



# Spirometric phenotypes from early childhood to young adulthood: a Chronic Airway Disease Early Stratification study

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Shareable abstract (@ERSpublications)

**Obstructive and restrictive phenotypes are present from childhood to adulthood but without age trends. Established risk factors for airway disease are associated with the obstructive phenotype, whereas low BMI is associated with the restrictive.** <https://bit.ly/3BMoMtI>

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## 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 49334 participants from 14 population-based cohorts in different age groups ( $\leq 10$ ,  $>10$ –15,  $>15$ –20,  $>20$ –25 years, and overall, 5–25 years). The obstructive phenotype was defined as forced expiratory volume in 1 s ( $FEV_1$ )/forced vital capacity (FVC) z-score less than the lower limit of normal (LLN), whereas the restrictive phenotype was defined as  $FEV_1/FVC$  z-score  $\geq$ 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, 95% CI 1.01–1.35) and family history of asthma (aOR=1.44, 95% CI 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 phenotype (aOR=1.05, 95% CI 1.03–1.06 and aOR=0.81, 95% CI 0.78–0.85, per  $kg \cdot m^{-2}$  increase in BMI, respectively). Current smoking was associated with the obstructive phenotype in participants older than 10 years (aOR=1.24, 95% CI 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 the obstructive phenotype, whereas only low BMI was associated with the restrictive phenotype, suggesting different underlying pathobiology of these two phenotypes.

## 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 a lower than expected forced expiratory volume in 1 s/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

14 European population-based cohorts from seven countries were included in the current meta-analysis. A total of 49334 participants were included in the current study, and 18430 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 supplementary material.



### Measurements and definitions of outcomes

Pre-bronchodilator lung function was tested in each cohort according to the American Thoracic Society (ATS/ERS spirometry criteria [15]). FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/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 centring approach to make the cohorts more comparable. Centring was performed separately for each cohort and age group by subtracting the mean z-score (of FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/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 (supplementary Table E1): normal lung function was defined as the FEV<sub>1</sub>/FVC ratio and FVC z-scores equal to or higher than LLN. The obstructive phenotype was

**TABLE 1** Characteristics and forced expiratory volume in 1 s (FEV<sub>1</sub>), forced vital capacity (FVC) and FEV<sub>1</sub>/FVC ratio z-scores of each cohort included in the age groups

Cohorts	Nations	Age groups	n	Age <sup>#</sup>	FEV <sub>1</sub>		FVC		FEV <sub>1</sub> /FVC ratio	
					GLI fit <sup>#</sup>	Mean-centred <sup>¶</sup>	GLI fit <sup>#</sup>	Mean-centred <sup>¶</sup>	GLI fit <sup>#</sup>	Mean-centred <sup>¶</sup>
ALSPAC <sup>+</sup>	UK	>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 <sup>+</sup>	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 <sup>+</sup>	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 <sup>+</sup>	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
IoW	UK	>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
MAAS <sup>+</sup>	UK	>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
		>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
PIAMA <sup>+</sup>	Netherlands	>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
		>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
SEATON <sup>+</sup>	UK	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
		>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 are expressed as mean±sd. GLI: Global Lung Function Initiative. <sup>#</sup>: based on the whole group of participants; <sup>¶</sup>: based on non-asthmatic, asymptomatic lifelong nonsmokers; <sup>+</sup>: they are longitudinal cohorts with repeated measurement at different age.

defined as FEV<sub>1</sub>/FVC ratio z-score lower than LLN, and severity defined according to QUANJER *et al.* [16] as mild, moderate and severe according to thresholds of FEV<sub>1</sub>: z-score less than LLN but  $\geq -2$ ,  $< -2$  but  $\geq -3$  and  $< -3$ , respectively. In addition to these, a very mild group was added, defined as a FEV<sub>1</sub>/FVC ratio z-score lower than LLN and FEV<sub>1</sub> z-score greater or equal to LLN. The restrictive phenotype (“Low FVC, non-obstructive”) was defined as FEV<sub>1</sub>/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  $\geq -2$ ,  $< -2$  but  $\geq -3$  and  $< -3$ , 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<sub>1</sub>, FVC and FEV<sub>1</sub>/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 ( $\leq 10$ ,  $>10-15$ ,  $>15-20$ ,  $>20-25$  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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup>>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

