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 (≤10 weeks of pregnancy, maternal age ≥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)

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HUNT

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INMA

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IoW

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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

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OLIN

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PIAMA

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SEATON

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SUS

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IoW

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LEAD

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Lifelines

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MAAS

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James Trust (2005) and The JP Moulton Charitable Foundation (2004-current), The North West Lung Centre Charity (1997-current) and the Medical Research Council (MRC) G0601361 (2007-2012), MR/K002449/1 (2013-2014) and MR/L012693/1 (2014-2018), and MR/S025340/1 UNICORN (Unified Cohorts Research Network): Disaggregating asthma (2020-2024). AS CM and LL are supported by the NIHR Manchester Biomedical Research Centre.

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
Asthma family history	>10 - 15	6	0.0	0.59	-0.15	-0.21 to -0.084
	>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

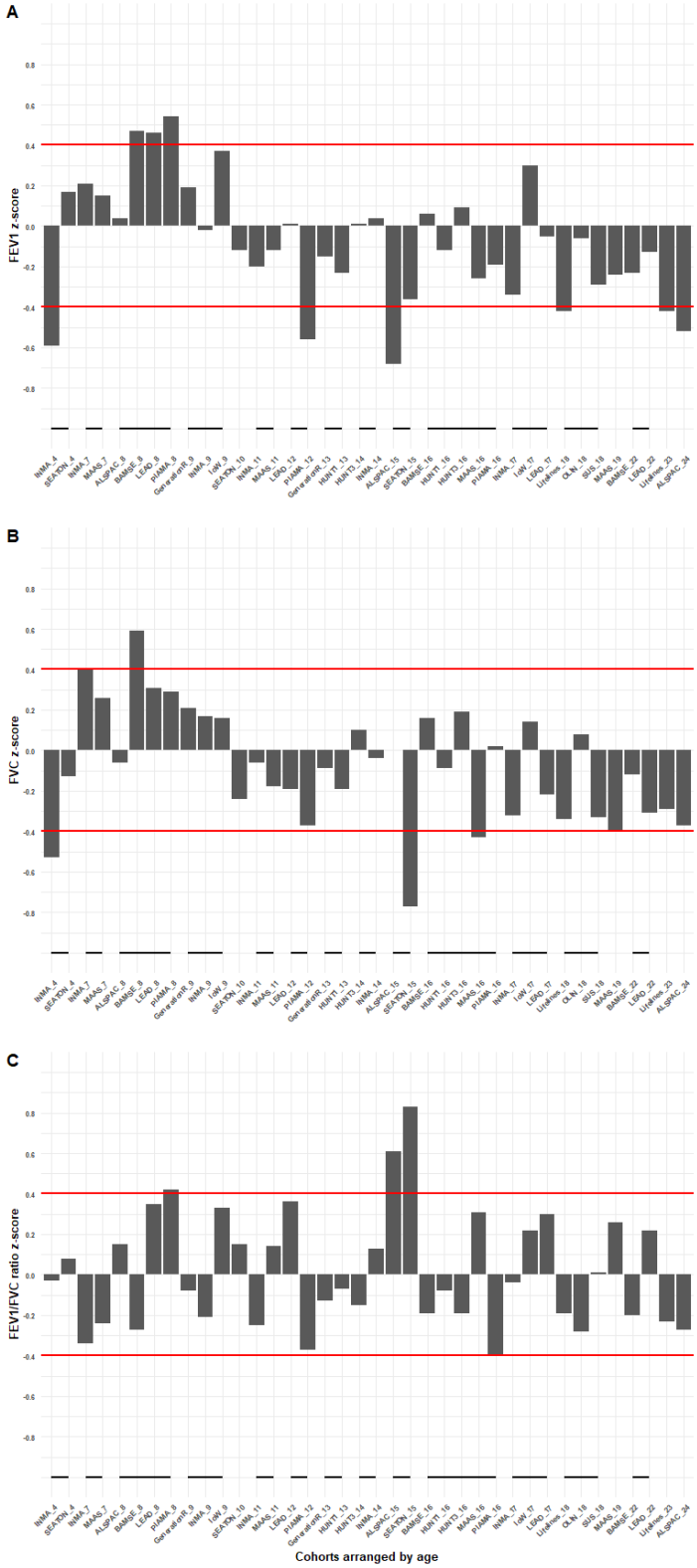


Figure E1. The GLI fit of FEV_1 (A), FVC (B) and FEV_1/FVC ratio (C) in each cohorts and time points. Cohorts linked by lines had the same mean age (in years).

