Supplement file

S1

Methodology

The entire author group initially discussed the approach. An overall framework developed by AC, SD and KG was circulated pre-discussion and modified post-discussion. We deliberately focused on the impact of important early life adverse exposures such as born preterm, specific diseases (asthma, chronic obstructive pulmonary disease [COPD], bronchiectasis) and undifferentiated respiratory symptoms across the lifespan, but excluded monogenic diseases (e.g. cystic fibrosis). While COPD is not strictly a childhood disease, we elected to include data from childhood that relates to adult COPD given the global importance of COPD and as a substantial proportion has its origins in childhood.

We did not consider generic adverse environmental (e.g. air pollution and tobacco smoke/vaping exposure) and other factors (e.g. nutrition, obesity, prenatal and social determinants) within the scope of our review as they are described in detail elsewhere (see references in main manuscript). However, given their importance, these factors are included in Panel-2 and strategies for optimising respiratory health.

Also, our review does not include (i) the known/unknown underlying pathophysiology or pathobiology of the conditions (ii) the importance of mechanisms such as persistent eosinophilic or neutrophilic airway inflammation, or (iii) current knowledge on 'omics' including the gut-lung microbiome axis. However, as these are important areas of research, they are included in our list of "Questions for future research to address important knowledge gaps linking lung growth and development with future pulmonary and non-pulmonary disease" (Panel-2).

We undertook PubMed searches using the strategy for the relevant topics as described below. Each of the topics were led by a different author: WB led the BPD and preterm birth section, SS the COPD, SD the asthma, RI the undifferentiated section for adults, and AC the bronchiectasis and paediatric cough sections. Based on the results, we formulated a list of potential interventions to assist policymakers and healthcare workers develop strategies for optimising respiratory health spanning the whole-life course (Panel-1 and Figure-3 in manuscript). Following that, we identified a series of research needs and questions (Panel-2) to help address important knowledge gaps. This section was led by KG and DG who then presented the panels and text for all authors to review. RF oversaw that the approach was suitable for general practitioners and primary care, ZP oversaw the consumer/patient aspects and EB ensured the sections for lower-middle income countries were relevant for Central/South America. All authors had input and fully agreed on the suggestions/recommendations in the panels and accompanying text.

Search strategies

PubMed searches for articles published in English from inception until January, 2025 were undertaken using the search strategies below. Papers were selected by the lead authors of each section based on their relevance to the review. Further articles were identified from the authors' own collections and from references cited in the selected articles. The final reference list was generated based on relevance to the scope of this review.

<u>Bronchopulmonary dysplasia/chronic neonatal lung disease and preterm infants</u>
"Preterm OR bronchopulmonary dysplasia" AND "lung OR respiratory OR outcomes."
Last search date 1 Jan 2025.

<u>Asthma</u>
"Asthma" AND "Child" AND "Longitudinal OR Cohort studies" AND "Adult Asthma."

("group based trajectory" OR "latent class analysis") AND ("wheeze" OR "wheezing" OR "asthma").
Last search date 14 Jan 2025.

Chronic obstructive pulmonary disease (COPD)
"Asthma" AND "Child" AND "Longitudinal OR Cohort studies" AND "Pulmonary disease, chronic obstructive."
"Lung function test" AND "Longitudinal studies" AND "Child" AND "Pulmonary disease, chronic obstructive."
Last search date 30 Dec 2024.

Bronchiectasis
"bronchiectasis and children and outcomes";
"adult bronchiectasis from child"
"bronchiectasis and long term and children."
Last search date 1 Jan 2025

Undifferentiated chronic wet cough (children)
"cough and trajectory and children";
"chronic cough and children and outcomes."
Last search date 1 Jan 2025.

Undifferentiated chronic wet cough (adults)
"cough OR lung function decline" AND cardiovascular diseases AND "longitudinal studies OR prospective studies" NOT COVID-19.
Additional Limits: adult, young adult, preschool child, child, adolescent.
Last search date 20th Dec 2024.

Additional limits for inclusion of studies into Supplementary file-S2
For children we included studies where follow-up data extends to adolescents (aged ≥12-years).
When a systematic review had been performed and an individual study included in the systematic review, we did not describe this study in the Table in Supplementary file-S2, unless additional information was provided by the original paper.

