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Predictors of lung function trajectories in population-based studies: A systematic review

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ABSTRACT

Despite the growing body of evidence on lung function trajectories over the life course and their risk factors, the literature has not been systematically synthesised. Publications related to lung function trajectories were identified from PubMed, EMBASE and CINAHL databases. Two authors independently identified publications for inclusion according to predefined selection criteria. Studies that modelled lung function trajectories and reported associated exposures were included. Meta-analyses could not be conducted due to heterogeneity in the exposures and methods used to model lung function trajectories. Nine publications were eligible for inclusion of which four used group-based trajectory modelling to model lung function trajectories while five used latent profile analysis. Studies with repeated lung function measurements over the life-course identified more trajectories than others. Only one study spanning from childhood to middle age reported catch-up trajectory. The following childhood risk factors for subnormal lung function trajectories were observed in at least across two studies: low birth weight, early wheezing, asthma, allergic sensitisation, eczema, and allergic rhinitis, lower respiratory tract infections, family history of asthma, and second-hand smoke exposure. Adult active asthma and personal cigarette smoking were observed to be associated with accelerated decline lung trajectories. Our review identified ten risk factors associated with the growth, catch-up, reduced plateau, and decline trajectories of lung function. Intervention directed at childhood asthma and infections, and tobacco smoke exposure at all ages would help promote lung health and prevent subnormal lung function trajectories.

Keywords: lung function trajectories, predictors, risk factor, early onset, COPD
Short title: Predictors of lung function trajectories

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INTRODUCTION

Over an individual's life, lung function grows, peaks, plateaus and then declines.[1-3] During the "growth phase" from birth to the mid-twenties, lung function increases and reaches a peak.[1,2] A brief "plateau phase" then follows, extending to around 30 years of age.[1,2] Thereafter is the long "decline phase" due to physiological ageing.[1,2] These phases may be influenced by several modifiable or non-modifiable adverse exposures leading to lung function deficits and subsequently to Chronic Obstructive Pulmonary Disease (COPD).[2-6] Genetic susceptibility, chronic lung conditions and environmental factors may influence lung function trajectory.[1,6-11] Adverse impacts from preconception, intrauterine and early life exposures may result in lower lung function at birth and/or reduced lung function growth leading to failure to attain maximal peak lung function, while impacts from adult life exposures may result in early or accelerated lung function decline.[6,12]

Recent evidence shows that failure to attain peak lung function is a risk factor for an early onset of COPD,[1-3,13] even if the decline phase is normal.[2,14] It is well known that even with normal attainment of lung function, the risk of COPD is greatly increased among individuals with accelerated lung function decline.[15] To effectively prevent and manage COPD requires a comprehensive understanding of the predictors that influence the underlying disease(s) and lung function trajectories over the life course. For this reason, several studies have used a longitudinal design to identify these factors, but the associations between these factors and lung function trajectories over the life course have not yet been systematically reviewed.

This review aims to synthesise all available evidence on factors associated with lung function trajectories and where possible, the interactions between them. Such knowledge would

enhance understanding of links between time-dependent exposures and the life-course trajectory of lung function. This could facilitate the design of evidence-based public health strategies to prevent the burden caused by subnormal lung function trajectories.

METHODS

Search Strategy

Publications were identified from the PubMed, EMBASE and CINAHL databases. The last search was performed on the17th of June 2021. Both keywords and MeSH terms for lung function and trajectory modelling terms were used, Table S1 in the supporting information. This review was prospectively registered in PROSPERO (CRD42020145366). The Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines were followed.[16]

Selection of studies

Inclusion and exclusion criteria are specified in Table S2 in the supporting information. Briefly, all population-based studies with at least three repeated lung function measurements that modelled lung function trajectories were included. Studies conducted amongst specific disease groups and high-risk populations were excluded. Two authors independently reviewed titles and abstracts of all identified records. Any uncertainty or disagreement was resolved by a third reviewer.

Data extraction

Two authors independently extracted relevant information from eligible studies and populated two predefined tables. Data were extracted for study characteristics (first author,

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year, study name, country), exposure characteristics, clinical lung function measurements and trajectory analysis.

Quality assessment

Study quality was assessed independently by two authors using the Newcastle Ottawa Scale (NOS).[17] The NOS uses a star rating system to assess the quality of non-randomised control trial, cohorts, and case-control studies based on eight items which are broadly classified into three main domains (selection, comparability, and outcome).[17] Given that a number of risk factors were considered in our review, confounders were not prespecified and studies that considered any confounders received a star for comparability.

RESULTS

Selection process for the studies included

The searches identified a total of 1536 publications. After removal of duplicates, 1016 titles and abstracts were screened, of which 990 were excluded. Full texts of the remaining 26 publications were screened and 17 was excluded, leaving nine eligible publications[3,18-25] arising from nine population-based cohort studies with two including more than one cohort.[19,23] [Figure 1]. The population-based cohort studies included six birth cohort studies [18-20,22], and three starting from ages 7, 18 and 26 years respectively.[3,21,25] Studies were based in the United States,[18,21] United Kingdom,[19,20] Australia,[3,19] The Netherlands,[25] and Brazil[22] [Table 1].

Study quality

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The included studies scored between seven and eight stars out of nine on the Newcastle-Ottawa Scales (NOS), indicating good quality.[17] A common area of limitation was the ascertainment of exposure. Four studies [19,22] did not adjust for any confounders. One[22] had loss to follow up of 26·4%, however, except for sex, the description of those lost suggested no difference from those followed.[22,26] See Table S3 in the supporting information.

Exposure characteristics

Exposure definition and measurement differed considerably among studies ranging from self-reported questionnaires to mixed methods [Table 1]. Our review categorised exposures into genetic susceptibility, and gestational, perinatal, childhood, or adulthood exposures. According to WHO guidelines, birth to 18 years was considered childhood, and after 18 years as adulthood.[27]

Lung function characteristics and trajectory modelling

Spirometry was the primary lung function measurement used in all studies included. Eight studies conducted spirometry according to the American Thoracic Society/European Respiratory Society guidelines.[3,19-22-25] Eight studies reported pre-bronchodilator measures[3,18-22,25] while one reported both pre- and post-bronchodilator measures.[19] One also used whole-body plethysmography for more complex lung function measurements.[19] [Table 1]. Repeated lung function measurement ranged from infancy to the seventh decade of life across studies. All studies measured lung function at a minimum of three timepoints within the "growth" or "plateau" phases. Only one study had six timepoints incorporating both the growth and decline phases of the lung function trajectory[3] [Figure 2]. Publications used different methods to develop lung function trajectories; four used group-based trajectory modelling[3,20-22] while the remaining five used latent class profile analysis[18,19,25] [Table 1].

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Lung function trajectories and their consequences

The studies identified between two and six trajectories. In the Tasmanian Longitudinal Health Study (TAHS),[3] six distinct pre-bronchodilator FEV_1 (z-score) trajectories were identified from ages 7-53 years. These were "early below average, accelerated decline", "persistently low", "early low, accelerated growth, normal decline", "persistently high", "below average", and "average" FEV_1 trajectories. Subnormal trajectories were associated with an increased risk of COPD. In the Coronary Artery Risk Development in Young Adults (CARDIA),[21] five pre-bronchodilator FEV_1 (% predicted) trajectories were identified from ages 25-55 years. These were "preserved ideal", "preserved good", "preserved impaired", "worsening", and "persistently poor" FEV_1 trajectories. Subnormal trajectories were found to be associated with increased odds of future emphysema independent on smoking status. In the Deotinchem Cohort Study (DCS),[25] three pre-bronchodilator FEV_1 trajectories (%predicted) were identified from ages 26-66 years. These were "normal decline", "decelerating decline" and "accelerating decline" trajectories. Subnormal trajectories were associated with an increased risk of airflow limitation or COPD. In the Tucson Children's Respiratory Study (CRS),[18] two pre-bronchodilator FEV_1(% predicted) trajectories were identified from ages 11-32 years. These were "normal" and "low" trajectories. The subnormal trajectory is established at birth and predisposes individual to later development of COPD. Four FEV_1(% predicted) trajectories were identified from the Manchester Asthma Allergy Study Cohort (MAAS)[19] and the Avon Longitudinal Study of Parents and Children (ALSPAC).[19] These were "persistently high", "normal", "below average", and "persistently low" pre-bronchodilator FEV_1 trajectories from age 8-24 years in ALSPAC[19] and both pre- and post-bronchodilator from age 5-16 years in MAAS.[19] Two pre-bronchodilator FEV_1, FVC, and FEV_1/FVC ratio trajectories ("high" and "low") were also identified from the ALSPAC.[23] In the Pelotas 1993 birth cohort,[22] three pre-bronchodilator FEV_1, FVC, and FEV_1/FVC (z-score) trajectories

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were identified from ages 15-22 years. These were "low", "average", and "high" trajectories. In the Isle of Wight (IOW),[20,23,24] two pre-bronchodilator FEV_1, FVC, and FEV_1/FVC ratio trajectories ("high" and "low") and three FEF_{25-75} trajectories[20] ("high", "medium", and "low") were identified from ages 10-26 years. In the Australian Perth Infant Asthma (PIAF),[19] three mean pre-bronchodilator FEV_1(% predicted) trajectories "above average", "normal", and "below average" trajectories from ages 6-8 years and two mean % predicted V'_{MaxFRC} trajectories "above average", and "below average" from 1 month to 12 months were identified. These above studies did not comment on consequences of identified subnormal trajectories.

Factors associated with lung trajectories: Genetic susceptibility and family history of asthma

Weighted genetic score based on 77 single nucleotide polymorphisms (SNPs) that have previously been reported to be associated with FEV_1/FVC or FEV_1 decline, was observed to be modestly associated with subnormal trajectories in MAAS[19] and ALSPAC.[19] Epigenome-wide associations of DNA-methylation (DNA-M) at specific cytosine phosphate-guanine dinucleotide sites (CpGs) at birth and at age 7 years were observed to be associated with lung function trajectories in two studies. IOW[23,24] and ALSPAC[24] observed DNA-M of eight CpGs on genes GLUL, MYCN, HLX, LHX1, COBL, COL18A1, STRA6, and WNT11 at birth and DNA-M at 44 distinct CpGs mapped with 42 genes to be associated with FEV_1, FVC, and FEV_1/ FVC trajectories between ages 10-26 years[23,24] respectively. [Table 2 & Table S6]. Sex defined as male and female was explored by two studies.[3,18] TAHS[3] observed that female children were at increased risk of "early below average, accelerated FEV_1" decline trajectories between ages 7-53 years. CRS[18] observed no such associations. Family history of asthma was associated with subnormal trajectories in four out of the six studies.[3,18-20,22] CRS[18] observed that history of maternal asthma was associated with

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"persistently low" FEV_1 trajectories between ages 11-32 years, TAHS[3] observed that parental asthma was associated with an increased the risk of "persistently low" FEV_1 trajectories between ages 7-53 years. Pelotas 1993 birth cohort[22] observed that a family history of asthma was associated with "low" FEV_1/FVC trajectories between ages 15-22 years. ALSPAC[19] also observed paternal asthma to be associated with "persistently low" FEV_1 trajectories between ages 8-24 years [Table 2 &3].