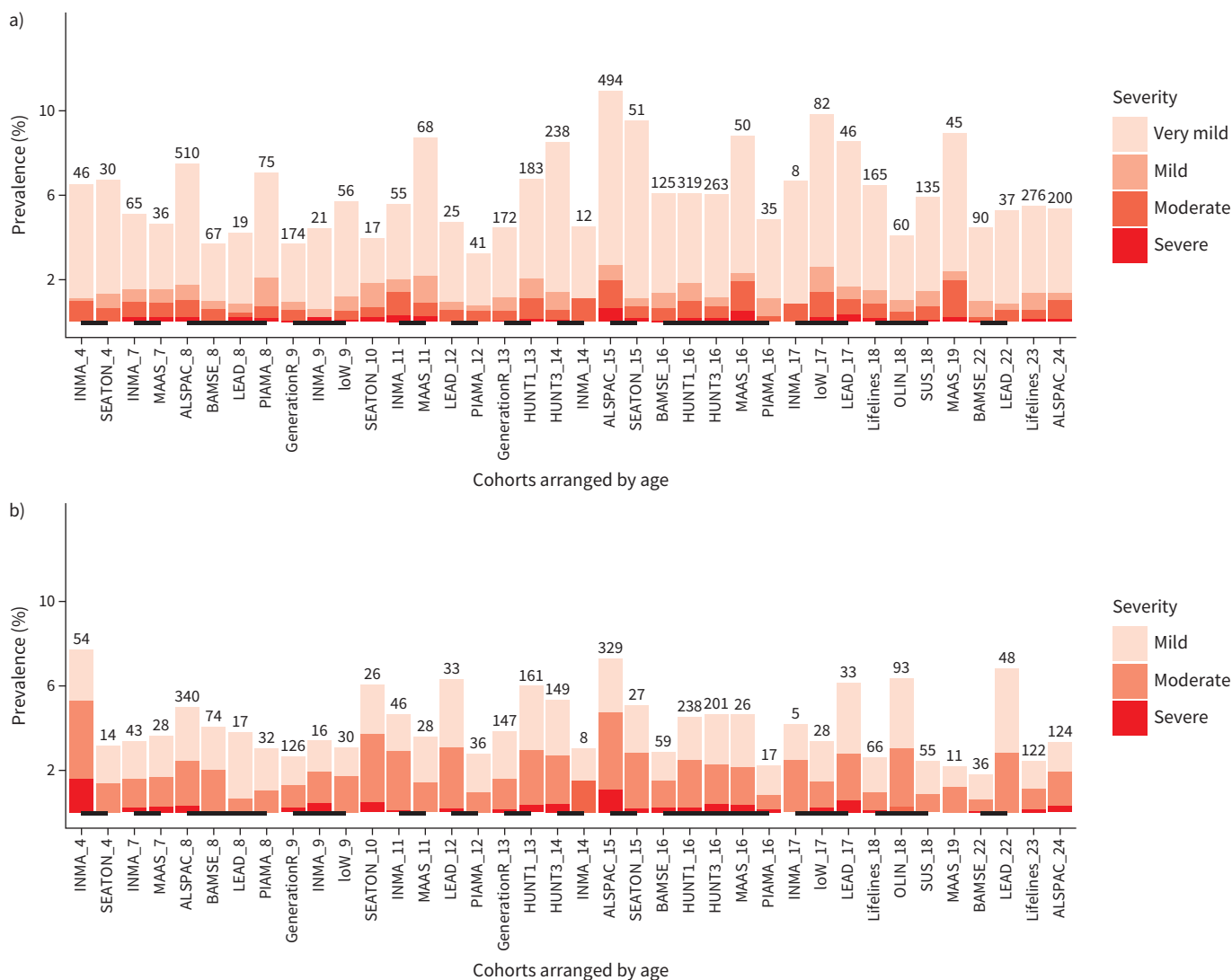
Table 1 illustrates the basic characteristics of the cohorts. Of the 14 included cohorts, seven (ALSPAC, BAMSE, Generation R, INMA, MAAS, PIAMA, SEATON) contributed repeated data from early childhood to young adulthood (age 4 to 25 years). Two, eight, eight, 13 and four cohorts contributed results in 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 nonsmokers 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, four and three cohorts, GLI fit estimates for FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC z-scores, respectively, were outside the suggested range using 0.4 as a cut-off [20] (supplementary Figure E1). Therefore, we proceeded with mean-centred 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.