Definitions relating to bronchopulmonary dysplasia (BPD)/preterm birth section

- BPD: Usually defined as "oxygen or ventilator dependency at 36 weeks postmenstrual age".[1], We used definitions as defined by authors in respective papers.
- Extreme low birth weight (ELBW): Birth weight <1000g [2]
- Extreme preterm: Birth <28-weeks gestational age [2]
- Low birth weight (LBW): Birth weight <2500g [2]
- Moderate to late preterm: Birth 32 to <37-weeks gestation age [3]
- Normal birth weight: Birth weight 2500g or more [4]
- Preterm: Birth before 37-weeks gestation
- Term: Birth at or after 37-weeks gestation

- Very low birth weight (VLBW): Birth weight <1501g [4]
- Very preterm: Birth before 32-weeks gestation [4]

S2

Table: Disease-specific studies describing the relationship between child and adult lung function and respiratory health and other health outcomes[*†]

First author, year, country	Study type; Inclusion and exclusion criteria	Sampling demographics	Aim of study	Main findings specific to question of this review	Solutions proposed by authors of the paper (if any)	Comments
PRETERM INFANTS AND BRONCHOPULMONARY DYSPLASIA						
Bui [5], 2022, Australia^	Population-based longitudinal cohort of children born in 1961 and attending school in Tasmania in 1968 (N=8583 recruited).	N=1445 (41% of cohort), 51% females. Lung function at 53y. Very preterm (28-<32wk) + moderate preterm (32-<34wk) combined n=46, late preterm (34-<37wk) n=172, term (≥37wk) n=1227.	Investigate associations b/w prematurity, lung function and COPD in the 6th decade of life	Very-to-moderate preterm birth had lower post-bronchodilator FEV_1/FVC ratio (β coefficient -2.9%, [95%CI -4·9, -0·81]), FEV_1 (-190 mL [-339, -40]), DLCO (-0·55 mmol/min/kPa [-0·97, -0·13]), and $FEF_{25-75\%}$ (-339 mL/s [-664, -14]), vs terms. Association b/w very-to-moderate preterm birth and FEV_1/FVC ratio was only significant among smokers ($p_{interaction}$ 0·0082). Compared with term birth, late preterm birth was not associated with lower FEV_1/FVC or COPD, but very to moderate preterm birth significantly associated with an increased COPD risk (OR_{adj} 2.9, 95%CI 1.1, 7.7). Very-to-moderate preterms (vs term) had more rapid decline in FEV_1/FVC b/w ages 45 and 53y but only in current smokers.	Preterm survivors should be specifically educated that their lungs are more likely to be affected by smoking through targeted health education	
Carrega [6], 2023, Portugal	Systematic review. Inc: studies assessing the outcomes of adolescents aged 10-19y with BPD. Exc: review articles and other secondary studies	Studies assessing outcomes in preterm-born adolescents with BPD, born b/w 1978 and 2005. Controls were adolescents born preterm without BPD or adolescents born at term. 31 studies included: 25 cohort, 4 cross section, one case-control, 1 RCT.	Assess the impact of BPD on respiratory and non-respiratory outcomes in adolescents	BPD-adolescents had higher recurrent wheeze (22–28%) vs non-BPD (0–12%), respiratory morbidity (cough or exercise associated symptoms) in the previous 2y (70% vs 44%), use of respiratory medications (17–50%) vs controls (2–11%). Differences in rate of current diagnosis of asthma was inconsistent (4 found no difference, 1 found higher asthma prevalence in BPD (25%) vs non-BDP preterm group (13%). Of 9 studies that examined BDR, 8 showed either BDR or methacholine response, which was higher in BPD group vs non-BPD. 25 studies examined lung function-all showed reduction in 1 or more spirometry variables in BPD-adolescents	Need for further investigations and FU of these patients	A history of BPD negatively impacts pulmonary outcomes in adolescents.