Prenatal, childhood, and adolescent clinical characteristics

Low birth weight (<2500g) was associated with subnormal lung function trajectories in two of the four studies.[19,20,22] IOW[20] observed an association with "low" FEV_1 trajectories in both males and females and "low" FEV_1/ FVC trajectories in females between ages 10-26 years. Pelotas 1993 birth cohort[22] also observed an association with "low" FEV_1, FVC, and FEV_1 /FVC trajectories between ages 15-22 years. The remaining two studies observed only modest associations for low birth weight.[19]

In utero smoke exposure was associated with subnormal lung function trajectories in one of the four studies.[18-20,22] Pelotas 1993 birth cohort[22] observed maternal smoking during the first trimester of pregnancy to be associated with "low" FEV_1/FVC trajectories between ages 15-22 years. The remaining three studies observed no associations with subnormal lung function trajectories.[18-20] Pelotas 1993 birth cohort[22] additionally explored the relationship between maternal alcohol use during pregnancy and observed no association for subnormal trajectories [Table 2 &3].

Two studies investigated childhood weight and lung function trajectories. TAHS[3] found that children who were underweight were more likely to belong to the "early low, accelerated growth, normal decline" trajectories but this association was no longer significant when adjusted for weight gain between ages 7-11 years. Pelotas 1993 birth cohort[22] found higher

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BMI at all ages to be associated with "high" FEV_1 and FVC trajectories. The authors also observed that this association may have been due to a higher proportion of fat-free mass rather than obesity.

Low maximal expiratory flow at functional infant residual capacity (V'_{MaxFRC}) was associated with subnormal lung function trajectories in one of two studies.[18,19] CRS[18] observed that individuals with "persistently low" FEV_1 trajectories by 6 years were found to have had lower V'_{MaxFRC} during infancy. PIAF[19] observed that participants with low V'_{MaxFRC} in infancy were more likely to develop a "below average" FEV_1 trajectory in early childhood, but most transitioned to above "average" or "normal" FEV_1 trajectories by age 12 years.

Childhood lower respiratory tract infections (LRTIs) was associated with subnormal lung function trajectories in all five studies that explored the association.[3,18-20,22] LRTIs was defined among studies as bronchitis or pneumonia,[3,22] an infection caused by the respiratory syncytial virus (RSV),[18] and recurrent chest infections,[20] respectively. The remaining study did not report a specific definition.[19] Pelotas 1993 birth cohort[22] observed hospitalisation due to bronchitis, bronchiolitis, or pneumonia by age 4 years to be associated with "low" FEV_1 and FEV_1/FVC trajectories between ages 15-22 years. MAAS[19] observed that children with LRTIs within the first 3 years of life were at an increased risk of "persistently low" FEV_1 trajectories between ages 5-16 years. CRS[18] observed a history of LRTIs, particularly infection with the RSV, was associated with an increased risk of "persistently low" FEV_1 trajectory between 11-32 years. TAHS[3] observed that history of early life pneumonia and childhood bronchitis by age 7 years were associated with "below average" FEV_1 and "early below average, accelerated decline" FEV_1 trajectories between ages 7-53 years. IOW[20] observed an association between recurrent chest infections at ages 1-2 years with "low" FEV_1 trajectory between ages 10-26 years but only in males [Table 2 &3].

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Early day care attendance was associated with subnormal lung function trajectories in one of three studies.[18,19] ALSPAC[19] observed that day care was associated with an increased risk of "below average FEV_1" trajectories between ages 8-24 years. CRS[18] and MAAS[19] observed no association for subnormal trajectories.

Childhood wheezing was associated with subnormal lung function trajectories in all three studies that explored the association.[19,22] Pelotas 1993 birth cohort[22] observed wheezing (last 12 months) at ages 4, 11, 15, 18 and 22 years to be associated with "low" FEV_1 and FEV_1/FVC ratio trajectories between ages 15-22 years. Recurrent wheeze with severe exacerbation by age 3 years was observed to be associated with an increased risk of "persistently low" FEV_1 trajectories between ages 5-16 and 8-24 years in MAAS[19] and ALSPAC[19] respectively.

Childhood asthma was associated with subnormal lung function trajectories in all six studies that explored the relationship.[3,18-20,22] Asthma categorisation varied between studies, including frequent,[3] current,[3,18-20,22] active asthma[3,18], or severe asthma.[19] Pelotas 1993 birth cohort[22] observed diagnosis of asthma by ages 4, 11, 15 and 22 years to be associated with "low" FEV_1 and FEV_1/FVC trajectories between ages 15-22 years. CRS[18] observed that physician-diagnosed active asthma at ages 6 and 11 years was associated with an increased risk of "persistently low" FEV_1 trajectories between ages 11-32 years. MAAS[19] and ALSPAC[19] similarly observed childhood asthma to be associated with "persistently low" FEV_1 trajectories between ages 5-16 years and 8-24 years respectively. TAHS[3] identified the onset of childhood asthma by age 3 years and frequent asthma symptoms by age 7 years to be associated with an increased risk of "early below average, accelerated decline" FEV_1 trajectories and "persistently low" FEV_1 trajectories between ages 7-53 years. IOW[20] found current asthma at age 4 and 10 years to be associated with "low" FEV_1/FVC and $FEF_{25–75}$ trajectories between ages 10-26 years.

Allergic sensitisation was associated with subnormal lung function trajectories in two of three studies.[19,20] IOW[20] observed a positive skin prick test at age 4 years to be associated with an increased risk of "low" FEV_1/FVC trajectories in males and "low" FEV_1 trajectories in female participants between ages 11-26 years. MAAS[19] observed allergic sensitisation at age 8 years to be associated with an increased risk of "persistently low" FEV_1 trajectories between ages 5-16 years. However, no association was observed in adolescence. ALSPAC[19] did not observe an association for allergic sensitisation at age 7 years [Table 2 &3].

Allergic phenotypes were associated with subnormal lung function trajectories in all three studies that examined the relationship.[3,20,22] Allergic phenotypes were defined as childhood eczema,[3,20] allergic rhinitis,[3] and a reported allergy diagnosis.[22] IOW[20] observed eczema in the first year of life to be associated with "low" FEV_1 trajectories between ages 11-26 years. TAHS[3] observed eczema and allergic rhinitis by age 7 years to be associated with "early below average, accelerated decline" FEV_1 between ages 7-53 years. Pelotas 1993 birth cohort[22] observed that reported allergy diagnosis at ages 11, 18 and 22 years was associated with "low" FEV_1 and FEV_1/FVC trajectories between ages 15-22 years [Tables 2].

Childhood and adolescent environmental characteristics

Early-life second-hand smoke exposure (SHS) was associated with subnormal lung function trajectories in three of five studies.[3,19,20,22] TAHS[3] observed maternal smoking to be associated with "early below average, accelerated decline" FEV_1 trajectory between ages 7-53 years. In MAAS[19] and ALSPAC[19], continuous SHS exposure from birth to age 16 years was observed to be associated with an increased risk of "persistently low" and "below average" FEV_1 trajectories between ages 5-16 years and ages 8-24 years respectively. The remaining two studies observed no associations for subnormal trajectories.[20,22]

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Current personal smoking was associated with subnormal lung function trajectories in one of two studies.[18,22] Pelotas 1993 birth cohort[22] observed current smoking at age 18 years to be associated with "low" FEV_1/FVC trajectories between ages 15-22 years. The authors also explored physical activity (commuting and in leisure time) and observed that more active people were associated with "low" FEV_1/FVC trajectories, however reported that this association is an overestimation due to high self-reported measurement of physical activity. CRS[18] observed no association for current personal smoking.

Breastfeeding was associated with subnormal lung function trajectories in one of two studies.[3,20] IOW[20] found that longer duration of breastfeeding was associated with a reduced risk of "low" FVC trajectories between the age 10-26 years but only in males. The authors also examined the relationship with introduction of solid foods and observed no association. TAHS[3] examined the relationship of bottle, breast and both feeding techniques (first three months of life) with their trajectories from age 7-53 years and did not observe any significant associations.

Childhood social-economic status (SES) defined either as parental occupations[3] or family income,[22] was associated with subnormal lung function trajectories in one of two studies.[3,22] Pelotas 1993 birth cohort[22] observed lower family income to be associated with "low" FEV_1 trajectories between ages 15-22 years but TAHS[3] observed no such associations. [Table 2 &3].

Adult clinical characteristics

Adult active asthma was associated with subnormal lung function trajectories in all four studies that explored the relationship.[3,18,21] CARDIA[21] observed an association between self-reported asthma by age 25 years with "persistently poor" FEV_1 trajectories between ages 25-55 years. CRS[18] observed history of physician-diagnosed active asthma at age 32 years to be

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associated with "low" FEV_1 trajectories between ages 11-32 years. While TAHS[3] found "active" adult asthma at age 40, 45 and 53 years to be associated with "below average", "persistently low" and "early below average, accelerated decline" FEV_1 trajectory between ages 7-53 years. DCS[25] observed asthma symptoms, self-reported physician diagnosed asthma and higher BMI (30 kg/m^2 or above) by age 20 years to be associated with accelerated decline" FEV_1 trajectory between ages 26-66 years. [Tables 2].

Adult Environmental characteristics

Cigarette smoking was associated with subnormal lung function trajectories in the three studies that explored the relationship.[3,21,25] Smoking was defined as ever smoking[3,21,25] and 10 pack-year smoking.[3] CARDIA[21] observed ever-smokers to be at increased risk of "worsening" and "persistently poor" FEV_1 trajectories between ages 25-55 years. DCS[25] observed smoking by age 20 to be strongly associated with "accelerated decline" FEV_1 trajectories between ages 26-66 years. This association was stronger in women and in persistent smokers compared to those that quit smoking. TAHS[3] similarly observed smoking to be associated with an increased risk of "below average", "persistently low", and "early below average, accelerated decline" FEV_1 trajectories between ages 7-53 years [Tables 2].

Interactions between exposures

TAHS[3] is the only study that examined the interactions between exposures. Interactions between "heavy" maternal smoking and personal smoking in adulthood were observed to be associated with an increased risk of "early below average, accelerated decline" FEV_1 trajectory between ages 7-53 years. Similarly, interactions between childhood and adulthood asthma were observed to be associated with an increased risk of "early below average, accelerated decline" FEV_1 trajectory between ages 7-53 years [Table 2 &3].

