaire. Subsequently, individuals who were interested to participate received detailed information by mail about the LifeLines Cohort Study, and an informed consent form. After the signed informed consent was received by the LifeLines organization, the participants received a baseline questionnaire and an invitation to a comprehensive health assessment at the LifeLines research site. During the visit, participants were asked to indicate whether their family members, such as partners, parents, parents-in-law and children would also be willing to participate in the study. If so, permission was asked to send them an invitation to participate. Children could only participate if one of their parents was a participant. In addition, inhabitants of the northern provinces could also register themselves via the LifeLines website. Aged between 25 and 50 and living in the 3 northern provinces of The Netherlands (Friesland, Groningen, Drenthe). Of these included subjects the children, partners, and parents were also invited (could be any age). Subjects had to master Dutch so that they could complete the questionnaire and understand the instructions during the visit. severe psychiatric or physical illness, limited life expectancy (<5 years), insufficient knowledge of the Dutch language to complete a Dutch questionnaire.

Definitions of potential confounders and covariates

Premature birth was defined as babies who were delivered before 37 completed weeks of gestation.

Maternal smoking during pregnancy was self-reported in the questionnaires. Positive answers were considered if they reported that the mother smoked less or as usual during pregnancy.

Asthma family history was defined as any parent with a doctor's diagnosis of asthma at the baseline visit.

Parental smoking during childhood was defined as any of the parents smoked regularly during childhood in the self-reported question.

Smoking status were defined as positive answers to the question related to smoke, excluding recent starters, ex-smokers who smoked less than a year, current/ex-smokers without information on duration.

Asthma was defined as ever been diagnosed asthma by a doctor at the baseline visit. .

Asthma in the last 12 months was not defined in Lifelines cohort.

Any wheeze ever was defined as positive answer in the self-reported question: "Have you ever suffered from wheezing?"

Manchester Asthma and Allergy Study (MAAS)

Design and study population

MAAS is an unselected birth cohort study established in 1995 in Manchester, UK [15]. It consists of a mixed urban-rural population within 50 square miles of South Manchester and Cheshire, United Kingdom located within the maternity catchment area of Wythenshawe and Stepping Hill Hospitals. All pregnant women were screened for eligibility at antenatal visits (8-10th week of pregnancy). Of the 1499 couples who met the inclusion criteria ($\leq$10 weeks of pregnancy, maternal age $\geq$18 years, and questionnaire and skin prick data test available for both parents), 288 declined to take part in the study and 27 were lost to follow-up between recruitment and the birth of a child. A total of 1184 children were born into the study between February 1996 and April 1998. They were followed prospectively for 19 years to date and attended follow-up clinics for assessments, which included lung function measurements, skin

prick testing, biological samples (serum, plasma and urine), and questionnaire data collection. The study was approved by the North West – Greater Manchester East Research Ethics Committee.

Definitions of potential confounders and covariates

Preterm birth was defined as babies who were delivered before 37 completed weeks of gestation.

Maternal smoking during pregnancy was defined as the mother smoking at recruitment.

Parental smoking status was defined as maternal and/or paternal current smoking at each follow-up.

Asthma family history was defined as any parent with a doctor's diagnosis of asthma at recruitment.

Asthma was defined as ever being diagnosed with asthma by a doctor at all follow-up times.

Current wheeze was defined wheezing or whistling in the chest in the last 12 months. Number of wheeze attacks was defined as 1-3, 4-12, >12 wheeze attacks in the last 12 months.

Current asthma medication is defined as the use of medicines, pills, puffers or other medication for wheezing or asthma in the last 12 months.

Obstructive Lung Disease in Northern Sweden (OLIN)

Design and study population

The OLIN (Obstructive Lung Disease in Northern Sweden) studies is an epidemiological research programme about asthma, allergy, chronic obstructive pulmonary disease (COPD) ongoing since 1985. In 2006, the second OLIN-paediatric cohort was recruited, consisting of a prospective population-based cohort of schoolchildren followed through childhood and adolescence. All 2704 children in first and second grade (median age 8 years) in three municipalities in Norrbotten, Sweden were invited to a parental questionnaire and n=2585 participated (97% of invited). The study design has been described in detail elsewhere [16]. The questionnaire included the International Study of Asthma and Allergy among children (ISAAC) core questions and additional questions about respiratory symptoms, family history, physician-diagnoses and treatment of asthma, rhinitis and eczema as well as background

characteristics and exposures. The cohort was followed-up by a parental questionnaire at age 12 years, and by self-completed questionnaires at age 15 and 19 years of age. At age 19 years, the children in two of the municipalities were invited to clinical examinations including spirometry and n=1470 participated.

Definitions of potential confounders and covariates

Maternal smoking during pregnancy was defined as an affirmative answer to the question "Did the mother smoke during pregnancy?"

Asthma family history was defined as mother or father having asthma.

BMI was calculated based on height and weight measured at the follow-up at age 19 years.

Smoking status was based on the question "Are you a non-smoker, former smoker or current smoker?" in the follow-up at age 19 years.

Asthma was defined as an affirmative answer to the question "Have you been diagnosed by a physician as having asthma?"

Any wheeze in the last 12 months was defined as an affirmative answer to the question "Have you had wheezing or whistling in the chest in the last 12 months?"

Prevention and Incidence of Asthma and Mite Allergy (PIAMA)

Design and study population

PIAMA (Prevention and Incidence of Asthma and Mite Allergy) is an ongoing birth cohort study. Details of the study design have been published previously [17, 18]. In brief, pregnant women were recruited from the general population through antenatal clinics in the north, west and center of the Netherlands in 1996-1997. The baseline study population consisted of 3963 newborns. Questionnaires were completed by the parents during pregnancy, when the child was 3 months old, and then annually from 1 up to 8 years; at ages 11, 14 and 17 years, questionnaires were completed by the parents as well as the participants themselves. Data were obtained on child and family characteristics, a wide range of environmental and lifestyle exposures and on asthma and other allergic and respiratory outcomes. Lung function was measured at age 8-, 12-, and 16-years using spirometry. The Medical Ethical Committees of

the participating institutes approved the study, and written informed consent was obtained from all parents or legal guardians.