				compared to controls (non-BPD or term). Severe BPD was associated with worse spirometry results. Lung function trajectory: 5 reported worsening of spirometry variables, 1 reported no difference and 1 reported improvement. 2 studies compared older to newer cohorts: lower z-FVC (z-FVC difference: -1.01) and higher z-FEV_1/FVC (z-FEV_1/FVC difference: 1.02) in moderate-severe BPD group. Radiographic abnormalities common (87.5%); linear (72.2 %) and subpleural opacities (58.3 %) were commonest findings, but no significant differences b/w BPD vs non-BPD.		
Doyle [7], 2019, Australia	Prosp cohort study. Inc: children born ELBW (birth weight <1,000 g) or EP (gestation <28wk). Controls: Children with birth weight ≥2500g, randomly selected from births on the date that a preterm survivor was due to be born. Exc: no respiratory function data.	Participants born in 1991-1992 in Victoria (Australia) in surfactant era. Survival rates to 18y were 56%, (n=297 survivors). Cohort's expiratory airflows reassessed at aged 25y. Preterm group n=164 (55% of above cohort). Controls n=130 (50%). Trajectories (change in z-scores per year) from childhood compared b/w groups.	(1) Compare expiratory airflow when cohort above[2], were aged 25y; (2) Within the preterm group, compare those with BDP to those without.	Preterm group had substantially reduced airflow compared with controls at age 25y: mean differences in z-score (95%CI) for FEV_1 -0.97 (-1.23, -0.71); FVC -0.33 (-0.56, -0.10); FEV_1/FVC -0.96 (-1.23, -0.69), $FEF_{25-75\%}$ -1.20 (-1.47, -0.93). Preterm participants had lower airflow trajectories than controls b/w 8 and 18y: mean differences in trajectories of airflow zFEV_1/FVC 8y -0.03 (-0.059, -0.001), z$FEF_{25-75\%}$ -0.025 (-0.046, -0.005), but not b/w 18 and 25y: mean differences in trajectories for zFEV_1/FVC 0.009 (-0.015, 0.032), $FEF_{25-75\%}$ 0.015 (−0.005, 0.036). Within the preterm group, BPD group had substantially lower values for all spirometry values, except for FVC vs non-BPD group; mean differences b/w groups: zFEV_1 -0.66 (-0.99, -0.33); zFVC -0.26 (-0.59, 0.06); zFEV_1/FVC -0.55 (-0.92, -0.19); z$FEF_{25-75\%}$ -0.67 (-1.05, -0.28). BPD also had lower airflow trajectories b/w 8 and 18y (vs non-BPD group); mean differences b/w groups: zFEV_1/FVC 8y -0.057 (-0.092, -0.021), z$FEF_{25-75\%}$ -0.043 (-0.068, -0.018), but not b/w 18 and 25y; mean differences b/w groups: zFEV_1/FVC 0.012 (-0.015, 0.04), z$FEF_{25-75\%}$ 0.016 (−0.008, 0.04).		Young adults born ELBW/EP in the surfactant era, particularly those who had BPD, have substantially reduced airway function compared with controls. Some may develop COPD in later adult life.
Doyle [4], 2019, Global	Meta-analysis of individual participant data.	Cohort studies were mostly in the pre-surfactant era. 11 studies	Compare expiratory airflow	VP/VLBW lung function values were significantly lower than controls (whose z-scores group were close to zero); mean difference b/w		Individuals born VP or with VLBW are at