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DISCUSSION

To the best of our knowledge, this review is the first to systematically collate evidence on the predictors of lung function trajectories in the general population. Evidence from this review is from nine population-based cohort studies that identified trajectories of lung function and its associated risk factors. One study identified six trajectories, one identified five, and the others four or fewer. Studies with larger sample sizes and repeated lung function measurements conducted over a longer period identified more trajectories than the others. Interestingly, the only study that captured both childhood and adulthood lung function measures identified the highest number of trajectories including a trajectory that demonstrates a 'catch up' from childhood to young adulthood.[3] The predictors of 'subnormal' trajectories described in the results section above were those observed in at least two across studies. Infants with low lung function were likely to develop the "below average" or "persistently low" FEV_1 trajectory between ages six to 18 years.[18,19] On the other hand, recent studies show that about two-thirds of children with low infant lung function can catch-up to normal lung function by puberty.[1,4,28] The majority of these children had improvement in lung function and transitioned to above average and normal trajectories.[19] Though the reason for this transition is unclear within the literature, our review found that accelerated childhood weight gain plays a significant role in this transition.[3]

Severe and/or longstanding childhood asthma is generally well known to be a risk factor for low lung function in early adulthood,[30,31] and our finding supports this association. We observed childhood asthma, especially frequent and persistent phenotypes, and asthma medication use were associated with the persistently low trajectories.[3,20] It has also been identified that the risk of developing these subnormal trajectories increased with a

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combination of asthma, positive allergic sensitisation, eczema, and allergic rhinitis consistent with type 2 allergic phenotype.[3,19,20] These findings are consistent with the "allergic march" hypothesis. Hence, public health innovations should emphasise this understanding of the natural history of allergic diseases and its multi-morbidities. Emphasis should also be on reinforcing the development of comprehensive population-based and/or individual-based prevention of asthma exacerbations programs, as all evidence suggests effectiveness in behaviour change on medication adherence, avoidance of triggers, reduction in visits to emergency services, hospitalisation, and overall improvement of asthma control.[32,33]

Adulthood risk factors identified in this review were found to be mainly associated with the "accelerated decline" FEV_1 trajectories and the "persistently low" FEV_1 trajectories by the seventh decade of life. Although the effects of cigarette smoking on lung function outcomes are generally well known, the influence of the interactions it has with other exposures confirms that personal cigarette smoking not only accelerates the decline of FEV_1, but accentuates early lung damage.[1,3,12] This finding is crucial because all evidence shows that the rapid decline of FEV_1 in adulthood is a marker for premature mortality from all causes.[1,2] Furthermore, the evidence that smoking accentuates adverse childhood impacts on lung function in later life highlights the importance of targeting health promotion messages to high-risk groups.

Our review highlights the importance of genetic susceptibilities, together with early life and adulthood influences on lung function trajectories up to the seventh decade of life, but several limitations are acknowledged. Due to the heterogeneity of exposures and lung function ascertainment, as well as differing trajectory definitions and modelling techniques across studies, it was not possible to conduct a meta-analysis within this review. Given the number of risk factors evaluated in our review, an in-depth evaluation of potential residual confounding was beyond the scope of our review. Hence it is possible that residual

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confounding has influenced the results of this review; however, all studies were of reasonably good quality according to the Newcastle-Ottawa scale (NOS). NOS is the most appropriate tool for assessing the quality of longitudinal observational study designs although its limitations have also been acknowledged.[17] The potential for reverse causation should be acknowledged with some of the risk factors and persistently low trajectories, especially with lower respiratory tract infections. Furthermore, the generalizability of the findings of this review is limited as the included studies have been conducted mainly in Europe, Australia, and the USA. There is also some potential for review bias, given that some co-authors of this review were also authors of one of the included studies. However, this review used a standard methodology and prospectively registered the prespecified protocol in PROSPERO.

In conclusion, there is strong evidence that associates early life factors, such as childhood asthma, allergic sensitisation, early childhood wheezing, and SHS exposure, to "below average" and "persistently low" lung function trajectories. Additionally, personal cigarette smoking, and active adult asthma were strongly associated with the "accelerated decline" and "persistently low" FEV_1 trajectories. Thus, subnormal trajectories could be a result of low lung function at birth, reduced lung growth, shorter plateau phase and/or accelerated lung function decline. All subnormal trajectories are likely to increase the risk of early onset of COPD, though the COPD cases arising out of these trajectories are likely to be phenotypically and pathogenically heterogeneous, and so may respond differently to treatment. Indeed, without knowing the underlying airway/lung processes involved in each phenotype, it is impossible to adequately tailor therapy rationally. Hence, understanding the biomarkers that can help discriminate COPD cases with different trajectory pathways is a much-needed area of research. Our review highlights that there is a significant paucity of data in this area, which critically limits understanding of the mechanisms behind the various lung

function trajectories. Therefore, to provide a more comprehensive picture and enable early identification of high-risk populations susceptible to developing subnormal lung function trajectories, adequate resources should be directed towards the establishment and continuation of large, long-term cohorts with multiple timepoints for lung function measures, which encompass the growth, plateau, and decline phases of lung function trajectories. Overall, public health interventions and new strategies should be directed towards early identification and monitoring of children with low lung function with the aim of intervening on risk factors such as asthma, infections and smoking may help to realign their trajectories and promote lung health.

Conflict of Interest: None declared.

Human Ethics Approval Declaration: Not applicable.
The protocol for this systematic review was prospectively registered in PROSPERO: CRD42020145366 at crd.york.ac.uk/prospero/

Author contribution:

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Table 1: Details of studies included in this review

First author, year Study name Country	Exposure characteristics	Clinical lung measurements	Lung function trajectory analysis Number of trajectories Sample (n§) analysed
Birth Cohort studies			
Weber, 2020 **Pelotas 1993 Birth Cohort** **Brazil**	**Genetic susceptibility:** Family history of asthma, gender **Gestational and perinatal:** [Prematurity (gestational age <37weeks), pregestational Body Mass Index (BMI) (kg.mg^{-2}), weight and height, smoking, alcohol consumption (mothers)] **Childhood and adolescent clinical:** family income (minimum wage per month), birth weight (<2500g), hospitalisation (bronchitis, bronchiolitis, pneumonia), wheezing, asthma diagnosis, allergic diagnosis **Childhood and adolescent environmental:** paternal smoking, early second-hand smoke exposure (SHS), current smoker, physical activity **Adulthood environmental:** current smoker **Age measured:** Perinatal period, infancy, 4, 11, 15, 18, 22 years **Measurement tools/ techniques:** Self-reported questionnaire	**Procedure:** Pre-BD spirometry* **Age measured:** 15, 18, 22 years	**Statistical analyses:** Group-based trajectory modelling **Number of trajectories:** Three FEV_1, FVC (z-score) and FEV_1/FVC ratio trajectories **n**=2917
Karmaus, 2019 **Isle of Wight (IOW)** **UK**	**Genetic susceptibility:** Maternal smoking during pregnancy, Maternal history of asthma, height **Gestational and perinatal:** Maternal smoking during pregnancy, cord serum IgE (kU/L) **Childhood and adolescent clinical:** birth weight, duration of breastfeeding, the introduction of formula, solids feeding, recurrent chest infections, eczema, physician-diagnosed/ prevalence of asthma, positive skin prick test. **Childhood and adolescent environmental:** pet ownership, second-hand smoke (SHS), ever lived on a farm **Age measured:** 1, 2, 4, 10, 18, 26 years **Measurement tools/ techniques:** Self-reported questionnaire, primary medical records, and clinical assessments	**Procedure:** Pre-BD spirometry* **Age measured:** 10, 18, 26 years	**Statistical analyses:** Group-based trajectory modelling **Number of trajectories:** Two FEV_1, FVC, FEV_1/FVC ratio trajectories & Three FEF_{25-75} trajectories. **n**= 808
Sunny, 2021a **Isle of Wight (IOW)** **UK**	**Genetic susceptibility:** DNA-methylation (DNA-M) at each cytosine-phosphate-guanine dinucleotide sites (CpG) **Age measured:** 10 years **Measurement tools/ techniques:** Peripheral blood samples collected. DNA-M was measured using HumaMethylation450K and HumanMethylationEPIC BeadChips	**Procedure:** Pre-BD spirometry* **Age measured:** 10, 18, 26 years	**Statistical analyses:** Group-based trajectory modelling **Number of trajectories:** Two FEV_1, FVC, FEV_1/FVC ratio trajectories **n**= 809

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Sunny, 2021b **The Avon Longitudinal Study of Parents and Children (ALSPAC)** **UK**	**Genetic susceptibility:** DNA-methylation (DNA-M) at each cytosine-phosphate-guanine dinucleotide sites (CpG) **Age measured:** 7 years **Measurement tools/ techniques:** Peripheral blood samples collected. DNA-M was measured using HumaMethylation450K and HumanMethylationEPIC BeadChips	**Procedure:** Pre-BD spirometry* **Age measured:** 8, 15, 24 years	**Statistical analyses:** Group-based trajectory modelling **Number of trajectories:** Two FEV_1, FVC, FEV_1/FVC ratio trajectories **n=** 4861
Mukherjee 2021 **Isle of Wight (IOW)** **UK**	**Genetic susceptibility:** DNA-methylation (DNA-M) at each cytosine-phosphate-guanine dinucleotide sites (CpG) **Age measured:** at birth **Measurement tools/ techniques:** Dried blood sports on Guthrie cards. DNA methylation (DNAm) was assessed using the Illumina Infinium MethylationEPIC BeadChip	**Procedure:** Pre-BD spirometry* **Age measured:** 10, 18, 26 years	**Statistical analyses:** Group-based trajectory modelling **Number of trajectories:** Two FEV_1, FVC, FEV_1/FVC ratio trajectories **n=** 1157
Belgrave, 2018a **Manchester Asthma and Allergy Study (MAAS)** **UK**	**Genetic susceptibility:** Parental history of asthma, weighted allele score from 77 single nucleotide polymorphisms (SNPs) for association with FEV_1: FVC and FEV_1 decline in adults **Childhood and adolescent clinical:** Birth weight, Current wheeze (last 12 months), current asthma (current wheeze, current use of asthma medication, physician-diagnosed asthma ever), wheeze phenotypes (no wheeze, transient early wheeze, late-onset wheeze, persistent wheezing), severe asthma/wheeze exacerbations (oral corticosteroids (OCS) use at least 3 days or hospital admission requiring OCS, Allergic sensitisation (>3mm diameter), Lower respiratory tract infection (LRTIs), SHS, **Childhood and adolescent environmental:** current smoking **Age measured:** Infancy to 16 years **Measurement tools/ techniques:** Self-reported questionnaires and primary medical records	**Procedure:** Pre-BD and Post-BD spirometry* **Age measured:** 3, 5, 8, 11, 16 years	**Statistical analyses:** Latent profile modelling **Number of trajectories:** Four childhood FEV_1 trajectories (% predicted) **n=** 1046
Belgrave, 2018b **The Avon Longitudinal Study of Parents and Children (ALSPAC)** **UK**	**Genetic susceptibility:** Parental history of asthma, weighted allele score from 77 single nucleotide polymorphisms (SNPs) for association with FEV_1: FVC and FEV_1 decline in adults **Childhood and adolescent clinical:** Birth weight Current wheeze (last 12 months), current asthma (current wheeze, current use of asthma medication, physician-diagnosed asthma ever), wheeze phenotypes (no wheeze, transient	**Procedure:** Pre-BD spirometry* **Age measured:** 8, 15, 24 years	**Statistical analyses:** Latent profile modelling **Number of trajectories:** Four childhood FEV_1 trajectories (% predicted)