### 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 b). 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, supplementary Figure E2A and E2B). Most participants with



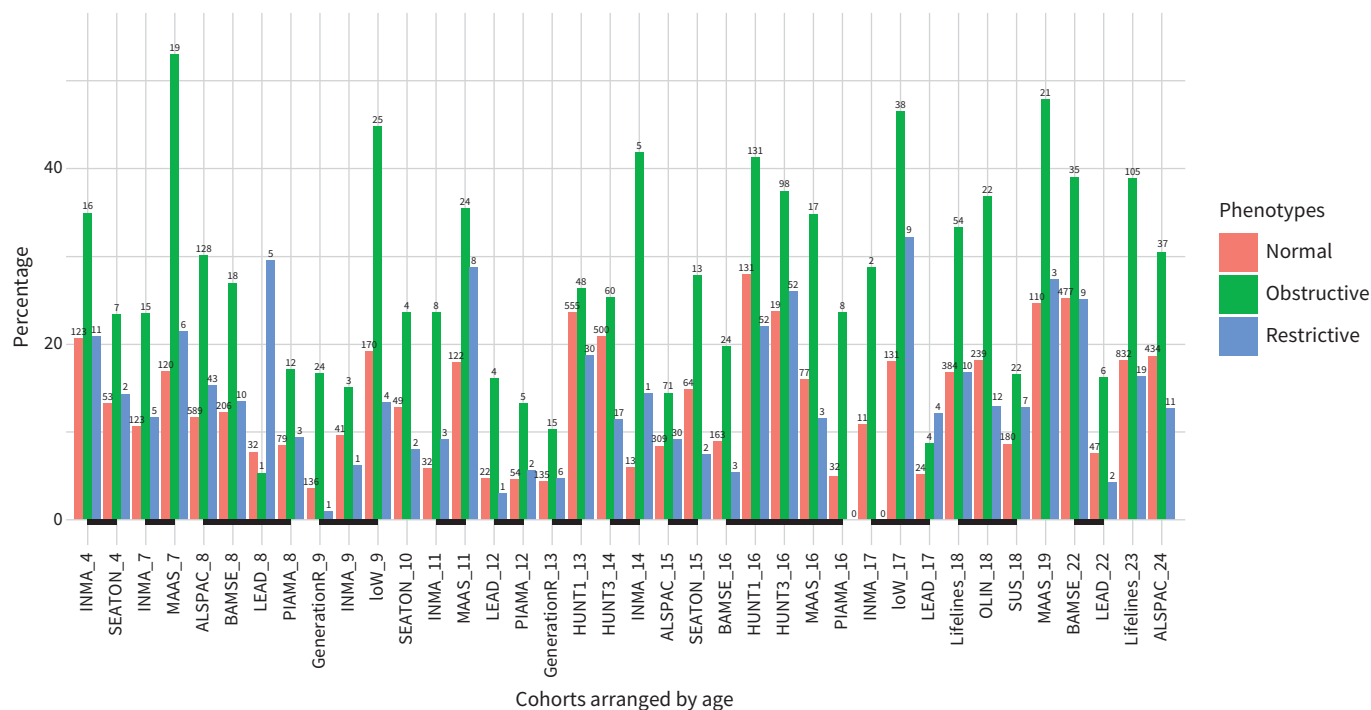
**FIGURE 1** Prevalence of the a) obstructive and b) restrictive phenotypes from early childhood to young adulthood. The numbers above each bar represent the number of cases in the respective study. Cohorts linked by lines had the same mean age (in years).