Definitions of potential confounders and covariates

Premature birth was defined as babies who were delivered before 37 completed weeks of gestation.

Maternal smoking during pregnancy was defined as the mother smoked at least during the first 4 weeks of pregnancy.

Asthma family history was defined as any parent with a doctor's diagnosis of asthma.

Passive smoking during childhood was defined as any person smoking ≥1 cigarette per week in the house at each visit time point.

Current smoking status was defined as any current smoking regardless of frequency.

Asthma was defined as ever been diagnosed asthma by a doctor at each visit time point.

Asthma in the last 12 months was defined if a child has a doctor's diagnosis of asthma ever and wheezing or shortness of breath in the last 12 months and use of asthma medication in the last 12 months.

Wheeze was defined as at least 1 episode of wheeze in the last 12 months prior to the visit data.

SEATON

Design and study population

SEATON is an unselected birth cohort study established in 1997 in Aberdeen, UK, which was designed to explore the relationship between antenatal dietary exposures and asthma outcomes in childhood [19]. 2000 healthy pregnant women attending an antenatal clinic, at median 12 weeks gestation, were recruited. An interviewer administered a questionnaire to the women and atopic status was ascertained by skin prick test (SPT). The cohort included 1924 children born between April 1998 and December 1999. Participants were recruited prenatally and followed up by self−completion questionnaire to 15 years of age using postal questionnaires to record the presence of asthma and allergic diseases. Lung function

measurements and SPT to common allergens was performed at 5, 10 and 15 years. The study was approved by the North of Scotland Research Ethics Committee.

Definitions of potential confounders and covariates

Preterm birth was defined as babies who were delivered before 37 completed weeks of gestation.

Maternal smoking during pregnancy was defined as the mother smoking at recruitment. Parental smoking status was not available.

Asthma heredity was defined as any parent with asthma at recruitment. Asthma was defined as asthma ever confirmed by a doctor at all follow-up times.

Current wheeze was defined wheezing in the chest in the last 12 months.

Number of wheeze attacks was defined as 1-3, 4-12, >12 wheeze attacks in the last 12 months.

SUS

Design and study population

SUS contains a cross-sectional and a longitudinal study of young farmers and, as controls, a group of male army recruits. The cohort was established during the period February 1992 to February 1994 and consisted of 1,734 male and 230 female farming students. Additionally, 407 randomly chosen army recruits served as controls. At baseline, data on demographics, respiratory health, and exposure characteristics were collected. The participation rate was 79% among the farming students and 61% among the army recruits. For five years, the participants were followed with annual questionnaires and phone interviews. A comprehensive follow-up was done in 2007 tracking new addresses, deaths, and emigration by use of the Danish Civil Registration System. At this follow-up, 1170 participants were re-examined, representing an overall attrition rate of 51.7%. Further information on the cohort can be found elsewhere [20].

Definitions of potential confounders and covariates

Asthma was defined as self-reported, doctor diagnosed asthma.

Parental asthma heredity was defined as reported asthma among one or both parents.

Any wheeze was defined as ever being bothered by wheeze without having a cold.

Smoking status was classified in three groups. Smoking status was defined as “Never” if the person reported to never have smoked one or more cigarettes a day in a period longer than 14 days and to not be a current smoker. Smoking status was defined as “Former” if the person reported to have smoked one or more cigarettes a day in a period longer than 14 days, but not to be a current smoker. Smoking status was defined as “Current” if the person reported to be a current smoker.

Cohort-specific acknowledgements (alphabetical order)

ALSPAC

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

BAMSE

We thank the children and parents participating in the BAMSE cohort and all staff involved in the study through the years.

Generation R

We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam, and the whole Generation R team.

HUNT

We thank the population of the Nord-Trøndelag Region as well as the staff involved for their contribution to the data collection.

INMA

The authors would particularly like to thank all the participants for their generous collaboration. A full roster of the INMA Project Investigators can be found at https://www.proyectoinma.org/en/inma-project/inmaproject-researchers/.

IoW

The IOW research team are grateful to all the participants and their families for their support over the years and also to the many fellow researchers who have contributed to the cohort's follow up.

LEAD

We thank all participants for their willingness to contribute to medical research as well as all field workers for their daily work.

Lifelines

NA

MAAS

We thank study participants and their parents for their continued support and enthusiasm, and greatly appreciate the commitment they have given to the project. We also acknowledge the hard work and dedication of the study teams (post-doctoral scientists, physiologists, research fellows, nurses, technicians, and clerical staff).

OLIN

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PIAMA

We would like to thank the PIAMA participants and their parents, all researchers, fieldworkers, and data managers for their contributions to the study.

SEATON

The SEATON research team are grateful to all the participants and their families for their support over the years and also to the many fellow researchers who have contributed to the cohort's follow up.

SUS

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Cohort-specific funding statements (alphabetical order)

ALSPAC

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BAMSE

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Generation R

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HUNT

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INMA

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IoW

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LEAD

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MAAS

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OLIN

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PIAMA

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SEATON

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SUS

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Tables

Table E1. The definitions of spirometry phenotypes and severity.