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	early wheeze, late-onset wheeze, persistent wheezing), Allergic sensitisation (>3mm diameter), LRTIs **Childhood and adolescent environmental:** SHS, current smoking **Age measured:** Infancy, 7-24 years **Measurement tools/ techniques:** Self-reported questionnaires and primary medical records		**n=** 1390
Belgrave, 2018c **Australian Perth Infant Asthma (PIAF)** **Australia**	**Childhood and adolescent clinical:** Birth weight, current wheeze, current asthma, wheeze phenotypes, airway hyper-reactivity **Childhood and adolescent environmental:** allergic sensitisation, LTRIs, SHS, current smoking **Age measured:** Infancy, 6, 12, 18 years **Measurement tools/ techniques:** Self-reported questionnaires, primary medical records, clinical assessments	**Procedure:** Infant plethysmography and Pre-BD spirometry* **Age measured:** (1, 6, 12 months) & (6, 12, 18 years)	**Statistical analyses:** Latent profile modelling **Number of trajectories:** Four childhood FEV_1 trajectories (% predicted) & V'_{maxFRC} (% predicted) **n**=196
Berry, 2016 **Tucson Children's Respiratory Study (CRS)** **USA**	**Genetic susceptibility:** Gender, race/ethnicity (White, Mexican American, African American), parental asthma **Gestational and perinatal:** in utero smoke **Childhood and adolescent clinical:** Birth weight, parental age, low lung function in infancy (V'_{MaxFRC}), physician diagnosed active asthma, LRTI's **Childhood and adolescent environmental:** Parental smoking, early day care, active smoking. **Adulthood clinical:** Active asthma **Age measured:** infancy, 2 to 13, 16 years **Measurement tools/ techniques:** Self-reported questionnaires, clinical assessments	**Procedure:** Pre-BD Spirometry **Age measured:** 11, 16, 22, 26, 32	**Statistical analyses:** Latent profile modelling **Number of trajectories:** Two childhood FEV_1 trajectories (% predicted) **n=** 599
Post-Birth Cohort Studies			
Washko, 2020 **Coronary Artery Risk Development in Young Adults (CARDIA)** **USA**	**Genetic susceptibility:** Gender, race **Adulthood clinical:** Asthma, body mass index (kg/m^2) **Adulthood environmental:** Aggregated tobacco smoke (current, former), **Age measured:** Baseline (18 to 30 years) + every 2, 5, 7, 12, 10, 15, 20, 25, 30 years. **Measurement tools/ techniques:** Self-reported questionnaires.	**Procedure:** Pre-BD spirometry* **Age measured:** 25, 28, 30, 40, 55	**Statistical analyses:** Group-based trajectory modelling **Number of trajectories:** Five FEV_1 trajectories (% predicted) **n=** 3171
Bui, 2018	**Genetic susceptibility:** Gender, parental asthma **Childhood and adolescent clinical:** Asthma phenotype; ever (asthma, bronchitis, eczema, allergic rhinitis, food allergy, pneumonia, or pleurisy);	**Procedure:** Pre-BD spirometry*	**Statistical analyses:** Group-based trajectory modelling

Tasmanian Longitudinal Health Study (TAHS) **Australia**	childhood weight status, breastfeeding, mean FEV_1 at 7 years, current asthma, active asthma, atopy, atopic asthma. **Childhood and adolescent environmental:** Socioeconomic status (parental occupation), maternal smoking, parental smoking, current smoking **Adulthood clinical**: Current asthma, active asthma, atopy, atopic asthma, COPD **Adulthood environmental:** Personal smoking, current smoking, socio-economic status **Age measured:** 3, 7, 53 years **Measurement tools/ techniques:** Self-reported questionnaire	**Age measured:** 7, 13, 18, 45, 50, and 53	**Number of trajectories:** Six distinct FEV_1 trajectories (z-scores) **n=** 2438
Oostrom, 2018 **The Doetinchem Cohort Study (DCS)** **The Netherlands**	**Adulthood clinical:** Asthma symptoms (wheezing in the past 12 months, shortness of breath at the night in the past 12 months, self-reported physician diagnosed asthma), COPD symptoms (chronic cough at least 3months, chronic sputum production or breathlessness when walking on ground level with people of same age, BMI (normal, overweight obese), medication for respiratory symptoms (within 24 hours) **Adulthood environmental:** Smoking, SHS (home/work), physically inactive, Education level (low, medium, high), No paid job, living alone **Age measured:** 20 to 66 years **Measurement tools/ techniques:** Self-reported questionnaire	**Procedure:** Pre-BD spirometry* **Age measured:** 26, 35, 45, 55, and 66	**Statistical analyses:** Latent profile modelling **Number of trajectories:** Three FEV_1 trajectories (%predicted) n=5727

V'_{maxFRC}: maximum flow at Functional Residual Capacity, Pre-BD= Prebronchodilator, Post-BD= Postbronchodilator, sRaw = specific airways resistance
⁎ : Spirometry was done according to the American Thoracic Society and European Respiratory Society joint guidelines.
§: sample size for modelling of lung function trajectories within the studies

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Table 2: The association between exposures and lung function trajectories

First author, year Study name	Exposures associated with Lung Function Trajectories (FEV_1, FVC, FEV_1 /FVC)										Authors' conclusion
Birth cohort											
Weber, 2020 **Pelotas 1993 Birth Cohort**			**FEV_1 Trajectories**			**FEV_1 /FVC Trajectories**					Pregestational BMI, birth weight, hospitalisations due to respiratory diseases in childhood, participant's BMI, report of wheezing, medical diagnosis and family history of asthma, gestational exposure to tobacco and active smoking in adolescence and young adulthood are associated with lower trajectories of pulmonary function.
			Low N=435	**Average N=1776**	**High N=706**	**Low N=249**	**Average N=1279**	**High N=1389**			
	Family history of asthma		165 (38.7)	588 (33.6)	230 (33.0)	109 (44.8)§	465 (37.0)	409 (29.8)			
	Male sex %		245(56.3)§	809 (45.6)	381 (54.0)	153 (61.4)§	710 (55.5)	572 (41.2)			
	Birth weight (g)		3164.8±25.4‡	3175.8±12.4	3232.0±19.8	3240.1±37.3*	3204.3±14.7	3163.3±13.7			
	Pregestational BMI		22.4±0.2§	22.8±0.1	23.3±0.1	23.0±0.25‡	23.1±0.10	22.6±0.10			
	Smoking in 1° trimester		133 (30.6)	499 (28.1)	220 (31.0)	94 (37.7)‡	384 (30.0)	374 (26.9)			
	Alcohol in pregnancy %		17 (3.9)	93 (5.2)	40 (5.7)	14 (5.6)	60 (4.7)	76 (5.5)			
	Hospitalisation due to respiratory disease (Age 4)		22 (14.9)*	64 (11.0)	13 (6.1)	16 (22.8)§	44 (11.7)	39 (7.4)			
	Wheezing (last 12 months) %										
	4 years		29 (22.5)	98 (20.0)	27 (15.7)	18 (26.7)‡	78 (23.9)	58 (14.4)			
	11 years		87 (20.4)§	234 (13.4)	76 (10.9)	67 (27.6)§	200 (15.9)	130 (9.5)			
	22 years		68 (15.7)§	174 (9.8)	50 (7.1)	69 (27.9)§	136 (10.6)	87 (6.3)			
	Asthma diagnosis %										
	11 years		158 (37.1)§	481 (27.5)	162 (23.2)	120 (49.4)§	390 (31.0)	291 (21.2)			
	15 years		161 (37.1)§	516 (29.1)	162 (23.0)	124 (50.0)§	409 (32.0)	306 (22.5)			
	18 years		125 (28.7)§	381 (21.5)	115 (16.3)	107 (43.0)§	310 (24.3)	204 (14.7)			
	22 years		131 (30.1)§	407 (22.9)	120 (17.0)	109 (43.9)§	317 (24.8)	232 (16.7)			
	Allergy diagnosis %										
	11 years		79 (18.5)	298 (17.0)	142 (20.4)	58 (23.9)	223 (17.7)	238 (17.3)			
	15 years		99 (22.9)‡	339 (19.2)	169 (24.1)	59 (23.9)	270 (21.2)	278 (20.1)			
	22 years		97 (22.4)	433 (24.4)	179 (25.4)	75 (30.2)‡	283 (22.1)	351 (25.3)			
	Current Smoking %										
	18 years		55 (12.6)	230 (12.9)	96 (13.6)	50 (20.1)§	192 (15.0)	139 (10.0)			
	22 years		80 (18.4)	291 (16.4)	100 (14.6)	64 (25.8)§	235 (18.4)	471 (16.1)			
Karmaus, 2019 IOW	**Male**	**n**	**FVC trajectory**		**FEV_1 trajectory**		**FEV_1 /FVC**		**$FEF_{25-75\%}$ trajectory**		Men and women showed distinctive lung function trajectories and associated risk factors. Lower lung function can be explained by not
			LT n=329 %	**HT n=248 %**	**LT n=329 %**	**HT n=248 %**	**LT n=140 %**	**HT n=437 %**	**LT n=273 %**	**MT, n=267 %**	**HT n=37 %**
	Maternal asthma	573	12.3	9.8	12.2	9.8	11.4	11.1	9.9	12.9	8.1

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Paternal asthma	569	10.4	11.1	10.1	11.5	13.0	10.0	9.3	11.5	16.2	achieving maximally attainable function at age 18
Birth weight (g), mean	566	3386*	3539	3373*	3554	3378	3476	3394*	3475	3714	years and by a function
Chest infections (Age 1 or 2)	492	21.5	15.4	23.2*	13.4	23.4	17.6	21.9	16.0	20.0	decline from 18 to 26 years
Prevalence of asthma											
4 years	510	16.2	15.1	18.9*	11.8	25.4*	12.6	19.5*	12.8	11.1	
10 years	560	20.1	15.3	20.9*	14.2	29.1*	14.6	22.4*	15.3	5.7	
18 years	523	19.3	15.6	20.1	14.4	32.0*	13.1	25.2*	11.6	5.7	
26 years	406	15.3	12.5	17.8*	9.4	26.0*	10.3	20.2*	9.0	6.7	
Positive (SPT) (Age 4)	523	23.2	22.4	24.6	20.5	34.3*	19.3	30.1	14.6*	32.1	
Duration of breastfeeding (weeks)	524	8*	12	8.5	12	12	11	12	10	13	
Height (age 4) (cm)	458	102.8*	106.0	102.9*	105.9	104.6	104.1	103.6	104.5	105.6	