	Inc: studies on expiratory flow rates beyond ages 16y of individuals born VP (gestation <32wks) or with VLBW (≤1500 g), and controls born at term or with normal BW (≥2500g). Exc: highly selected cohorts (eg. only BPD) or few children born VP or VLBW	comprising a total of 935 participants born VP/VLBW and 722 controls. Mean age at testing was 21y (range 16-33).	(FEV_1, FVC, $FEF_{25-75\%}$, FEV_1/FVC) in individuals born VP or with VLBW during late adolescence and early adulthood with controls.	groups: $zFEV_1$ -0.78 (95%CI -0.96, -0.61), zFVC -0.25 (-0.40, -0.10), $zFEV_1$/FVC -0.74 (-0.85, -0.64), and $zFEF_{25-75\%}$ -0.88 (-1.12, -0.65). The proportions of individuals with values below the 5th percentile in the VP/VLBW group were significantly higher than the control group for FEV_1 (24% vs 7%), FVC (11% vs 6%), FEV_1/FVC (23% vs 6%), $FEF_{25-75\%}$ (29% vs 8%). Analyses restricted to those who had spirometry at least twice (aged 18 and 25y) - rate of airflow change b/w groups were significantly lower in VP/VLBW group for FVC but not for other indices (adjusted mean change b/w groups -0.32 (-0.52, -0.11).		risk of not reaching their full lung growth potential in adolescence and early adulthood, suggesting an increased risk of COPD in later adulthood.
Gibbons [8], 2023, Global	Meta-analysis. Inc: studies reporting FEV_1/FVC in (1) survivors of preterm birth (gestation <37wk) and controls born healthy at term, or (2) survivors of preterm birth with and without BPD. Exc: not reported.	55 cohorts were eligible. The mean age of the survivors in each cohort was b/w 5-30y. Each group extracted was assigned one of the following statuses: 1) preterm with BPD, 2) preterm without BPD, 3) preterm with mix of participants (both with and without BPD) or BPD status not specified, or 4) term.	Determine if (1) survivors of preterm birth have increased airway obstruction compared to those born at term, and (2) preterm birth or BPD are risk factors for developing COPD	Compared to control populations born at term, survivors of preterm birth had lower values of spirometry variables (FEV_1, FVC, FEV_1/FVC and $FEF_{25-75\%}$) and those with BPD showed greater differences. Lower $zFEV_1$/FVC were seen in all individuals born preterm: overall mean difference -0.56 (95%CI -0.68, -045), preterm with BPD -0.87 (-1.02, -0.71), preterm without BPD -0.45 (-0.62, -0.59). Lower gestation was associated with a greater lung function deficit. Meta-regression identified age as a significant predictor of FEV_1/FVC in those with BPD that FEV_1/FVC moved -0.04 SD away from the term controls for every year of increased age (r^2=0.488). Over a 25y period, this amounts to the FEV_1/FVC ratio being 1 SD below those born healthy at term.	Need for lifelong health trajectories to identify those where intervention can be possible.	Increased airway obstruction is significant in survivors of preterm birth, with those diagnosed with BPD as infants having worse airway obstruction.
Gough [9], 2012, United Kingdom	Systematic review. Inc: studies assessing outcomes of adult survivors of BPD (age >18y). Exc: studies without information on outcomes for adult BPD survivors, review articles,	14 cohort studies; 8 high quality, 5 moderate quality, one low quality. In total, 5 studies did not include a control group, 7 used unmatched full-term control subjects, 2 used either matched normal control subjects and/or matched preterm	Examine empirical research on general and respiratory health outcomes in adult survivors of BPD	Most studies reported that compared to their peers, adult survivors of BPD had more respiratory symptoms and pulmonary function abnormalities ([significantly reduced FEV_1, FVC, PEF, and $FEF_{25-75\%}$ predicted). 6 studies reported conflicting findings on DLCO, however the number of adult survivors of BPD were small. Five studies reported radiographic structural changes persisting into adulthood, including parenchymal opacities, hypoattenuated areas and	Need a multi-disciplinary research approach for these patients	Need for multi-disciplinary approach that encompasses measurement of all aspects of health, including psychological, physical and social

	commentaries, case studies, & editorials.	survivors without BPD.		bronchial wall thickening.		functioning.
Lundberg [3], 2024, Sweden	Swedish birth cohort called BAMSE. Inc: Born in predefined areas of Stockholm b/w 1994-1996 and had valid lung function at 24y FU. Exc: Poor Swedish language comprehension, plan to move within the coming year, sibling already included or have severe disease.	Original cohort n=4089. At ages 16 and 24y, individuals invited for FU visits including lung function measurements. Current cohort: Term-born n=1885, moderate-to-late preterm (32-36 wk gestation) born n=110.	Investigate (1) lung function from adolescence into young adults, & (2) phenotypes in individuals born moderate-to-late preterm.	Compared to males born term. $zFEV_1$ at aged 24y was lower in males born moderate-to-late preterm (-0.28, p=0.045). No difference between females born term or preterm, partly explained by a significant catch up in $zFEV_1$ b/w 16 and 24y (0.18, p=0.01). No difference b/w groups for LCI or proportion with FeNO >25 parts per billion. Using latent class analysis, lung function phenotypes were "asthma-like", "dysanapsis-like" and "preterm reference" were identified within the preterm group. Maternal overweight in early pregnancy associated with "asthma-like" group (OR 3.59, p=0.02).		
Smith [10], 2023, Australia	Prosp cohort. Inc: VP (≤32 wk gestation with or without BPD). Controls (≥37 wk gestation) and recruited at earlier cohort FU. Exc for controls: history of cardiopulmonary disease or recurrent respiratory symptoms.	Adolescents and young adults from the pre-existing Western Australian lung health prematurity cohort born b/w 1997-2003 (age 16–23y): n=127 ≤32 wk gestation (64%, n=81 with BPD). Controls n=41 term-born controls assessed at mean age of 19.31y (SD 1.39).	Obtain 'peak' lung health data from survivors of VP birth and identify neonatal and life-course risk factors for poorer respiratory outcomes in adulthood.	In the 3 mo prior, the VP with and without BPD had higher proportions than the term for using asthma medication (16.5% vs 0%), wheezing during exercise (18.1% vs 4.9%) shortness of breath (29.1% vs 12.2%); and the VP with BPD had higher proportions than the VP without BPD for cough (58% vs 37%) and rattling breathing (23.5% vs 4.3%). Airflow obstruction was evidenced by reduced FEV_1, FEV_1/FVC, $FEF_{25-75\%}$ in adults born VP, with increased severity in those with BPD. Baseline spirometry variable z-score <−1.64 of the term vs VP without BPD vs the VP with BPD: FEV_1 5% vs 14% vs 30.8%, FEV_1/FVC 10.5% vs 31% vs 41.7%, BDR response 7.7% vs 16.7% vs 31.2%. Decreased DLCO; increased RV, RV/TLC and LCI; and poorer peripheral lung mechanics on oscillometry were detected in the preterm compared with the term, and worst in those with BPD. Structural abnormalities were present in 88% of those born ≤32 wks gestation, increasing to 92% in the BPD group. In those born VP, spirometry outcomes were reduced in those with a previous respiratory	Need for monitoring of these patients and anticipatory guidance on smoking, vaping and employment.	As the number of survivors of VP birth continues to grow, identifying those most at risk is key evidence needed to generate clinical guidelines for the management.