Spirometric phenotypes	Definition	Subgroups	Severity grading
Normal	FEV_1/FVC z-score >= -1.65 AND FVC z-score >= -1.65	NA	NA
Restrictive phenotype	FEV_1/FVC z-score >= -1.65 AND FVC z-score < -1.65	Mild	-2 ≤ FVC z-score < -1.65
		Moderate	-3 ≤ FVC z-score < -2
		Severe	FVC z-score < -3
Obstructive phenotype	FEV_1/FVC z-score < -1.65	Very mild	FEV_1 z-score ≥ -1.65
		Mild	-2 ≤ FEV_1 z-score < -1.65
		Moderate	-3 ≤ FEV_1 z-score < -2
		Severe	FEV_1 z-score < -3

Table E2. Meta-analysis results of z-scores in different age groups.*

Variables	Age groups	Number of cohorts	I2	P for Q statistic	OR	95% CI
FEV_1 z-score						
Preterm birth	<10	9	28.5	0.19	-0.22	-0.29 to -0.15
	>10 - 15	6	0.0	0.71	-0.15	-0.25 to -0.04
	>15 - 20	9	0.0	0.74	-0.10	-0.20 to -0.0037
	>20 - 25	4	0.0	0.90	-0.048	-0.15 to 0.051
	5 - 25	10	18.2	0.26	-0.16	-0.23 to -0.10
Maternal smoking during pregnancy	<10	9	0.0	0.90	-0.056	-0.095 to -0.018
	>10 - 15	6	26.3	0.23	-0.068	-0.13 to -0.003
	>15 - 20	11	17.8	0.27	-0.086	-0.13 to -0.04
	>20 - 25	4	0.0	0.73	-0.044	-0.10 to 0.016
	5 - 25	12	0.0	0.47	-0.088	-0.12 to -0.054
Asthma family history	<10	9	0.0	0.90	-0.056	-0.095 to -0.018
	>10 - 15	6	26.3	0.23	-0.068	-0.13 to -0.003
	>15 - 20	11	17.8	0.27	-0.086	-0.13 to -0.04
	>20 - 25	4	0.0	0.73	-0.044	-0.10 to 0.016
	5 - 25	12	0.0	0.47	-0.088	-0.12 to -0.054
BMI	<10	9	70.3	<0.001	0.05	0.035 to 0.064
	>10 - 15	8	90.0	<0.001	0.064	0.046 to 0.082
	>15 - 20	12	99.8	<0.001	0.093	-0.012 to 0.20
	>20 - 25	4	98.1	<0.001	0.028	-0.006 to 0.063
	5 - 25	13	99.8	<0.001	0.088	0.023 to 0.15
Former smoker	>10 - 15	2	0.0	0.78	-0.018	-0.15 to 0.11
	>15 - 20	10	11.0	0.34	-0.036	-0.077 to 0.0064
	>20 - 25	4	0.5	0.39	0.12	0.058 to 0.18
	10 - 25	11	51.8	0.01	0.014	-0.044 to 0.073
Current smoker	>10 - 15	2	60.9	0.11	0.041	-0.25 to 0.34
	>15 - 20	11	0.0	0.59	-0.0046	-0.045 to 0.036
	>20 - 25	4	66.5	0.03	0.061	-0.044 to 0.17
	10 - 25	11	40.6	0.052	0.025	-0.024 to 0.073
FVC z-score						
Preterm birth	<10	9	28.8	0.19	-0.11	-0.19 to -0.043
	>10 - 15	6	0.0	0.95	-0.076	-0.18 to 0.026
	>15 - 20	9	0.0	0.93	0.031	-0.063 to 0.12
	>20 - 25	4	0.0	0.88	0.031	-0.067 to 0.13
	5 - 25	10	0.0	0.52	-0.061	-0.12 to -0.0015
Maternal smoking during pregnancy	<10	9	23.7	0.23	0.0096	-0.023 to 0.042
	>10 - 15	6	50.8	0.058	-0.018	-0.11 to 0.07
	>15 - 20	10	28.2	0.19	0.049	-0.007 to 0.11
	>20 - 25	4	0.0	0.78	0.08	0.016 to 0.14
	5 - 25	11	27.0	0.16	0.015	-0.015 to 0.044
Asthma family history	<10	9	0.0	0.94	0.019	-0.019 to 0.058
	>10 - 15	6	0.0	0.53	0.027	-0.037 to 0.091
	>15 - 20	11	0.0	0.71	0.015	-0.029 to 0.059
	>20 - 25	4	0.0	0.91	0.041	-0.016 to 0.097
	5 - 25	12	0.0	0.94	0.0049	-0.028 to 0.038
BMI	<10	9	65.1	0.0034	0.07	0.057 to 0.083
	>10 - 15	8	97.4	<0.001	0.096	0.062 to 0.13

	>15 - 20	12	97.6	<0.001	0.086	0.064 to 0.11
	>20 - 25	4	99.2	<0.001	0.064	0.012 to 0.12
	5 - 25	13	98.1	<0.001	0.099	0.077 to 0.12
	>10 - 15	2	0.0	0.91	0.043	-0.081 to 0.17
Former	>15 - 20	10	0.0	0.62	0.038	-0.0033 to 0.078
smoker	>20 - 25	4	63.4	0.042	0.11	0.0062 to 0.22
	10 - 25	11	34.2	0.095	0.062	0.015 to 0.11
	>10 - 15	2	53.1	0.14	0.11	-0.15 to 0.37
Current	>15 - 20	11	26.4	0.19	0.082	0.043 to 0.12
smoker	>20 - 25	4	0.0	0.52	0.16	0.11 to 0.22
	10 - 25	11	36.6	0.077	0.11	0.064 to 0.15
FEV_1/FVC z-score						
	<10	9	54.2	0.026	-0.12	-0.24 to 0.0051
	>10 - 15	6	0.0	0.58	-0.12	-0.22 to -0.016
Preterm birth	>15 - 20	9	37.8	0.12	-0.21	-0.31 to -0.11
	>20 - 25	4	0.0	0.90	-0.13	-0.23 to -0.032
	5 - 25	10	27.0	0.17	-0.16	-0.22 to -0.10
	<10	9	26.3	0.21	-0.066	-0.10 to -0.031
Maternal	>10 - 15	6	0.0	0.98	-0.093	-0.14 to -0.045
smoking during	>15 - 20	10	0.0	0.82	-0.13	-0.19 to -0.07
pregnancy	>20 - 25	4	10.0	0.34	-0.14	-0.21 to -0.074
	5 - 25	11	23.0	0.20	-0.074	-0.11 to -0.042
	<10	9	0.0	0.68	-0.13	-0.17 to -0.085
	>10 - 15	6	0.0	0.59	-0.15	-0.21 to -0.084
Asthma family history	>15 - 20	11	0.0	0.88	-0.17	-0.21 to -0.12
	>20 - 25	4	60.3	0.056	-0.13	-0.24 to -0.02
	5 - 25	12	0.0	0.56	-0.14	-0.18 to -0.11
	<10	9	65.8	0.0029	-0.04	-0.052 to -0.028
	>10 - 15	8	96.3	<0.001	-0.056	-0.084 to -0.028
BMI	>15 - 20	12	87.3	<0.001	-0.055	-0.068 to -0.043
	>20 - 25	4	98.0	<0.001	-0.066	-0.11 to -0.026
	5 - 25	13	95.9	<0.001	-0.064	-0.08 to -0.049
	>10 - 15	2	0.0	0.53	-0.086	-0.21 to 0.035
Former	>15 - 20	10	13.9	0.31	-0.12	-0.17 to -0.083
smoker	>20 - 25	4	51.5	0.10	-0.026	-0.12 to 0.071
	10 - 25	11	43.7	0.036	-0.075	-0.13 to -0.021
	>10 - 15	2	0.0	1.00	-0.09	-0.24 to 0.055
Current	>15 - 20	11	54.8	0.015	-0.13	-0.20 to -0.066
smoker	>20 - 25	4	76.4	0.0053	-0.15	-0.28 to -0.03
	10 - 25	11	60.2	0.0014	-0.13	-0.19 to -0.074