Female	**n**	**FVC trajectory**		**FEV $_1$ trajectory**		**FEV$_1$ /FVC**		**FEF $_{25-75\%}$ trajectory**		
		LT n=297 %	**HT n=283 %**	**LT n=283 %**	**HT n=302 %**	**LT n=110 %**	**HT n= 470%**	**LT n=141 %**	**MT n=323 %**	**HT n=116 %**
Maternal asthma	577	8.8	11.0	10.6	9.3	11.9	9.4	12.9	8.7	9.4
Paternal asthma	574	8.2	10.4	8.3	10.1	10.9	8.8	10.6	9.1	7.8
Maternal smoking during pregnancy	579	23.7	21.2	25.6	19.5	25.5	21.8	26.2	23.9	13.8*
Birth weight (grams)	571	3263*	3453	3270*	3434	3380	3350	3269	3363	3441*
Eczema in the first year	449	12.5*	5.6	12.4*	6.02	12.5	8.3	15.0	7.8	5.4*
Chest Infection (Age 1 or 2)	507	17.9	15.1	17.2	16.0	17.0	16.5	17.2	17.7	12.8
Prevalence of asthma										
4 years	510	14.4	15.4	16.3	13.7	18.8	14.0	20.5*	14.0	10.9
10 years	561	12.6	13.8	15.7	10.9	21.3*	11.3	21.7*	11.2	8.2
18 years	552	19.6	20.6	24.9*	15.7	36.1*	16.2	35.7*	16.4	10.9
26 years	484	16.4	17.5	20.2	14.1	29.8	13.4	28.6*	15.6	5.9
Positive (SPT) (Age 4)	488	21.4*	13.6	22.2*	13.3	21.8	16.6	25.2*	16.3	11.8
Duration of breastfeeding (weeks)	542	8	10	8	9	8	8	6.5	8.0	11.0
Height (Age 4) (cm)	462	101.7*	104.9	101.7*	104.8	103.5	103.3	102.1	103.5	104.5*

Mukherjee 2021		**Risk Ratio (95% CI)**			DNAm of eight CpGs on genes GLUL, MYCN, HLX, LHX1, COBL, COL18A1, STRA6, and WNT11 involved in developmental processes, were significantly associated with lung function in adolescence and early adulthood.
IOW	**Male**	**FEV_1 trajectory (LT Vs. HT)**	**FEV_1 /FVC (LT Vs. HT)**	**$FEF_{25-75\%}$ trajectory (LT Vs. HT)**	
	cg13529291 WNT11/UVRAG	··	··	1.14 (1.03,1.25)	
	cg01885814 COL18A1	··	··	0.93 (0.89,0.98)	
	cg01678802 COBL	··	··	0.92 (0.87,0.97)	
	cg07103093 LHX1	0.87 (0.81, 0.94)	··	··	
	cg06710742 STRA6/ CCDC33	0.77 (0.66, 0.89)	··	··	
	Female				
	cg00383081 GLUL	··	··	0.77 (0.66, 0.89)	
	cg22311507 MYCN	··	··	0.91 (0.85, 0.96)	
	cg16008148 HLX/MARCH1	··	0.89 (0.85, 0.94)		
Sunny 2021 IOW & ALSPAC			**IOW cohort**	**ALSPAC cohort**	Pre-adolescence DNA-M at 44 CpGs was associated with The lung function trajectories. The identified 44 CpG sites mapped to 42 genes, which were enriched in 18 KEGG and REACTOME pathways. These identified sites have a strong potential of high sensitivity to predict an individual's lung function development from pre-adolescence to young adulthood.
	CpGs gene name, location	**Chromosome number**	**Log Odd Ratio (95% CIs)**		
	Male				
	FEV_1 /FVC trajectories				
	cg14669749 SKI, Intergenic	1	− 3.94 (− 6.21, − 1.67)	− 1.39 (− 2.72, − 0.07)	
	cg21131402 C12orf50, Promoter	12	− 6.05 (− 9.41 − 2.7)	− 0.69 (− 1.41, 0.02)	
	Female				
	FVC trajectories				
	cg05597624 RNF220, 5′UTR	1	− 2.07 (− 3.63, − 0.52)	− 0.48 (− 1.04, 0.07)	
	FEV_1				
	cg23987789 VAMP3, Intergenic	1	1.55 (0.46, 2.63)	0.44 (0.09, 0.79)	
	FEV_1 /FVC trajectories				
	cg23190164 LGR5, Body	12	− 2.64 (− 4.31, − 0.97)		
	cg24479027 ABR, Promoter	17	− 0.63 (− 1.14, − 0.11)		
Belgrave, 2018a MAAS		**Persistently High FEV_1 Trajectory (n=46; 4.4%)**	**Normal FEV_1 Trajectory (n=468; 45.3%) (baseline group)**	**Below average FEV_1 Trajectory (n=496; 46.9%)**	**Persistently Low FEV_1 Trajectory (n=36; 3.4)**	Persistently low FEV_1 was associated with wheezing and asthma through childhood and tobacco smoke exposure and was predicted by

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					severe recurrent wheezing and allergic sensitisation by age 3 years.
	Paternal asthma	4/6 (8.7%)	68/469 (14.5%)	64/496 (12.9%)	8/36(22.2%)	
	Maternal asthma	5/46 (10.9%)	98/474 (20.7%)	96/490 (19.6%)	10/36 (27.8%)	
	Birth Weight (kg)	3.418 (3.266 - 3.569)	3.466 (3.421 - 3.511)	3.479 (3.433 - 3.525)	3.435 (3.222 - 3.647)	
	LRTIs (Age 3)	2/42 (4.8%)	49/405 (12.1%)	62/422 (14.7%)	11/34 (32.3%)§	
	Day-care	33/43 (76.7%)	307/446 (68.8%)	324/456 (71.1%)	15/32 (46.9%)*	
	Current wheeze (Age 3)	5/46 (10.9%)	90/448 (20.1%)	129/474 (27.2%)‡	16/33 (48.5%)§	
	Current wheeze (Age 8)	8/44 (18.2%)	62/437 (14.2%)	98/476 (20.6%)‡	14/36 (38.9%)§	
	Asthma (Age 3)	2/36 (5.0%)	57/329 (14.8%)	75/441 (19.4%)*	9/22 (37.5%)*	
	Asthma (Age 5)	5/39 (12.8%)	92/405 (22.7%)	125/419 (29.8%)‡	14/32 (43.8%)§	
	Asthma (Age 8)	7/37 (18.9%)	67/307 (17.9%)	91/363 (22.6%)	14/27 (46.7%)§	
	Asthma (Age 11)	7/37 (18.9%)	77/353 (21.8%)	90/359 (25.1%)	15/29 (51.7%)§	
	Sensitisation (SPT) (Age 5)	10/43 (23.3%)	111/429 (25.9%)	142/437 (32.5%)*	22/33 (66.7%)§	
	Sensitisation (SPT) (Age 8)	16/44 (36.4%)	120/410 (29.3%)	156/435 (35.9%)*	20/30 (66.7%)§	
		Main effect, OR (95%CI)				
	Any ETS exposure (Age 3)	··	··	··	21.36 (1.36-334.39)*	
		Relative risk ratio (95% CI) per unit score				
		Persistently High FEV_1 Trajectory	··	**Below average FEV_1 Trajectory**	**Persistently Low FEV_1 Trajectory**	
	Weighted genetic score based on 77 SNPs)	0.989 (0.930, 1.052)	··	1.006 (0.981, 1.031)	1.023 (0.973, 1.076)	
Belgrave, 2018b ALSPAC		**Persistently High FEV_1 Trajectory (n=52; 3.7%)**	**Normal FEV_1 Trajectory (n=632; 45.5%) (baseline group)**	**Below average FEV_1 Trajectory (n=613; 44.1%)**	**Persistently Low FEV_1 Trajectory (n=93; 6.7%)**	Persistently low FEV_1 was associated with wheezing and asthma through childhood and tobacco smoke exposure and was predicted by severe recurrent wheezing and allergic sensitisation by age 3 years.
	Paternal asthma	3 (9.1%)	49 (11.8%)	47 (11.4%)	13 (22.4%)*	
	Maternal asthma	4 (8.3%)	63 (11.4%)	47 (8.8%)	7 (8.6%)	

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Birth Weight (kg)	3.62 (3.51-3.74)‡	3.43 (3.38-3.47)	3.39 (3.34-3.43)	3.28 (3.13-3.43)*
ETS exposure (in-utero)	6 (11.5%)	93 (14.7%)	86 (14.0%)	16 (17.2%)
ETS exposure (birth to age 3)	8 (15.4%)	128 (20.3%)	115 (18.8%)	19 (20.4%)
Day-care	6/44 (11.5%)	78/523 (12.3%)	42/494 (6.9%)§	12/78 (12.9%)
Current wheeze (Age 3)	3 (6.7%)	64 (12.3%)	84 (17.0%)*	22 (27.9%)§
Current wheeze (Age 8)	2 (4.3%)	43 (8.7%)	60 (12.1%)*	18 (22.0%)§
Asthma (Age 8)	2 (5.3%)	50 (12.7%)	71 (18.1%)*	19 (31.2%)§
Asthma (Age 11)	1 (2.8%)*	59 (13.7%)	65 (15.9%)	22 (32.4%)§
Asthma (Age 15)	5 (12.8%)	59 (15.6%)	52 (14.4%)	24 (36.4%)§
Sensitisation (SPT) (Age 7.5)	6 (14.6%)	75 (16.8%)	75 (17.7%)	9 (13.9%)

Relative risk ratio (95% CI) per unit score

	Persistently High FEV_1 Trajectory	..	**Below average FEV_1 Trajectory**	**Persistently Low FEV_1 Trajectory**
Weighted genetic score based on 77 SNPs,)	0.989 (0.930, 1.052)	..	1.006 (0.981, 1.031)	1.023 (0.973, 1.076)

Belgrave, 2018c PIAF

Mean (95% CI)

V'_{MaxFRC}/ age	Above Average FEV_1 Trajectory(n=24)	Normal FEV_1 Trajectory (n=133)	Below Average FEV_1 Trajectory (n=39)	P value
1 month	106.38 (87.23 – 125.53)	102.46 (93.54 – 111.38	81.32 (67.46 – 95.18)	0.05
6 months	125.76 (103.58 – 147.94)	102.34 (93.99 – 110.69)	89.04 (76.44 – 101.64)	0.018
12 months	102.51 (83.87 – 121.15)	98.93 (90.36 – 107.50)	88.34 (77.28 – 99.39)	0.43

Most infants with low infant lung function trajectory during the first year after birth transitioned to normal or above average FEV1 trajectories

Berry, 2016 CRS

Exposures [%(n/N)]	**N**	**Low Trajectory**	**Normal Trajectory**
Maternal asthma	589	20.0 (11/55)*	9.9 (53/534)
Paternal asthma	562	5.8 (3/52)	12.4 (63/510)
Birth weight, g, mean (SD)	599	3,538 (506)	3,482 (466)
In utero smoke exposure (Maternal)	599	14.3 (8/56)	14.7 (80/543)
In utero smoke exposure (Paternal)	592	25.0 (14/56)	28.2 (151/536)
Early life RSV-LRTIs	533	41.2 (21/51)§	21.4 (103/482)
Early day care†	578	7.6 (4/53)	7.2 (38/525)

Persistently low lung function trajectory that may be partly established at birth and predisposes to chronic obstructive pulmonary disease later in life.