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 b).

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% *versus* 12.5%, IQR=7.9 to 18.1%,  $p<0.001$ , and 29.8%, IQR= 21.9 to 42.3% *versus* 12.3%, IQR=7.1 to 22.5%,  $p<0.001$ , respectively, figure 2 and supplementary Figure 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% *versus* 12.5%, IQR=7.9 to 18.1%,  $p=0.95$ , and 10.1%, IQR=7.1 to 20.9% *versus* 12.3%, IQR=7.1 to 22.5%,  $p=0.57$ , respectively, figure 2 and supplementary Figure E1). In the adjusted regression models, a current diagnosis of asthma was strongly associated with the obstructive phenotype (5–25 years age group aOR=2.55, 95% CI 2.14–3.04, figure 3, for other subgroups see supplementary Figure E4). No association between a current diagnosis of asthma and the restrictive phenotype (supplementary 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



**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).

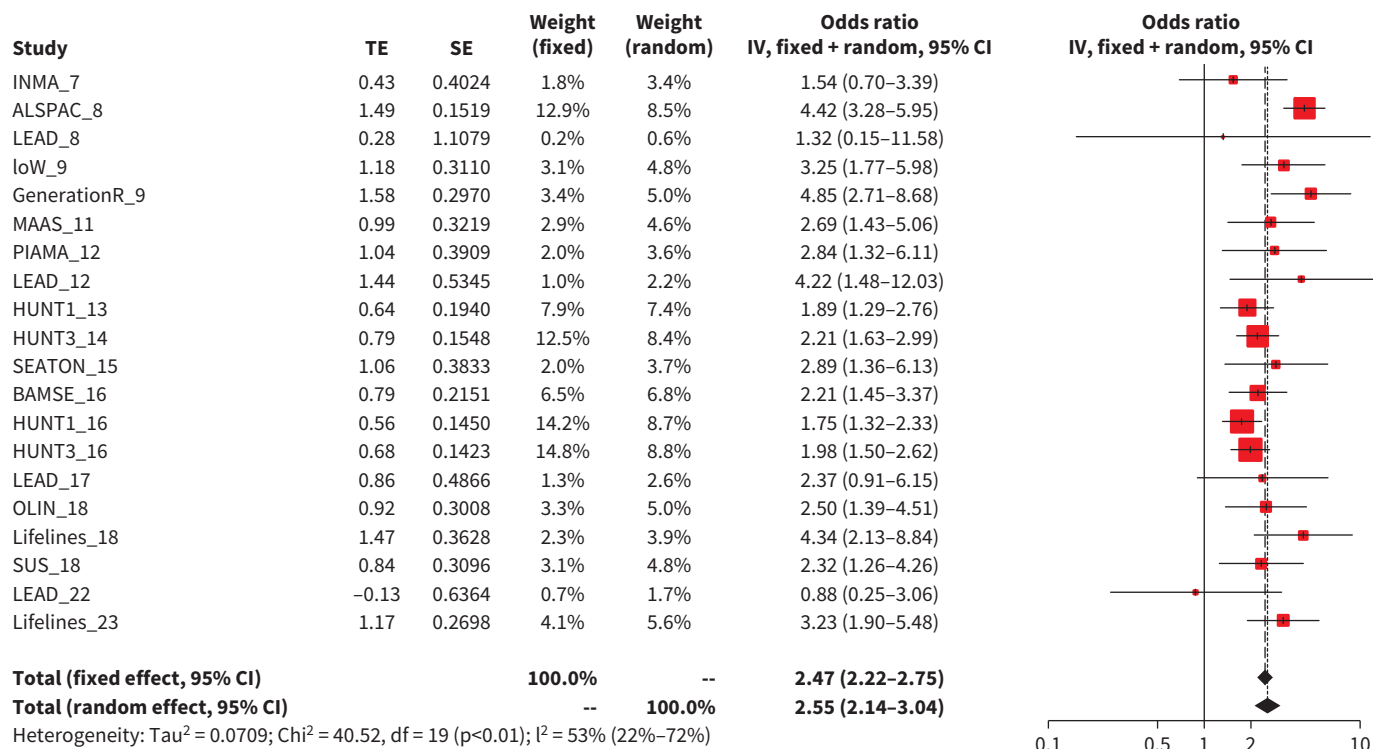
factors at the time of lung function testing, BMI and smoking status (former and current smoker) and obstructive and restrictive phenotypes as well as FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC ratio z-scores. The combined meta-analysis results are illustrated in table 2 (for spirometry phenotypes) and supplementary Table E2 (for z-scores) and results additionally adjusted for asthma in table 3 and supplementary Table E3.