* Model was adjusted for asthma family history, maternal smoking during pregnancy, preterm birth, body mass index (BMI) and smoking status.

Figures

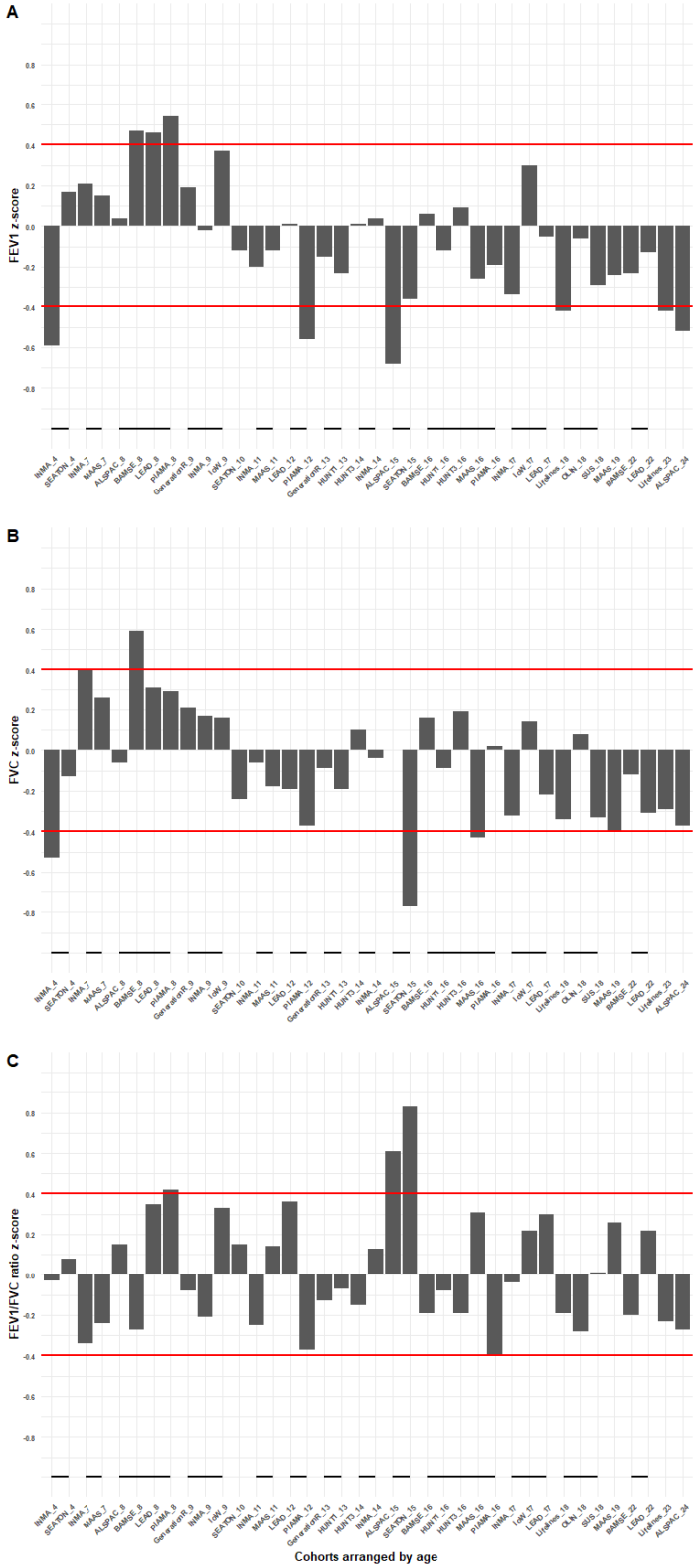


Figure E1. The GLI fit of FEV_1 (A), FVC (B) and FEV_1/FVC ratio (C) in each cohorts and time points. Cohorts linked by lines had the same mean age (in years).