Physician-diagnosed asthma (age 6)	589	24.6 (14/53)§	7.7 (41/536)
Physician-diagnosed asthma (age 11)	585	39.6 (21/53)§	15.2 (81/532)
Physician-diagnosed asthma (Age16)	540	30.8 (16/52)*	18.0 (88/488)
Physician-diagnosed asthma (Age 22)	542	41.8 (23/55)§	16.8 (82/487)
Physician-diagnosed asthma (Age 26)	499	40.4 (21/52)§	17.7 (79/447)
Physician-diagnosed asthma (age 32)	429	43.9 (18/41)§	16.2 (63/388)
Active smoking (Age 16 to 26)	596	35.7 (20/56)	32.4 (175/540)
		mean, (95%CI)	
V'_{MaxFRC}/ age, ml/s [N]			
V'_{MaxFRC} in Infancy [N= 107]	107	65.6 (45.0–95.7)§	118.5 (108.0–129.9)
V'_{MaxFRC} at 6 years [N= 444]	444	872.6 (795.0–957.7)§	1,212.2 (1,180.1–1,245.1)

Post-Birth Cohort Studies

Washko, 2020 CARDIA

	Preserved Ideal Lung Health	**Preserved Good Lung Health**	**Preserved Impaired Lung Health**	**Worsening Lung Health**	**Persistently Poor Lung Health**
	N= 187	N= 1478	N= 1264	N= 180	N= 62
Asthma, n %	3 (1.6%)	25 (1.7%)	71 (5.6%)	4 (2.2%)	13 (21.0%)
Smoking (Y30)					
Never, n (%)	125 (67.9%)	959 (65.5%)	792 (63.3%)	78 (44.3%)	32 (53.3%)
Former, n (%)	39 (21.2%)	340 (23.2%)	292 (23.3%)	37 (21.0%)	14 (23.3%)
Current, n (%)	20 (10.9%)	165 (11.3%)	168 (13.4%)	61 (34.7%)	14 (23.3%)
Lifetime pack-years of cigarettes (Y30)	3.53 (7.07)	4.49 (9.04)	6.39 (11.81)	11.00 (13.48)	11.15 (16.82)

Lower peak and accelerated decline in FEV_1 are risk factors for future emphysema independent of smoking status.

Bui, 2018 TAHS

	Odd Ratio (95%CI)				
	Early below average, accelerated decline	**Persistently low**	**Early low, accelerated growth, normal decline**	**Persistently high**	**Below average**
Female	0·8 (0·5–1·2)	0·8 (0·6–1·2)	1·7 (1·2–2·3)*	1·2 (0·9–1·5)	0·9 (0·8–1·1)
Parental asthma	1·2 (0·7–2·1)	1·8 (1·1–2·9)*	0·9 (0·5–1·4)	1·4 (0·9–2·0)	1·2 (0·9–1·6)
Underweight (Age 7)	1·3 (0·4–4·2)	2·2 (0·95–5·2)	2·6 (1·3–5·2)‡	0·7 (0·3–1·8)	1·5 (0·8–2·5)
Overweight (Age 7)	1·6 (0·9–2·8)	0·6 (0·3–1·2)	0·8 (0·5–1·4)	1·3 (0·9–2·0)	0·8 (0·6–1·1)
Bronchitis (Age 7)	2·0 (1·2–3·2)‡	1·1 (0·7–1·6)	1·1 (0·7–1·4)	0·9 (0·7–1·2)	1·1 (0·9–1·3)
Pneumonia or pleurisy	2·0 (1·2–3·5)‡	1·1 (0·6–1·9)	0·6 (0·4–1·1)	0·8 (0·5–1·3)	1·3 (1·0–1·8)*

Early below average, accelerated decline and persistently low had increased risk of COPD at age 53 years compared with the average group.

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	Childhood Asthma	3·1 (1·9–5·2)‡	1·7 (1·1–2·7)*	1·1 (0·7–1·8)	1·2 (0·8–1·8)	1·1 (0·8–1·5)	
	Asthma (Age < 3)	3·1 (1·7–5·5)§	2·0 (1·1–3·4)*	1·1 (0·6–2·0)	1·3 (0·8–2·0)	1·1 (0·8–1·5)	
	Frequent asthma (Age 7)	4·4 (2·1–9·1)§	4·1 (2·2–7·8)§	1·7 (0·8–3·5)	1·3 (0·7–2·5)	1·4 (0·9–2·2)	
	Eczema	1·3 (0·7–2·3)	1·8 (1·1–3·0)*	1·3 (0·8–2·3)	1·1 (0·6–1·6)	0·9 (0·6–1·3)	
	Allergic rhinitis	2·0 (1·2–3·4)‡	0·9 (0·5–1·6)	1·4 (0·8–2·2)	0·7 (0·5–1·1)	1·0 (0·8–1·4)	
	Maternal Heavy smoking	2·5 (1·1–5·9) *	1·7 (0·7–4·0)	1·0 (0·4–2·4)	1·5 (0·8–2·9)	1·3 (0·8–2·2)	
	Breast feeding only	0·7 (0·4–1·2)	0·7 (0·5–1·1)	0·7 (0·5–1·1)	1·1 (0·7–1·5)	0·8 (0·6–1·0)	
	Bottle and breast feeding	0·9 (0·5–1·6)	0·7 (0·4–1·1)	0·9 (0·6–1·4)	1·1 (0·8–1·7)	0·9 (0·7–1·2)	
	n/N (%)						
	Active asthma (Age 53)	56 (58%) *	53/135 (39%) *	35 (18%)	41/291 (14%)	179/771 (23%) *	
	Current (Age 53)	31/96 (32%) *	28/134 (21%) *	17/195 (9%)	26/291 (9%)	152/765 (20%) *	
Oostrom, 2018 DCS		**Odd Ratios (95% CI)**					The rate of lung function decline is accelerated with increasing age. Baseline determinants of the likelihood of following an unfavourable trajectory of lung function were in the presence of respiratory complaints and smoking. Smoking was the greatest predictor in women while higher BMI was associated with stronger FEV_1 decline in both men and women
		Male		**Female**			
		Decelerating decline trajectory	**Accelerating decline trajectory**	**Decelerating decline trajectory**	**Accelerating decline trajectory**		
	Educational level						
	Low	0.48 (0.20 1.18)	1.65 (0.61 4.43)	1.98 (0.74 5.29)	4.95 (0.37 67.17)		
	Medium	1.08 (0.49 2.37)	2.05 (0.77 5.50)	1.98 (0.70 5.57)	3.11 (0.20 47.85)		
	No paid job	1.08 (0.46 2.56)	0.97 (0.44 2.14)	1.28 (0.70 2.34)	0.58 (0.16 2.02)		
	Living alone	0.92 (0.26 3.28)	1.11 (0.38 3.25)	1.17 (0.49 2.78)	0.78 (0.07 8.15)		
	COPD symptoms	2.14 (0.94 4.84)	2.34 (1.13 4.81)	3.29 (1.78 6.10)	1.43 (0.31 6.58)		
	Asthma symptoms	1.62 (0.70 3.74)	2.42 (1.17 5.02)	2.23 (1.18 4.24)	3.16 (0.80 12.47)		
	BMI						
	Overweight	1.68 (0.82 3.45)	1.34 (0.67 2.69)	0.73 (0.38 1.39)	1.27 (0.34 4.83)		
	Obese	1.48 (0.47 4.66)	1.83 (0.73 4.62)	0.96 (0.41 2.25)	1.32 (0.19 9.16)		
	Smoking						
	Smoker	2.23 (0.81 6.14)	3.29 (1.06 10.19)	3.17 (1.33 7.56)	10.98 (1.22 98.49)		
	Ex-smoker	1.42 (0.57 3.58)	2.17 (0.72 6.56)	1.00 (0.40 2.50)	1.09 (0.11 10.52)		
	Tobacco exposure at home/work	1.15 (0.52 2.55)	1.66 (0.72 3.85)	1.92 (0.83 4.43)	0.49 (0.08 3.08)		
	Physically inactive	1.05 (0.55 2.00)	1.08 (0.58 2.01)	1.21 (0.70 2.09)	0.39 (0.10 1.52)		

Data presented in mean (SD) and n (%) unless otherwise specified.
*p≤0.05, ‡p≤0.01 §p≤0.001, SPT: Skin Prick Test(positive), HT: High trajectory, LT: Low trajectory, MT: Medium Trajectory, RSV: Respiratory syncytial virus, LRTIs: Lower respiratory tract infections, SNPs: Single nucleotide polymorphisms, ETS: Environmental tobacco smoke, SPT: Skin prick test, V'_{maxFRC} : maximum flow at Functional Residual Capacity, IOW: Isle of Wight Birth Cohort, ALSPAC: The Avon Longitudinal Study of Parents and Children, MAAS:

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Manchester Asthma and Allergy Study, PIAF: Australian Perth Infant Asthma, CRS: Tucson Children's Respiratory Study, CARDIA: Coronary Artery Risk Development in Young Adults, TAHS: Tasmanian Longitudinal Health Study, DCS: Doetinchem Cohort Study

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Table 3: Summary of Exposures and its association with subnormal trajectories

Risk factors/ age (years)	Studies investigated		Associated lung function trajectory	Timepoint of lung function measurement (years)
Genetic Susceptibility				
Family history of asthma	TAHS[3]	✓	Persistently low FEV_1 trajectories	7 to 53
	CRS[18]	✓	Persistently low FEV_1 trajectories	11 to 32
	Pelotas 1993 birth cohort[22]	✓	Low FEV_1/FVC trajectories	15 to 22
	ALSPAC[19]	✓	Persistently low FEV_1 trajectories	8 to 24
	IOW[20]	×	..	10 to 26
	MAAS[19]	×	..	5 to 16
Childhood and adolescent clinical characteristics				
Low birth weight (<2500g)	Pelotas 1993 birth cohort[22]	✓	Low FEV_1, FEV_1/FVC trajectories	15 to 22
	IOW[20]	✓	Lower FEV_1, FEV1/FVC and $FEF_{25–75}$ trajectories	10 to 26
	ALSPAC[19]	×	..	8 to 24
	MAAS[19]	×	..	5 to 16
LRTI'S (infants,1, 2, 3, 4 and 7)	Pelotas 1993 birth cohort	✓	Low FEV_1, FEV_1/FVC trajectories	15 to 22
	MAAS19	✓	Persistently low FEV_1 trajectories	5 to 16
	CRS[18]	✓	Persistently low FEV_1 trajectories	11 to 32
	TAHS[3]	✓	Persistently low FEV_1 trajectories	7 to 53
	IOW[20]	✓	Low FEV_1 trajectories	10 to 18
Early, current, recurrent, and severe wheezing exacerbations (age 3, 4, 11, 15, 18)	MAAS[19]	✓	Persistently low FEV_1 trajectories	5 to 16