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 1.08–3.06, aOR=2.73, 95% CI 1.67–4.46; aOR=1.61, 95% CI 1.13–2.29 and aOR=1.84, 95% CI 1.27–2.66, 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 1.01–1.35), 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<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC ratio z-scores (supplementary Table E2). Maternal smoking during pregnancy was negatively associated with FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratio. Asthma family history was negatively associated with FEV<sub>1</sub> and FEV<sub>1</sub>/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 1.01–1.05 to aOR=1.06, 95% CI 1.04–1.09 per kg·m<sup>-2</sup> increase, tables 2 and 3). In contrast, BMI was negatively associated with the restrictive phenotype in all age groups in both models (from aOR=0.79, 95% CI 0.74–0.84 to aOR=0.88, 95% CI 0.80–0.96 per kg·m<sup>-2</sup> increase, tables 2 and 3 and figure 4) except in the >20–25 age bin (supplementary Figure E6). In addition, a higher BMI was associated with higher FEV<sub>1</sub> and FVC but lower FEV<sub>1</sub>/FVC ratio z-scores (supplementary 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 smoking was both positively and negatively





**FIGURE 3** Meta-analysis results of association between asthma and obstructive phenotype in 5–25 years subgroup. TE: the estimated treatment effect; IV: inverse variance.

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<sub>1</sub>/FVC ratio z-scores (supplementary 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 ranges 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

TABLE 2 Meta-analysis results of obstructive and restrictive phenotypes in Model 1<sup>#</sup> in different age groups