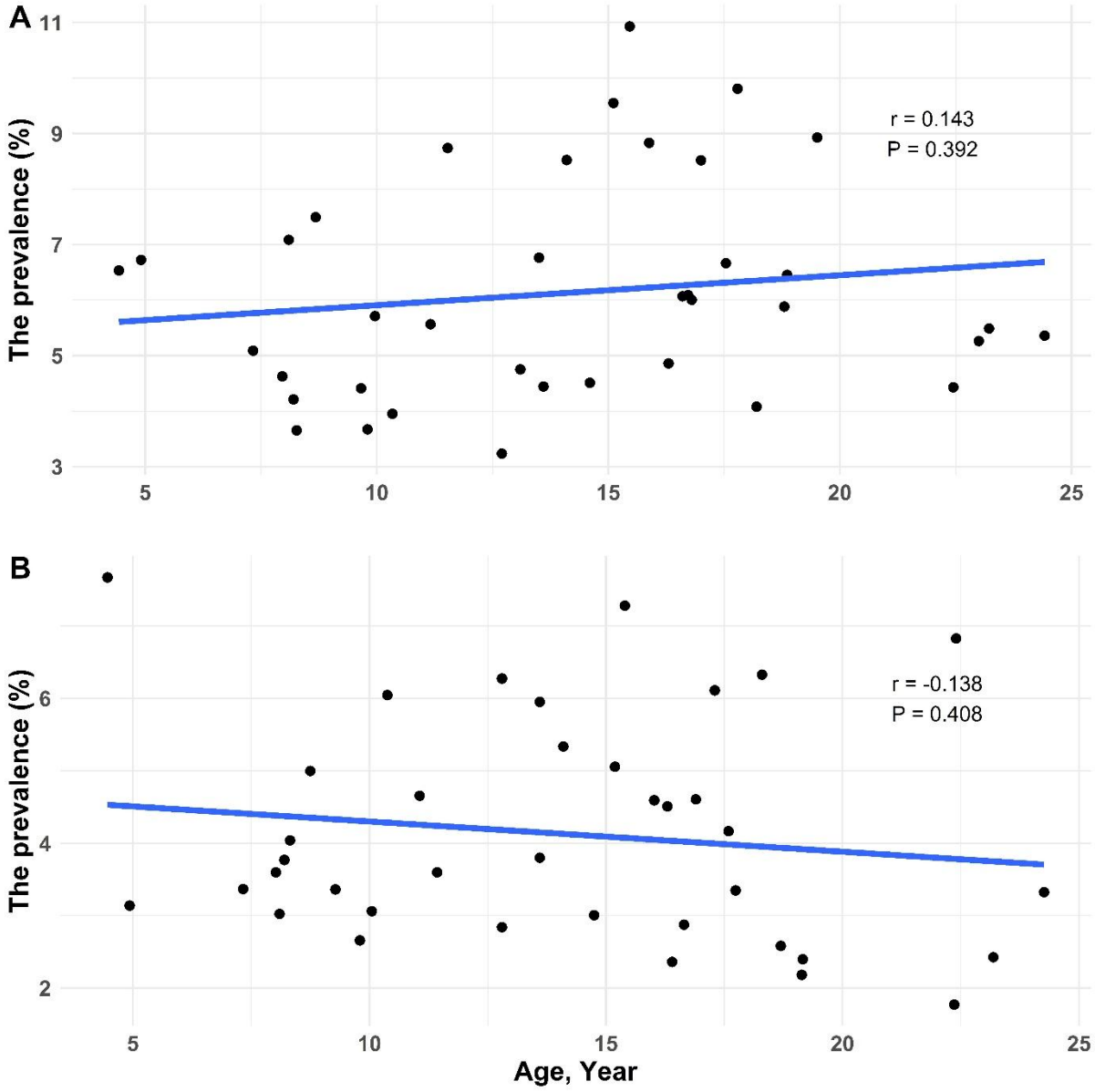


Figure E2. The associations between the cohort-specific prevalence of obstructive (A) and restrictive (B) phenotypes and age.