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	ALSPAC[19]	✓	Persistently low FEV_1 trajectories	8 to 24
	Pelotas 1993 birth cohort[22]	✓	Low FEV_1, FEV_1/FVC trajectories	15 to 22
Childhood asthma (age 3, 4, 6, 8,11, 15)	MAAS[19]	✓	Persistently low FEV_1 trajectories	5 to 16
	ALSPAC[19]	✓	Persistently low FEV_1 trajectories	8 to 24
	CRS[18]	✓	Persistently low FEV_1 trajectories	11 to 32
	TAHS[3]	✓	Persistently low FEV_1 trajectories	7 to 53
	IOW[20]	✓	Low FEV_1 trajectories	10 to 18
	Pelotas 1993 birth cohort[22]	✓	Low FEV_1, FEV_1/FVC trajectories	15 to 22
Allergic sensitisation (age 4, 7, 8)	MAAS[19]	✓	Persistently low FEV_1 trajectories	5 to 16
	IOW[20]	✓	Low FEV_1, FEV_1/FVC trajectories	10 to 26
	ALSPAC[19]	×	..	8 to 24
Allergic phenotypes (Infants, 7, 11, 18, 22)	TAHS[3]	✓	Persistently low FEV_1 trajectories	7 to 53
	IOW[20]	✓	Low FEV_1, FEV_1/FVC trajectories	10 to 26
	Pelotas 1993 birth cohort[22]	✓	Low FEV_1, FEV_1/FVC trajectories	15 to 22
Childhood and adolescent environmental characteristics				
SHS exposure (Infants, 3, 7)	TAHS[3]	✓	Persistently low FEV_1 trajectories	7 to 53
	MAAS[19]	✓	Persistently low FEV_1 trajectories	5 to 16
	ALSPAC[19]	✓	below average FEV_1 trajectories	8 to 24
	IOW[20]	×	..	10 to 26
	Pelotas 1993 birth cohort[22]	×	..	15 to 22

Adult clinical characteristics				
Active adult asthma (25-26, 32, 40, 45, 53, 66)	TAHS[3]	✓	Early below average, accelerated FEV_1 decline	7 to 53
	CRS[18]	✓	Persistently low FEV_1 trajectory	11 to 32
	CARDIA[21]	✓	Persistently poor lung health FEV_1 trajectory	25 to 55
	DCS[25]	✓	Accelerated decline" FEV_1 trajectory	26 to 66
Adult environment characteristics				
Personal cigarette smoking (16, 20, 25,26, 43, 53, 60-64)	CARDIA[21]	✓	Persistently poor lung health FEV_1 trajectory	25 to 55
	TAHS[3]	✓	"Below average"; "persistently low" and "early below average accelerated decline" FEV_1 trajectory	7 to 53
	DCS[25]	✓	Accelerated decline" FEV_1 trajectory	26 to 66
	CRS[18]	✗	..	11 to 32
Interactions between exposures				
Parental smoking and personal smoking	TAHS[3]	✓	Early below average, accelerated FEV_1 decline	7 to 53
Childhood asthma and adult active asthma	TAHS[3]	✓	Early below average, accelerated FEV_1 decline	7 to 53

IOW: Isle of Wight Birth Cohort, ALSPAC: The Avon Longitudinal Study of Parents and Children, MAAS19: Manchester Asthma and Allergy Study, PIAF: Australian Perth Infant Asthma, CRS: Tucson Children's Respiratory Study, CARDIA: Coronary Artery Risk Development in Young Adults, TAHS: Tasmanian Longitudinal Health Study, DCS: The Doetinchem Cohort Study, LRTI'S: Lower respiratory tract infections, bronchitis, bronchiolitis, pneumonia, recurrent chest infection, Allergic phenotypes: eczema, allergic rhinitis, allergy diagnosis, DNA-M: DNA methylation of cytosine–phosphate guanine (CpG) sites, SHS: Secondhand smoke exposure

✓= Studies with evidence of adverse association

✗ = studies reported no evidence of adverse association

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Figure Legends

Figure 1: Prisma flow chart for inclusion and exclusion of publications for the review

Figure 2: Timepoint measurement of lung function among studies
*: Three publications used this cohort study (Karmaus, 2019, Sunny, 2021 and Mukherjee, 2021,
‡: Two publication used this cohort study (Belgrave,2018 and Sunny, 2021)

Figure 3: The Predictors of subnormal trajectories observed among studies

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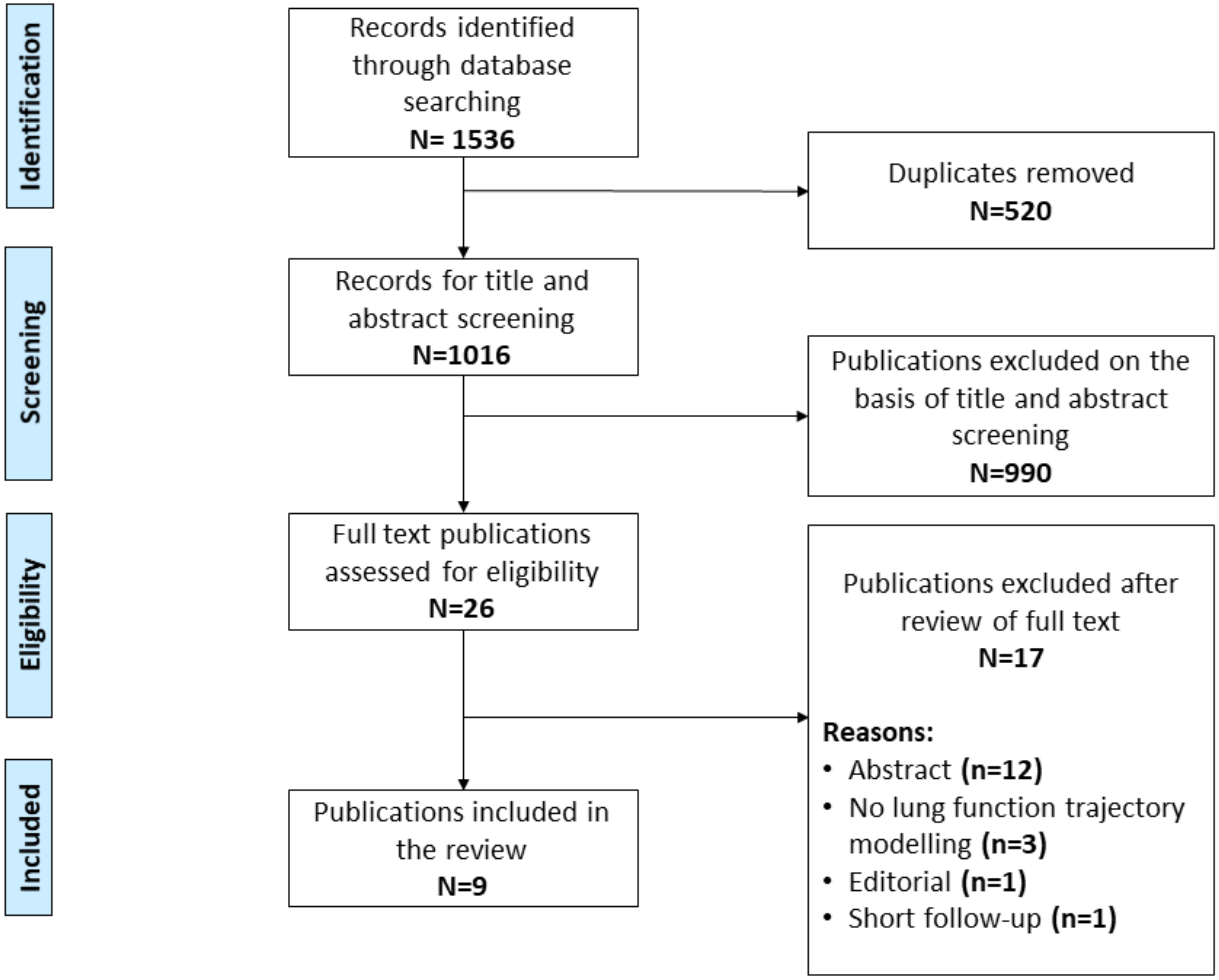

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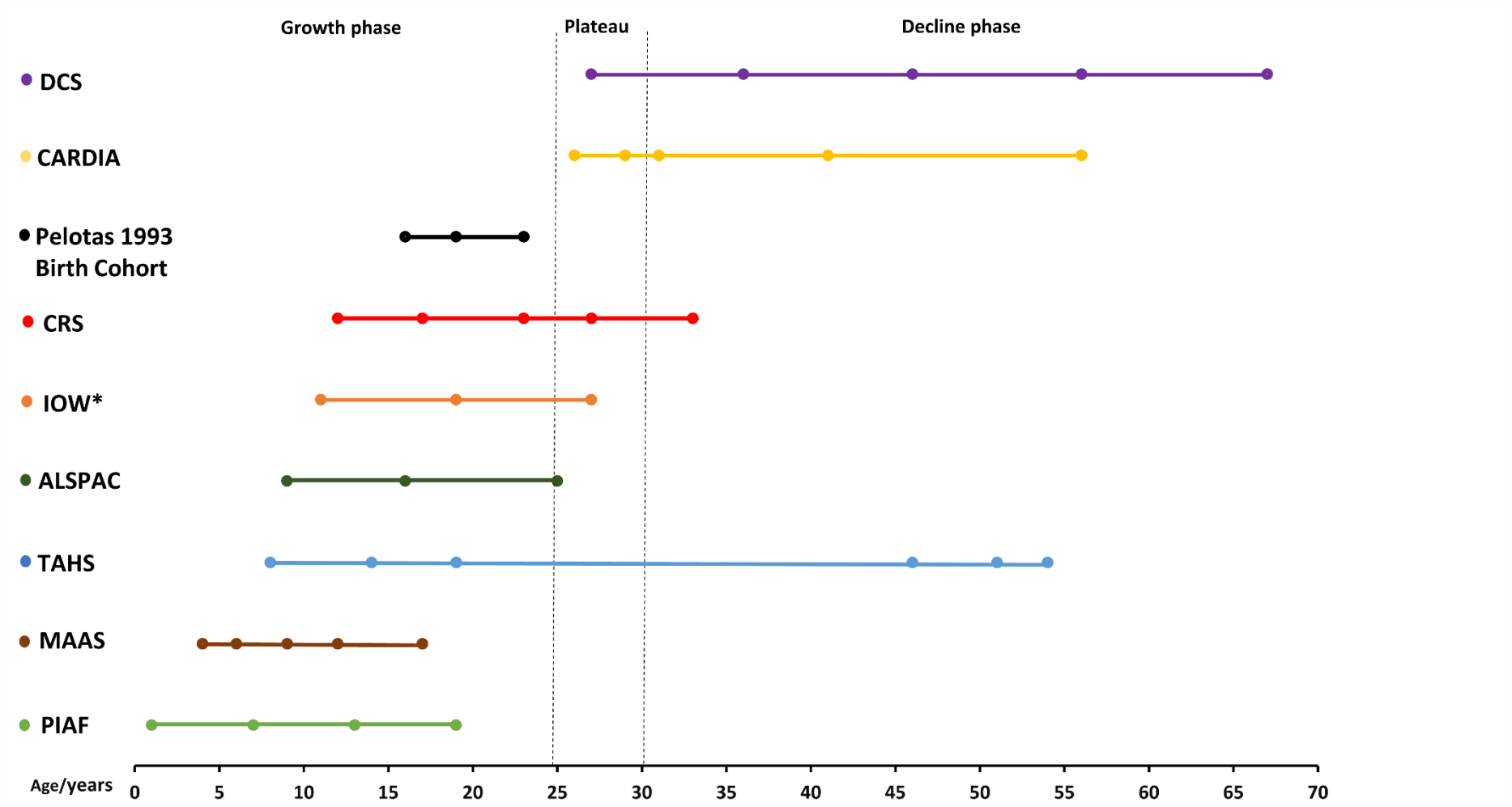