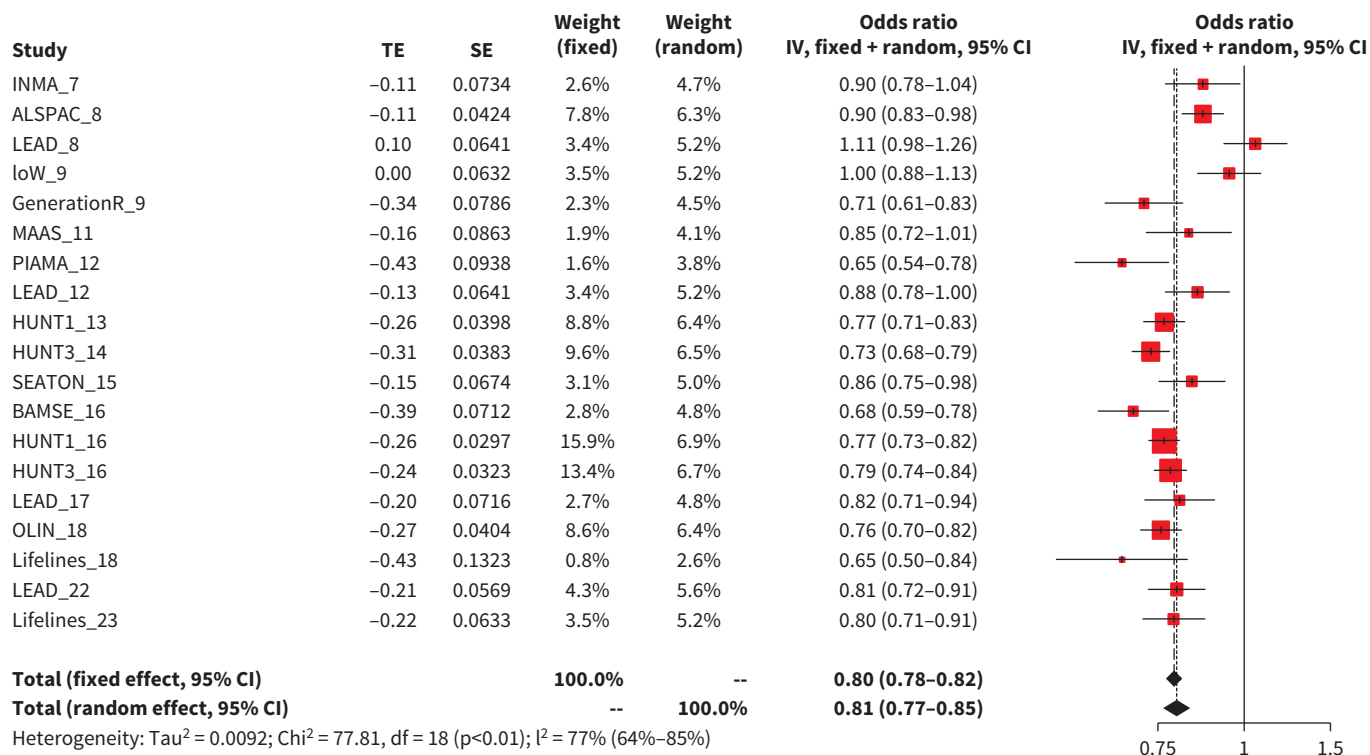
Variables	Age groups	Number of cohorts	I <sup>2</sup>	p-value for Q statistic	OR (95% CI)
<b>Obstructive phenotype</b>					
Preterm birth	<10	9	60.8	0.0089	1.82 (1.08–3.06)
	>10–15	5	17.6	0.30	2.73 (1.67–4.46)
	>15–20	8	6.7	0.38	1.61 (1.13–2.29)
	>20–25	4	0.0	0.63	1.37 (0.88–2.12)
	5–25	10	51.6	0.016	1.84 (1.27–2.66)
Maternal smoking during pregnancy	<10	9	0.0	0.61	1.11 (0.94–1.30)
	>10–15	6	0.0	0.98	1.20 (0.90–1.59)
	>15–20	10	9.1	0.36	1.43 (1.14–1.78)
	>20–25	3	0.0	0.41	1.43 (1.07–1.93)
	5–25	11	0.0	0.53	1.16 (1.01–1.35)
Asthma family history	<10	9	26.9	0.20	1.34 (1.14–1.58)
	>10–15	6	0.0	0.55	1.39 (1.01–1.93)
	>15–20	11	0.0	0.52	1.46 (1.24–1.72)
	>20–25	3	29.6	0.24	1.59 (1.22–2.07)
	5–25	12	0.0	0.83	1.44 (1.25–1.66)
BMI	<10	9	40.6	0.097	1.06 (1.02–1.10)
	>10–15	8	55.3	0.022	1.04 (1.00–1.09)
	>15–20	12	17.7	0.27	1.05 (1.04–1.07)
	>20–25	4	0.0	0.47	1.03 (1.01–1.05)
	5–25	13	44.7	0.019	1.05 (1.03–1.06)
Former smoker	>10–15	2	0.0	0.61	0.67 (0.45–1.01)
	>15–20	10	28.9	0.18	0.83 (0.71–0.98)
	>20–25	4	0.0	0.63	1.37 (1.04–1.82)
	10–25	11	41.3	0.048	0.93 (0.75–1.16)
Current smoker	>10–15	2	51.0	0.15	0.88 (0.38–2.05)
	>15–20	11	35.5	0.11	1.21 (1.01–1.44)