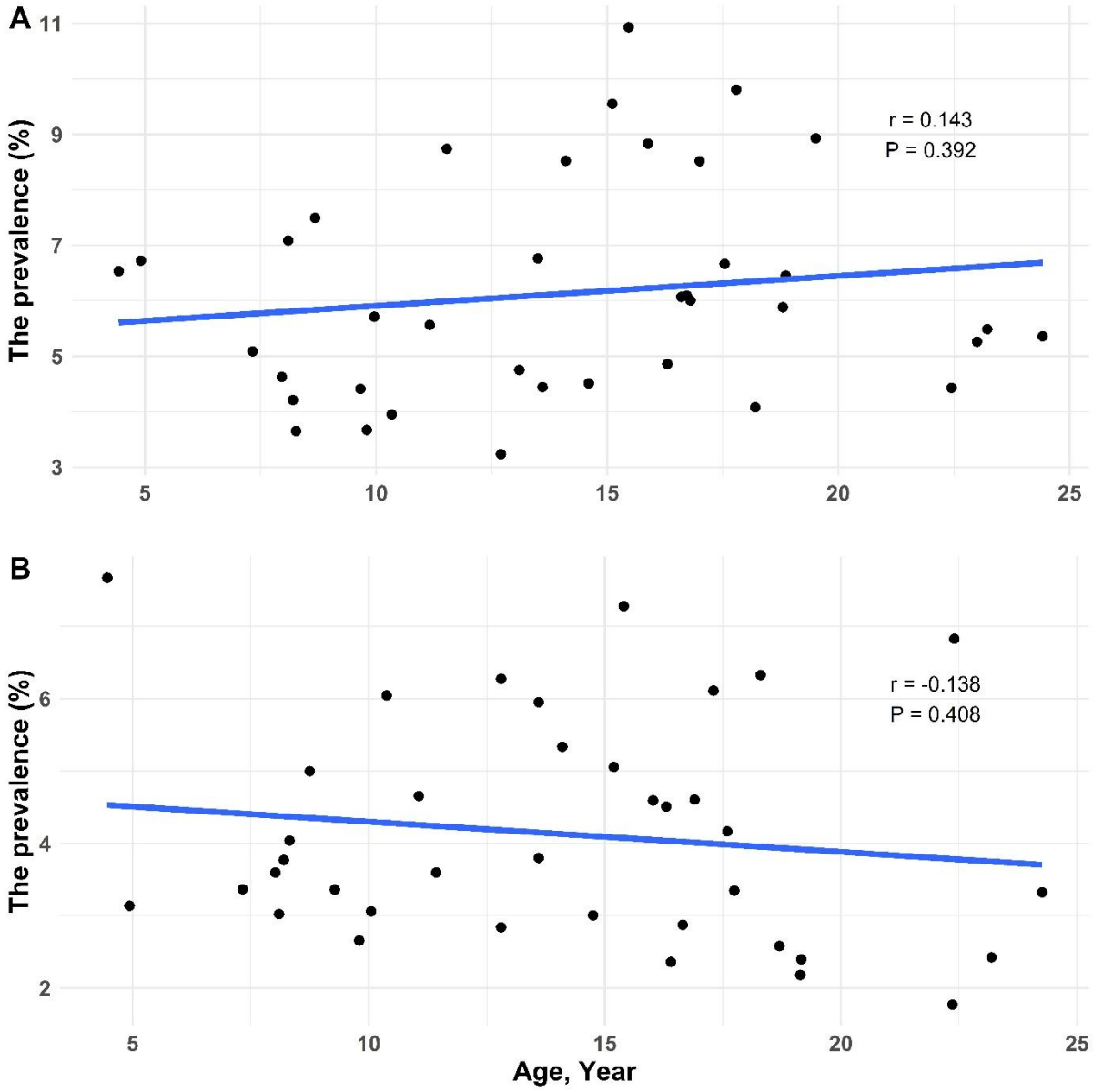


Figure E2. The associations between the cohort-specific prevalence of obstructive (A) and restrictive (B) phenotypes and age.

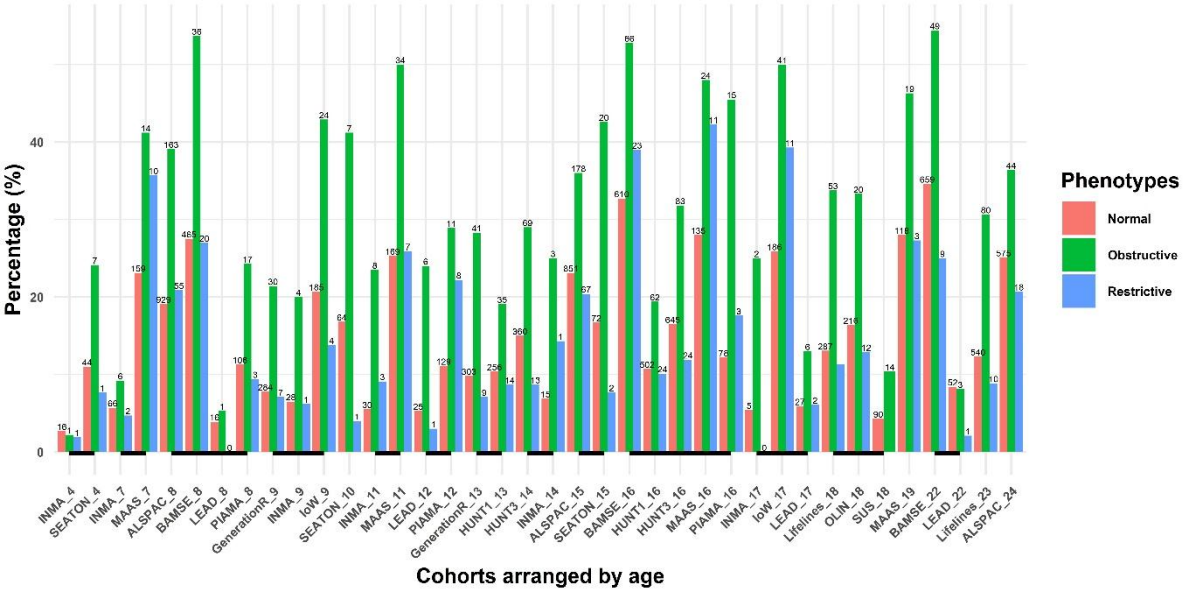
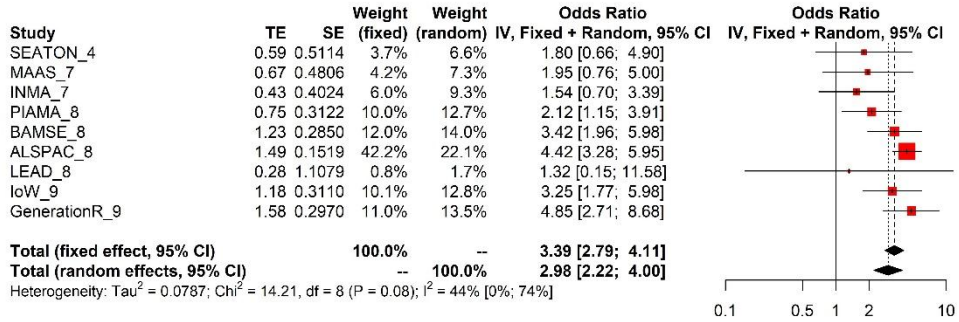
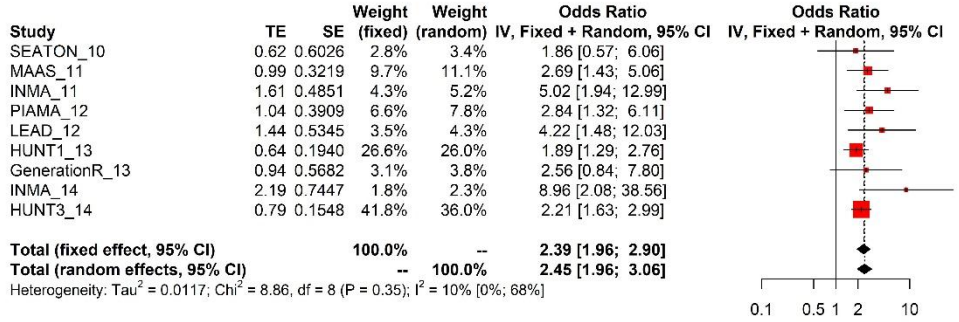