				admission. Mean FEV_1/FVC was –0.61 z-score in those born VP with a respiratory admission (95%CI 0.21, 1.02) and this difference was greatest in those with BPD (−0.74 z-score, (−0.24, –1.24). Atopy, maternal asthma and tobacco smoke exposure did not influence lung function or structure.		
Von Boven [11], 2024, Netherlands with studies worldwide	Meta-analysis. Inc: studies comparing FEV_1 preterm-born children aged ⩾5y to term-born controls or normative data. Exc: not reported.	42 studies with unique cohorts (4743 preterm children and 9843 controls). Median gestational age in the studies was 28.0 wks Age at assessment ranged 6.7-16.7y.	Quantify lung function in preterm-born children and identify risk factors for abnormal lung function.	Preterm-born children had lower $zFEV_1$ than controls (-0.58, 95%CI -0.69 to -0.47, p<0.001), RR 2.9 (95%CI 2.4, 3.4) of abnormal outcome. Difference b/w groups for zFVC was -0.34 (-0.42, -0.23); FEV_1/FVC -0.48, (-0.6, -0.36); $FEF_{25-75\%}$, -0.73 (-0.9, -0.56) FEV_1 significantly associated with gestational age, birth weight, BPD, and invasive mechanical ventilation in univariate meta-regression analyses.	Implement a structural pulmonary FU for children at highest risk of pulmonary impairment adult life. Need for new preventive or therapeutic interventions.	Uncertain why multivariate meta-regression was not used. Even with the use of surfactant and antenatal corticosteroids, preterm-born children have impaired long-term pulmonary outcomes.
Yang [12], 2020, New Zealand	Prosp cohort study. Inc: survivors of a VLBW cohort and term-born adults. Exc: invalid data.	Of 413 VLBW infants in the cohort in 1986, 250 cohort members, aged 26-30y participated in a FU study during 2013-2016. 229 VLBW adults and 100 term controls undertook lung function tests including spirometry, plethysmographic lung volumes, DLCO, and single breath N_2. washout.	(1) Compare lung function data in a New Zealand VLBW national cohort with term-born controls. (2) Within the VLBW group, compare those with/without a diagnosis of BPD.	The only significant inter-group difference in respiratory symptoms was wheeze in the past 12 mo (VLBW 34.8% vs. controls 23%). An obstructive spirometry pattern was identified in 35% VLBW vs 14% controls. VLBW survivors (vs controls) had significantly lower expiratory flows; mean difference b/w groups: $zFEV_1$ -0.54 (95%CI -0.83, -0.26), $zFEV_1$/FVC -0.56 (-0.82, -0.30), $zFEF_{25-75\%}$ -0.77(-1.07, -0.47) and higher zRV 0.42 (0.20, 0.65), zRV/TLC 0.46 (0.23, 0.68), decreased zDLCO -0.61 (-0.83, -0.38). All differences persisted when adjusted for sex and smoking. Within the VLBW group, those with BPD showed significant reduction in all lung function, except DLCO (vs those without): mean difference zFEV1 -0.85 (-1.23, -0.47), $zFEV_1$/FVC -0.58 (-0.94, -0.22), $zFEF_{25-75\%}$ -0.77 (-1.17, -0.36), zRV 0.59 (0.29, 0.90), zRV/TLC 0.68 (0.37, 0.99), zDLCO -0.33 (-0.66, -0.01). The differences persisted after adjustment for sex,	Importance of avoiding factors that may accelerate lung function decline. Need routine lung function testing and on-going monitoring.	Adult VLBW survivors showed a higher incidence of impaired pulmonary function. The findings suggest pulmonary effects due to VLBW persist into adulthood, and BPD is a further insult.