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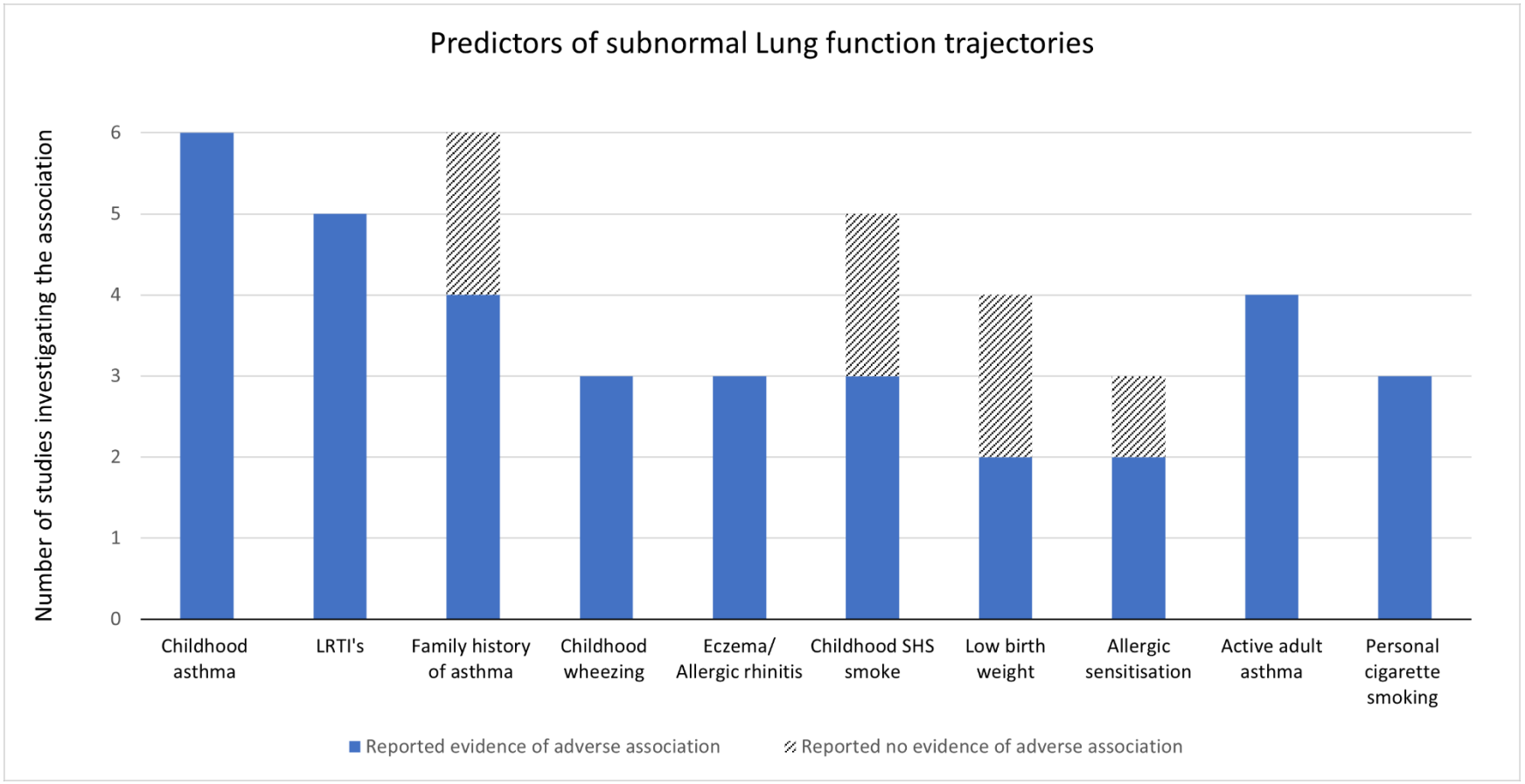

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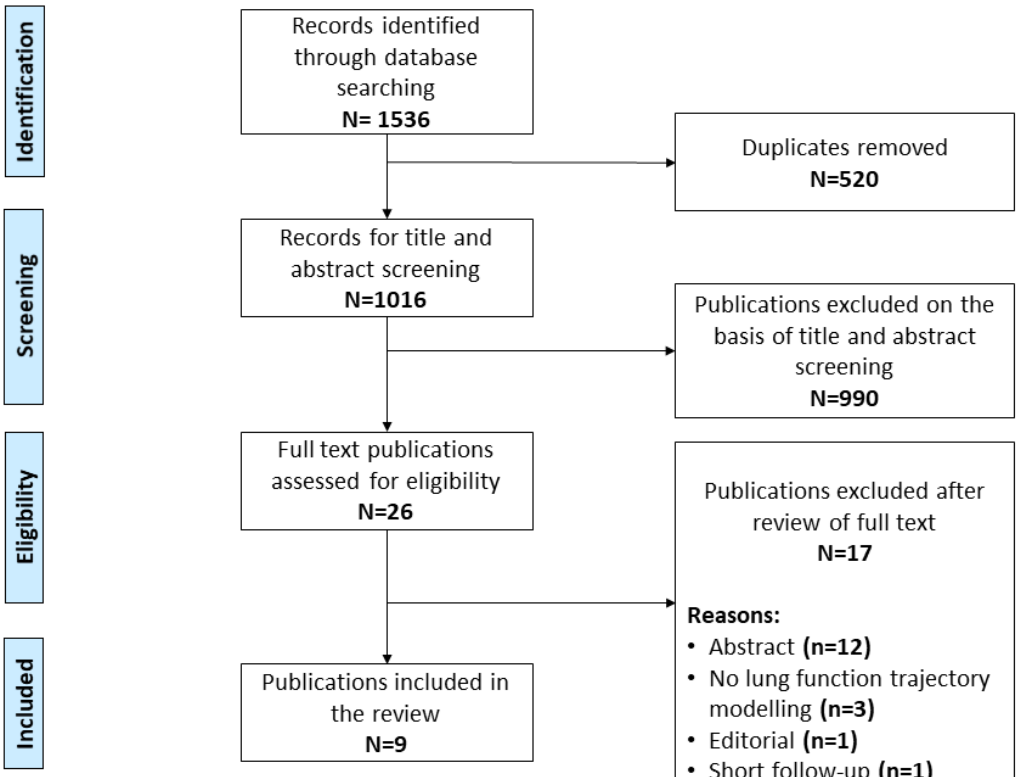

RESP_14142_Figure 1 Prisma flow chart.tif

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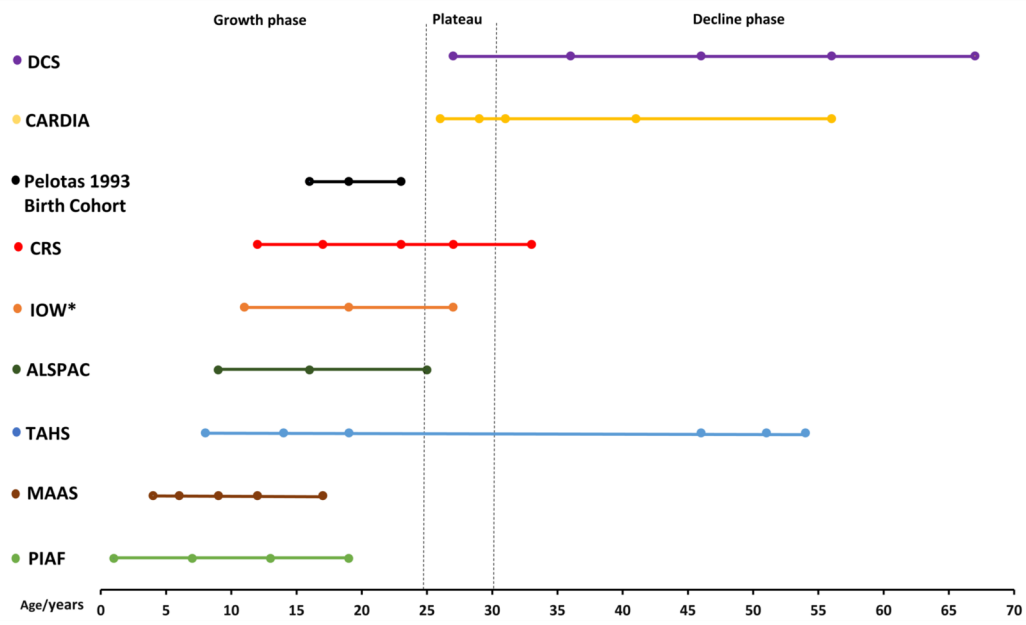

RESP_14142_Figure 2.tiff

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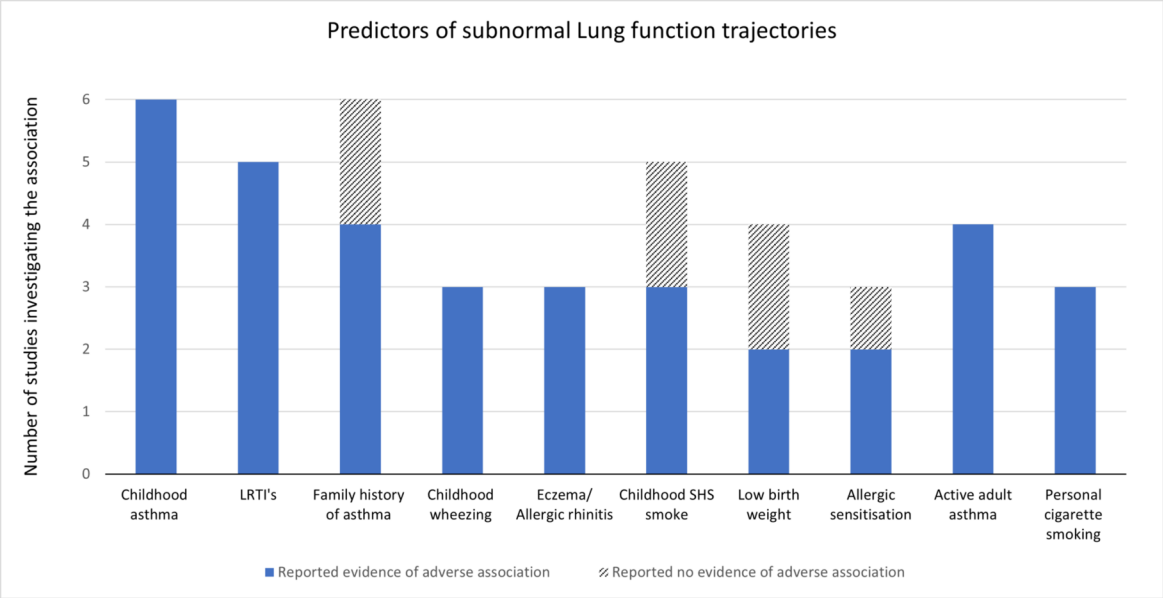

RESP_14142_Figure 3.tif