	>20–25	4	0.0	0.70	1.34 (1.01–1.78)
	10–25	11	29.8	0.13	1.24 (1.05–1.46)
<b>Restrictive phenotype</b>					
Preterm birth	<10	8	0.0	0.79	1.17 (0.78–1.75)
	>10–15	5	0.0	0.92	1.46 (0.72–2.97)
	>15–20	6	0.0	0.79	1.16 (0.72–1.87)
	>20–25	3	0.0	0.87	0.88 (0.41–1.92)
	5–25	9	0.0	0.98	1.20 (0.84–1.70)
Maternal smoking during pregnancy	<10	9	0.0	0.92	0.91 (0.73–1.14)
	>10–15	6	0.0	0.95	1.16 (0.79–1.70)
	>15–20	9	40.9	0.095	0.98 (0.61–1.58)
	>20–25	4	0.0	0.73	0.84 (0.52–1.36)
	5–25	11	0.0	0.66	1.00 (0.82–1.22)
Asthma family history	<10	9	3.8	0.40	0.92 (0.74–1.15)
	>10–15	6	0.0	0.97	0.91 (0.58–1.44)
	>15–20	10	13.4	0.32	0.89 (0.71–1.12)
	>20–25	4	0.0	0.64	0.97 (0.66–1.42)
	5–25	12	0.0	0.84	0.96 (0.79–1.16)
BMI	<10	9	69.3	0.001	0.88 (0.80–0.96)
	>10–15	8	51.6	0.035	0.80 (0.75–0.85)
	>15–20	12	78.8	<0.001	0.80 (0.75–0.85)
	>20–25	4	92.6	<0.001	0.84 (0.70–1.00)
	5–25	13	75.1	<0.001	0.81 (0.78–0.85)
Former smoker	>10–15	2	0.0	0.35	0.65 (0.40–1.04)
	>15–20	9	25.3	0.24	0.98 (0.79–1.21)
	>20–25	4	56.6	0.075	0.57 (0.27–1.23)
	10–25	11	35.9	0.10	0.93 (0.76–1.12)
Current smoker	>10–15	2	62.2	0.10	0.89 (0.27–2.97)
	>15–20	11	27.3	0.18	0.80 (0.60–1.05)
	>20–25	4	0.0	0.54	0.72 (0.48–1.06)
	10–25	11	19.6	0.23	0.85 (0.67–1.08)