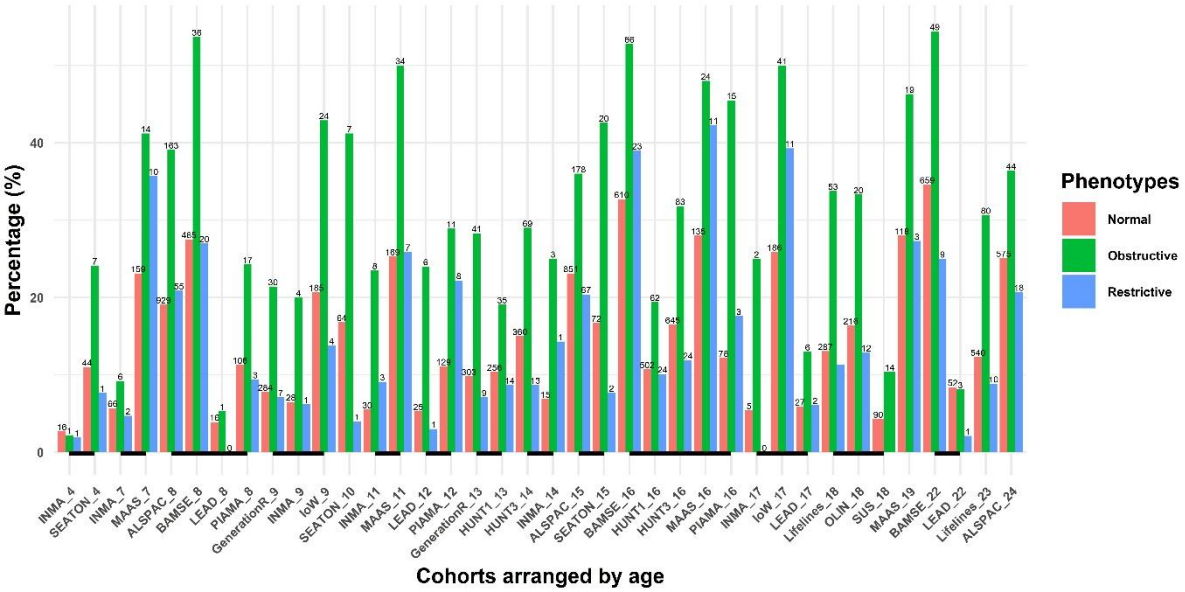
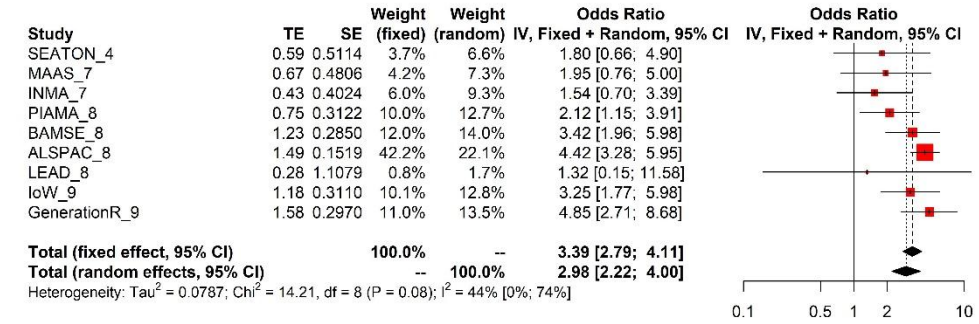
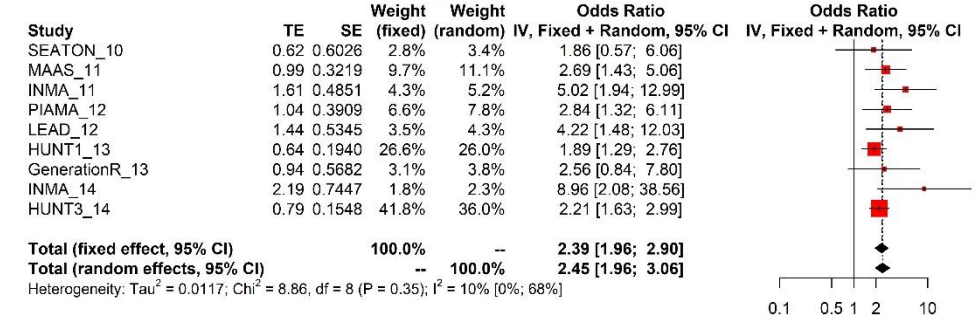