Figure E3. The prevalence of ever been diagnosed with asthma in participants with obstructive or restrictive phenotype, or normal lung function. The numbers above each bar represent the number of cases in the respective study. Cohorts linked by lines had the same mean age (in years).

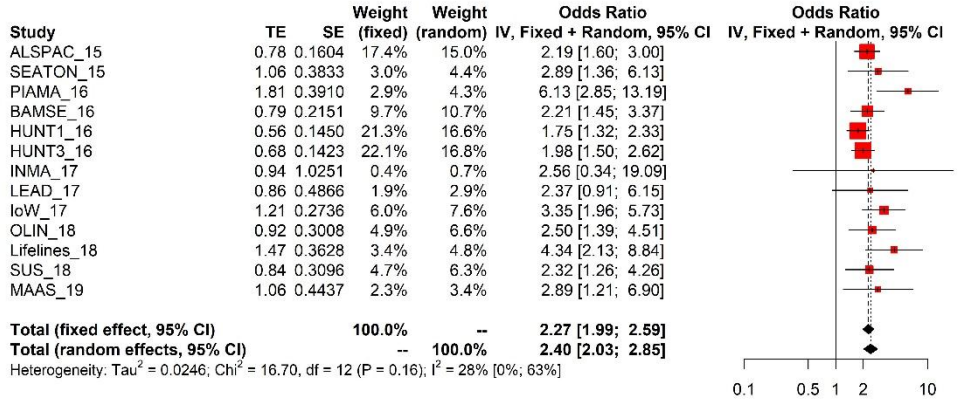
A



B



C



D

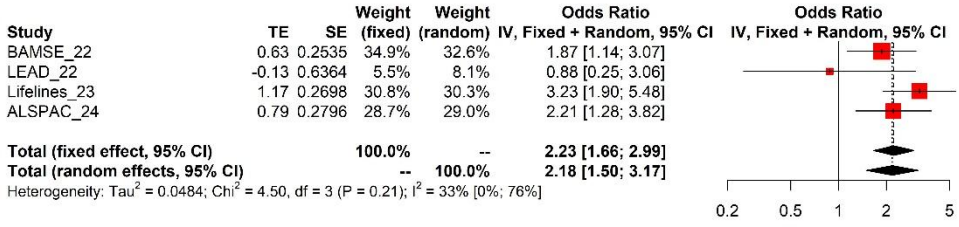
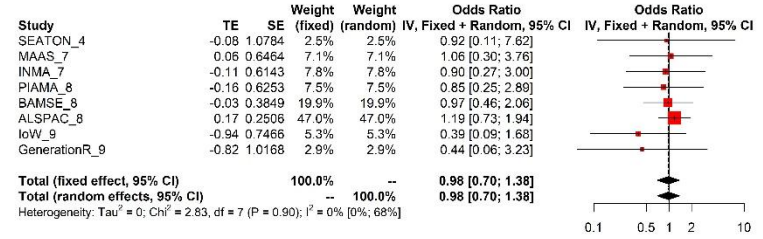
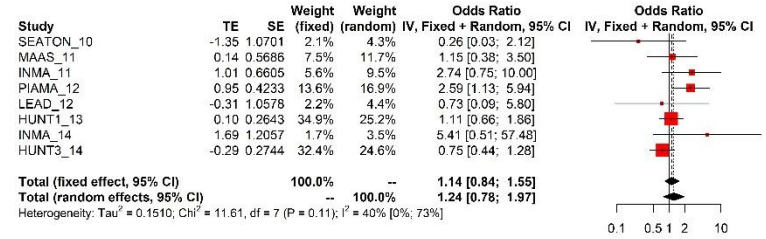


Figure E4. Meta-analysis results of association between asthma and obstructive phenotype in different age bins (A = age <10, B = age >10-15, C = age >15-20, and D = age >20-25).