<sup>#</sup>: 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<sup>#</sup> in different age groups

Variables	Age groups	Number of cohorts	I <sup>2</sup>	p-value for Q statistic	OR (95% CI)
<b>Obstructive phenotype</b>					
Preterm birth	<10	8	53.1	0.037	2.04 (1.24–3.34)
	>10–15	6	21.0	0.28	2.83 (1.73–4.46)
	>15–20	8	7.1	0.38	1.53 (1.06–2.22)
	>20–25	4	0.0	0.47	1.49 (0.94–2.36)
	5–25	10	40.1	0.06	1.83 (1.31–2.57)
Maternal smoking during pregnancy	<10	9	0.0	0.70	1.06 (0.89–1.28)
	>10–15	6	0.0	0.97	1.28 (0.95–1.73)
	>15–20	10	17.0	0.29	1.48 (1.20–1.82)
	>20–25	3	0.0	0.79	1.23 (0.86–1.75)
	5–25	11	0.0	0.58	1.13 (0.97–1.33)
Asthma family history	<10	9	21.9	0.25	1.09 (0.90–1.32)
	>10–15	6	0.0	0.63	1.17 (0.82–1.67)
	>15–20	11	0.0	0.84	1.28 (1.07–1.52)
	>20–25	3	69.6	0.037	1.33 (0.74–2.40)
	5–25	12	0.0	0.67	1.21 (1.04–1.41)
BMI	<10	9	53.7	0.027	1.05 (1.00–1.11)
	>10–15	8	0.0	0.50	1.06 (1.04–1.09)
	>15–20	12	16.5	0.28	1.04 (1.03–1.06)
	>20–25	4	0.0	0.88	1.04 (1.01–1.07)
	5–25	13	34.4	0.071	1.04 (1.03–1.06)
Former smoker	>10–15	2	0.0	0.72	0.67 (0.45–1.01)
	>15–20	10	20.8	0.25	0.83 (0.70–0.97)
	>20–25	4	0.0	0.59	1.55 (1.14–2.11)
	10–25	11	47.0	0.023	0.96 (0.76–1.22)
Current smoker	>10–15	2	54.1	0.14	0.89 (0.37–2.15)
	>15–20	11	45.1	0.052	1.18 (0.90–1.54)
	>20–25	4	0.0	0.67	1.28 (0.92–1.79)
	10–25	11	37.6	0.07	1.18 (0.93–1.49)
<b>Restrictive phenotype</b>					
Preterm birth	<10	8	0.0	0.70	1.08 (0.68–1.73)
	>10–15	5	0.0	0.85	1.80 (0.88–3.71)
	>15–20	6	0.0	0.83	1.17 (0.72–1.92)
	>20–25	3	0.0	0.95	0.76 (0.30–1.92)
	5–25	9	0.0	0.97	1.13 (0.77–1.68)
Maternal smoking during pregnancy	<10	9	0.0	0.71	0.95 (0.75–1.22)
	>10–15	6	0.0	0.98	1.19 (0.78–1.79)
	>15–20	9	43.8	0.076	0.98 (0.59–1.62)
	>20–25	4	0.0	0.99	1.01 (0.61–1.69)
	5–25	11	0.0	0.59	1.06 (0.86–1.32)
Asthma family history	<10	9	3.8	0.40	0.99 (0.77–1.27)
	>10–15	5	0.0	0.88	0.89 (0.54–1.46)
	>15–20	10	25.9	0.21	0.88 (0.69–1.12)
	>20–25	4	0.0	0.61	0.99 (0.63–1.56)
	5–25	12	0.0	0.84	1.02 (0.83–1.25)
BMI	<10	9	75.0	<0.001	0.86 (0.77–0.95)
	>10–15	8	50.8	0.039	0.79 (0.74–0.84)
	>15–20	12	75.9	<0.001	0.80 (0.75–0.85)
	>20–25	4	92.2	<0.001	0.84 (0.70–1.01)
	5–25	13	76.9	<0.001	0.81 (0.77–0.85)
Former smoker	>10–15	2	0.0	0.35	0.64 (0.40–1.04)
	>15–20	9	40.3	0.12	0.96 (0.77–1.20)
	>20–25	4	46.7	0.13	0.69 (0.43–1.08)
	10–25	11	35.2	0.11	0.91 (0.75–1.11)
Current smoker	>10–15	2	62.8	0.10	0.89 (0.26–3.07)
	>15–20	11	41.8	0.07	0.74 (0.49–1.13)
	>20–25	4	0.0	0.56	0.73 (0.47–1.15)
	10–25	11	19.2	0.24	0.87 (0.68–1.13)
#: 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.					



**FIGURE 4** Meta-analysis results of association between body mass index and restrictive phenotype in Model 2 in 5–25 years age group. TE: the estimated treatment effect; IV: inverse variance.

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 (>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 birthweight 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<sub>1</sub>/FVC ratio z-scores from childhood to young adulthood. In children, faster weight growth is associated with higher FVC and FEV<sub>1</sub> 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 calibre of the airways leading to a higher FVC than FEV<sub>1</sub>, and a lower than expected FEV<sub>1</sub>/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]. Owing 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 centred the z-scores in each cohort according to the mean values of non-asthmatic, asymptomatic lifelong nonsmokers [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 online supplementary material.

#### 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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Author contributions: E. Melén, A.H. Maitland van der Zee and J. Hallberg conceived and designed the study with input from the CADSET management group (A. Agusti, R. Faner, G.C. Donaldson, J.A. Wedzicha and E. Heuvelin), R. Granell (ALSPAC), G. Wang (BAMSE), A. Mian (Generation R), A. Langhammer (HUNT), M. Casas Sanahuja (INMA together with G. Wang), D. Charalampopoulos (IoW, MAAS and SEATON), R. Breye-Kohansal (LEAD), N. Olvera (Lifelines), H.M. Boezen (OLIN), J.M. Vonk (PIAMA) and L.M. Laustsen (SUS) conducted the cohort-specific analyses. G. Wang meta-analysed all results. G. Wang, J. Hallberg, A.H. Maitland van der Zee and E. Melén wrote the first draft of the manuscript. All authors read and critically revised subsequent drafts, and approved the final version.

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