Figure E3. The prevalence of ever been diagnosed with asthma in participants with obstructive or restrictive phenotype, or normal lung function. The numbers above each bar represent the number of cases in the respective study. Cohorts linked by lines had the same mean age (in years).

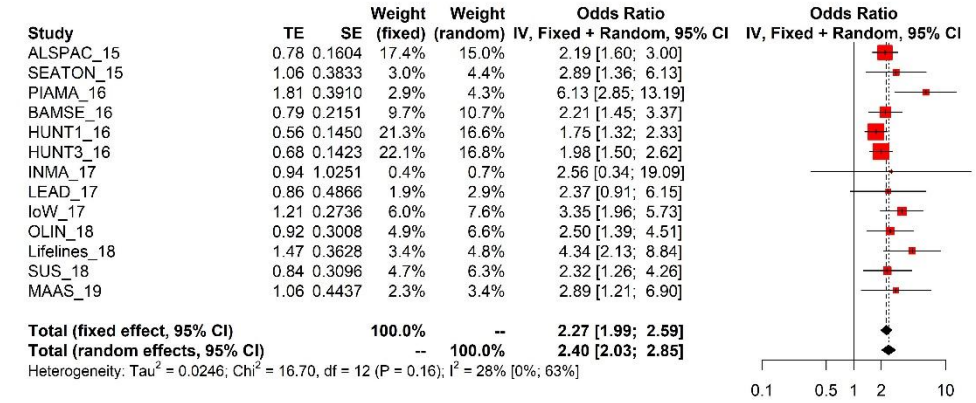
A



B



C



D

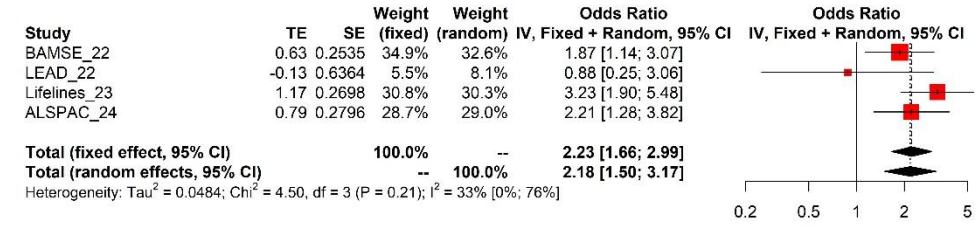
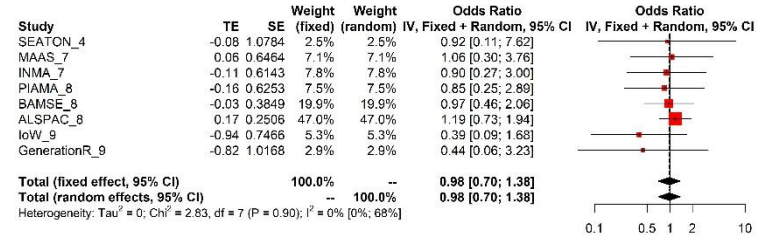
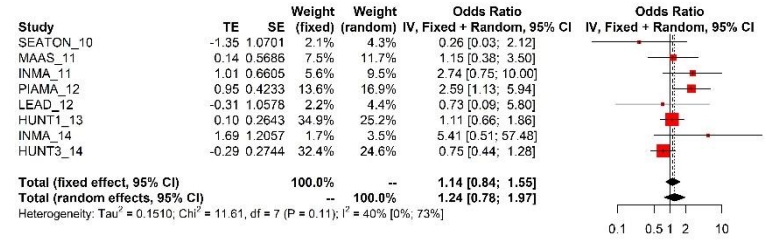


Figure E4. Meta-analysis results of association between asthma and obstructive phenotype in different age bins (A = age <10, B = age >10-15, C = age >15-20, and D = age >20-25).