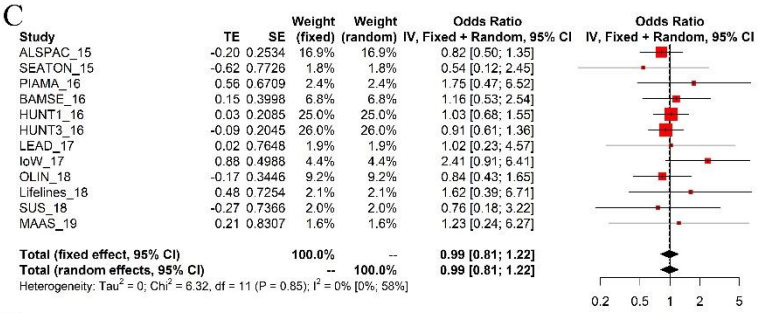
A



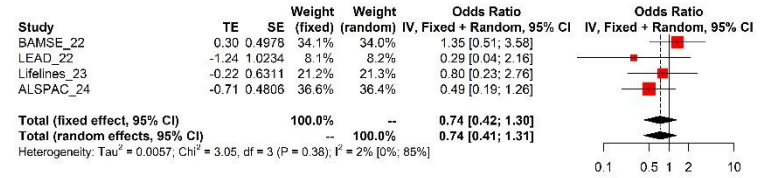
B



C



D



E

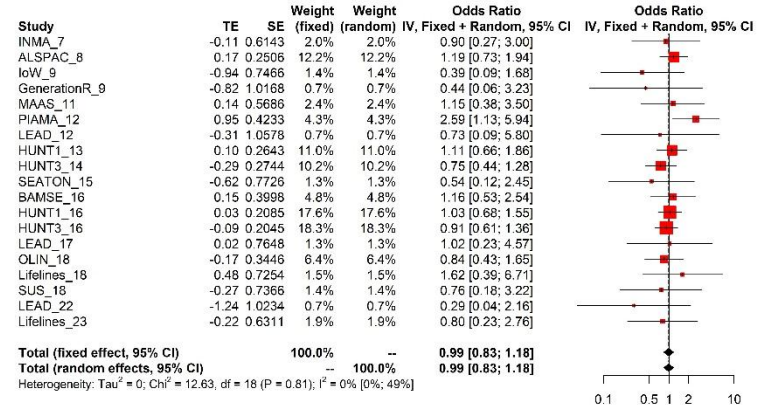
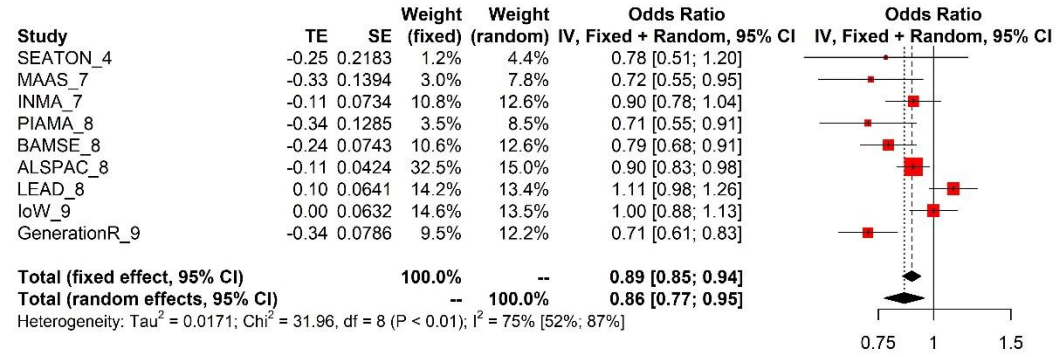
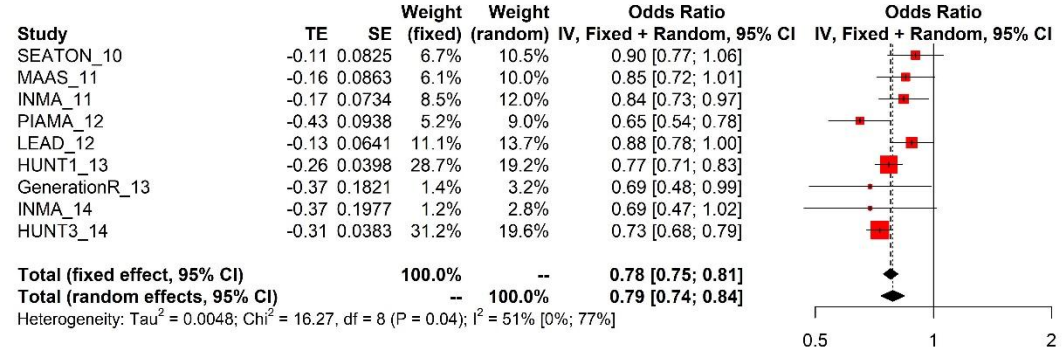


Figure E5. Meta-analysis results of association between asthma and restrictive phenotype in different age bins (A = age <10, B = age >10-15, C = age >15-20, D = age >20-25, and E = age 5-25 years).

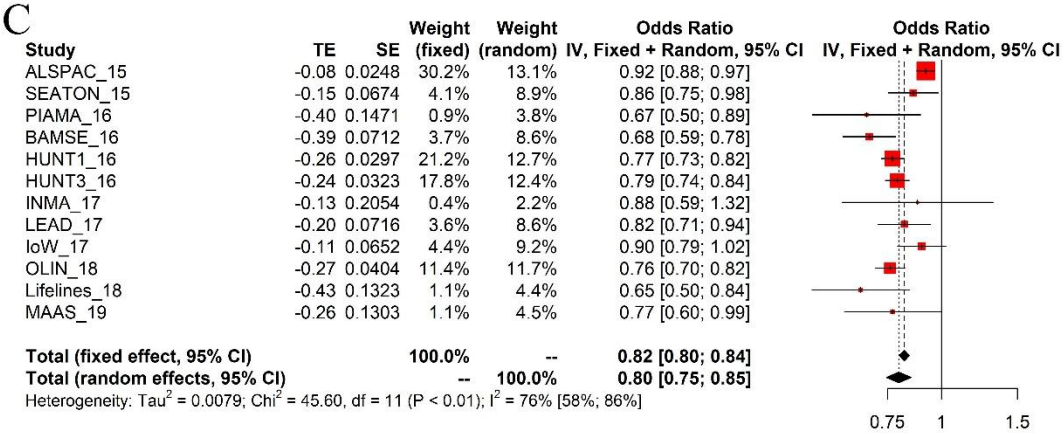
A



B



C



D

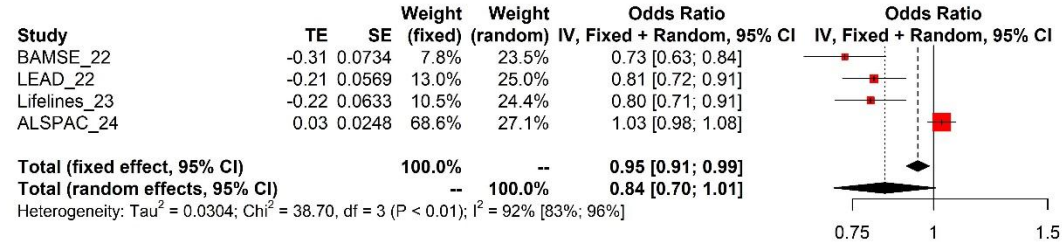


Figure E6. Meta-analysis results of association between body mass index and restrictive phenotype in Model 2 in different age bins (A = age <10, B = age >10-15, C = age >15-20, and D = age >20-25).