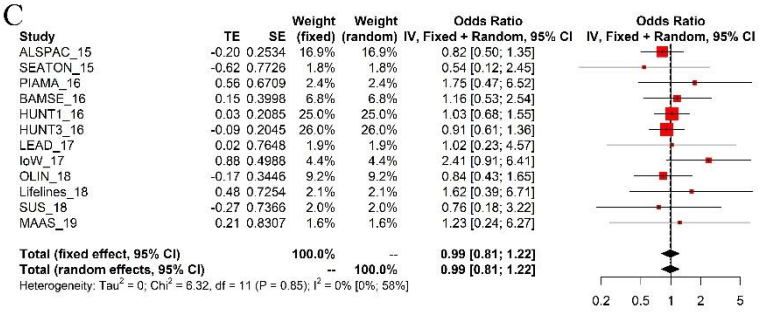
A



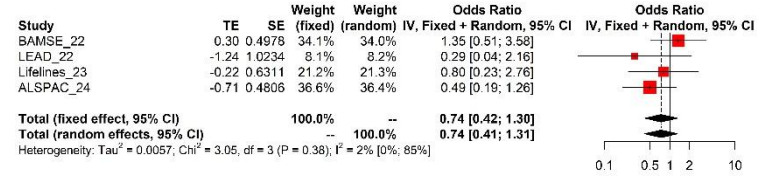
B



C



D



E

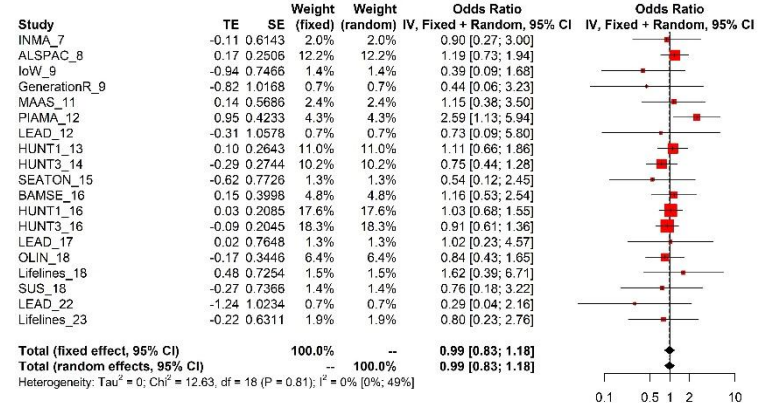
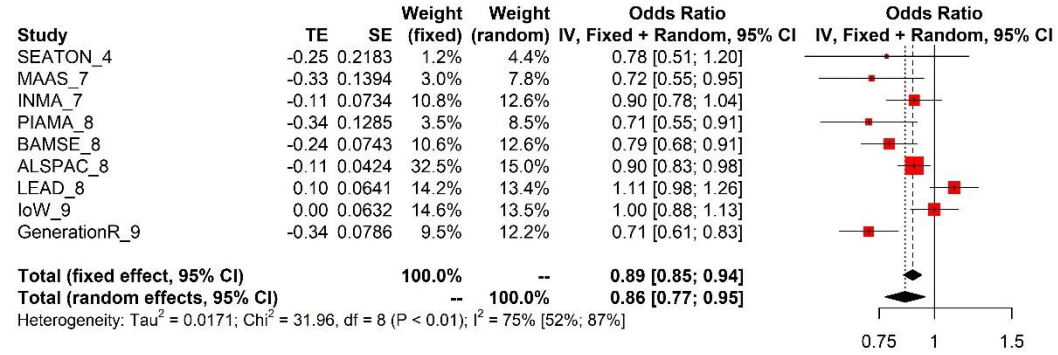
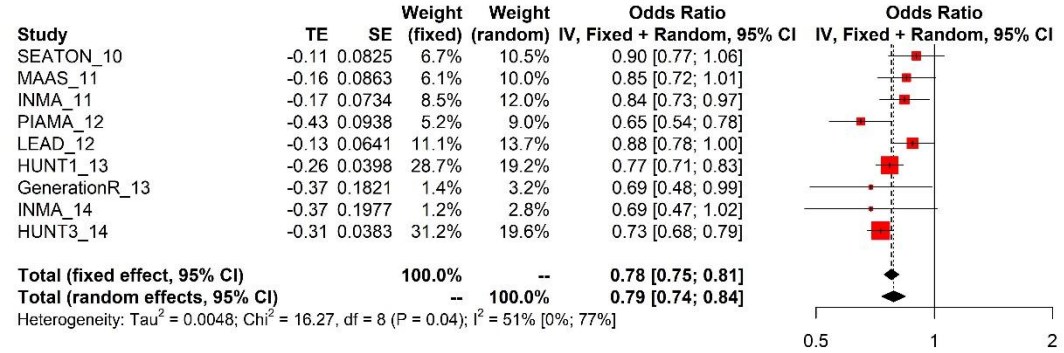


Figure E5. Meta-analysis results of association between asthma and restrictive phenotype in different age bins (A = age <10, B = age >10-15, C = age >15-20, D = age >20-25, and E = age 5-25 years).

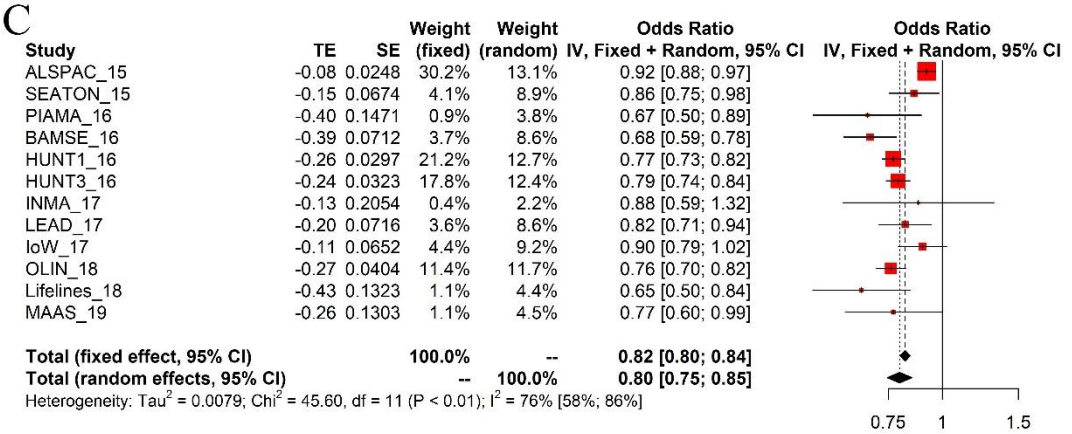
A



B



C



D

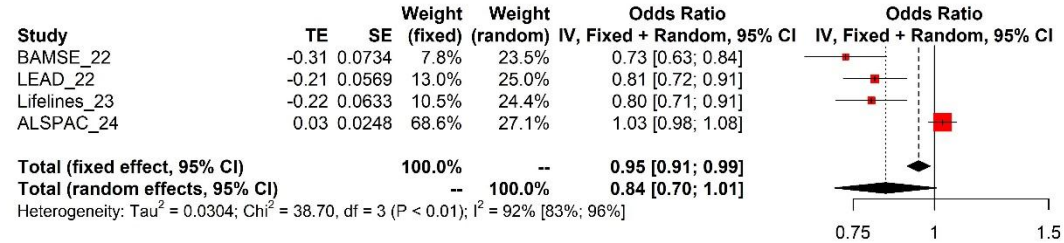


Figure E6. Meta-analysis results of association between body mass index and restrictive phenotype in Model 2 in different age bins (A = age <10, B = age >10-15, C = age >15-20, and D = age >20-25).

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