References

1. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* 2013: 42(1): 111-127.
2. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Henderson J, Macleod J, Molloy L, Ness A, Ring S, Nelson SM, Lawlor DA. Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol* 2013: 42(1).
3. Northstone K, Lewcock M, Groom A, Boyd A, Macleod J, Timpson N, Wells N. The Avon Longitudinal Study of Parents and Children (ALSPAC): an update on the enrolled sample of index children in 2019. *Wellcome Open Res* 2019: 4: 51.
4. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inf* 2009: 42(2): 377-381.
5. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol* 2002: 13(s15): 11-13.
6. Kooijman MN, Kruithof CJ, van Duijn CM, Duijts L, Franco OH, van Ijzendoorn MH, de Jongste JC, Klaver CCW, van der Lugt A, Mackenbach JP, Moll HA, Peeters RP, Raat H, Rings EHHM, Rivadeneira F, van der Schroeff MP, Steegers EAP, Tiemeier H, Uitterlinden AG, Verhulst FC, Wolvius E, Felix JF, Jaddoe VWV. The Generation R Study: design and cohort update 2017. *Eur J Epidemiol* 2016: 31(12): 1243-1264.
7. Holmen TL, Bratberg G, Krokstad S, Langhammer A, Hveem K, Midthjell K, Heggland J, Holmen J. Cohort profile of the Young-HUNT Study, Norway: a population-based study of adolescents. *Int J Epidemiol* 2014: 43(2): 536-544.
8. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, Bratberg G, Heggland J, Holmen J. Cohort Profile: the HUNT Study, Norway. *Int J Epidemiol* 2013: 42(4): 968-977.
9. Guxens M, Ballester F, Espada M, Fernández MF, Grimalt JO, Ibarluzea J, Olea N, Rebagliato M, Tardón A, Torrent M, Vioque J, Vrijheid M, Sunyer J. Cohort Profile: the INMA--INfancia y Medio Ambiente--(Environment and Childhood) Project. *Int J Epidemiol* 2012: 41(4): 930-940.
10. Kurukulaaratchy RJ, Fenn M, Twiselton R, Matthews S, Arshad SH. The prevalence of asthma and wheezing illnesses amongst 10-year-old schoolchildren. *Respir Med* 2002: 96(3): 163-169.
11. Kurukulaaratchy RJ, Fenn MH, Waterhouse LM, Matthews SM, Holgate ST, Arshad SH. Characterization of wheezing phenotypes in the first 10 years of life. *Clin Exp Allergy* 2003: 33(5): 573-578.
12. Arshad SH, Holloway JW, Karmaus W, Zhang H, Ewart S, Mansfield L, Matthews S, Hodgekiss C, Roberts G, Kurukulaaratchy R. Cohort Profile: The Isle Of Wight Whole Population Birth Cohort (IOWBC). *Int J Epidemiol* 2018: 47(4).
13. Breyer-Kohansal R, Hartl S, Burghuber OC, Urban M, Schrott A, Agusti A, Sigsgaard T, Vogelmeier C, Wouters E, Studnicka M, Breyer M-K. The LEAD (Lung, Heart, Social, Body) Study: Objectives, Methodology, and External Validity of the Population-Based Cohort Study. *J Epidemiol* 2019: 29(8): 315-324.
14. Scholtens S, Smidt N, Swertz MA, Bakker SJL, Dotinga A, Vonk JM, van Dijk F, van Zon SKR, Wijmenga C, Wolffenbuttel BHR, Stolk RP. Cohort Profile: LifeLines, a three-generation cohort study and biobank. *Int J Epidemiol* 2015: 44(4): 1172-1180.
15. Custovic A, Simpson BM, Murray CS, Lowe L, Woodcock A. The National Asthma Campaign Manchester Asthma and Allergy Study. *Pediatr Allergy Immunol* 2002: 13(s15): 32-37.
16. Rönmark E, Bjerg A, Perzanowski M, Platts-Mills T, Lundbäck B. Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden. *J Allergy Clin Immunol* 2009: 124(2): 357-363, 363.e351-315.
17. Brunekreef B, Smit J, de Jongste J, Neijens H, Gerritsen J, Postma D, Aalberse R, Koopman L, Kerkhof M, Wilga A, van Strien R. The prevention and incidence of asthma and mite

allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002: 13(s15): 55-60.
18. Wijga AH, Kerkhof M, Gehring U, de Jongste JC, Postma DS, Aalberse RC, Wolse APH, Koppelman GH, van Rossem L, Oldenwening M, Brunekreef B, Smit HA. Cohort profile: the prevention and incidence of asthma and mite allergy (PIAMA) birth cohort. *Int J Epidemiol* 2014: 43(2): 527-535.
19. Martindale S, McNeill G, Devereux G, Campbell D, Russell G, Seaton A. Antioxidant intake in pregnancy in relation to wheeze and eczema in the first two years of life. *Am J Respir Crit Care Med* 2005: 171(2): 121-128.
20. Elholm G, Omland O, Schlünssen V, Hjort C, Basinas I, Sigsgaard T. The cohort of young Danish farmers - A longitudinal study of the health effects of farming exposure. *Clin Epidemiol* 2010: 2: 45-50.