				smoking, birth weight (<1000 or ≥1000g), gestation (<28, ≥28wk), intrauterine growth restriction, maternal smoking in pregnancy.		
ASTHMA						
Bui [13], 2021 Australia^	Prosp Tasmanian Longitudinal Health Study over 46y of a birth cohort initially studied at the age of 7y.	Included 3609 who participated in 7 follow-up reviews since age 7y.	Characterise asthma/allergy trajectories and examine their associations with lung function outcomes and profiles of comorbidities.	Identified 5 asthma and allergy trajectories: minimal and least asthma and allergies (n= 1767 [49·0%]); late-onset hay fever, no asthma (n=1065 [29·5%]); early-onset remitted asthma and allergies (n=236 [6·5%]); late-onset asthma and allergies (n=317 [8·8%]); and early-onset persistent asthma and allergies (n=224 [6·2%]); and 4 profiles of extrapulmonary morbidities: minimal or least disease (n=2206 [61·1%]); dominant mental health disorders (n=861 [23·9%]); dominant CVDs or risks (n=424 [11·7%]); and multiple disorders (n=117 [3·2%]). The late-onset asthma and allergies trajectory was predominantly associated with the multiple disorders profile (relative risk ratio 3·3 [95%CI 1·9, 5·9]), whereas the other asthma and allergy trajectories were associated only with the dominant mental health disorders profile. Both spirometrically defined and clinical COPD were most strongly associated with the early-onset persistent asthma and allergies trajectory (OR 5·3 [3·2, 8·6]) and also with the late-onset asthma and allergies trajectory (OR 3·8 [2·4, 6·1]).	Distinct longitudinal trajectories of asthma and allergic disease from childhood to 53y are associated with different profiles of extrapulmonary comorbidities and varying risk of COPD.	These findings can inform a personalised approach in clinical guidelines and management focusing on treatable traits. Comorbidity profiles are a new target for early identification and intervention.
Burgess [14], 2011, Australia^	Prosp Tasmanian Longitudinal Health Study over 38y of a birth cohort initially studied at the age of 7y.	Of 5729 respondents to the age 45y survey, a study sample of 1811 who had either self-reported or parent reported asthma were studied.	Examine asthma remission from childhood to middle age.	Asthma had remitted in 1177 (65.0%) of whom 649 (55.1%) were male. Childhood (OR 0.38, [95%CI 0.25, 0.58]) and later-onset allergic rhinitis (0.42, [0.29, 0.63]), childhood (0.66, [0.47, 0.94]) and later-onset eczema (0.66, [0.47, 0.92]), maternal asthma (0.66, [0.47, 0.92]) and childhood chronic bronchitis (0.56, [0.41, 0.76]) were negatively associated with remission. There was weaker evidence for a negative association between passive smoking (0.75, [0.54, 1.04]) and lower socio-economic status (p-trend 0.09) and	While inherited factors cannot be changed, the effect of allergic rhinitis or eczema on asthma remission might be altered by	Childhood allergies, childhood chronic bronchitis and passive smoke exposure increase the risk of persistence of childhood asthma into

				remission. Childhood-onset asthma (3.76, [2.58, 5.49]) was more likely to remit than adult-onset asthma.	early, aggressive treatment. Need to lessen passive exposure to tobacco smoke.	middle-age
Guerra [15], 2020, US	Prosp Tucson Children's Respiratory Health Study over 26y of a birth cohort initially studied at birth	Of the 1246 infants enrolled at birth, 376 infants had infant pulmonary function testing. Of them 180 had at least one index for lung function in the first 6 mo. Active asthma was assessed in up to 12 questionnaires between ages 6 and 36y. Spirometry and chest HRCT imaging were completed in a subset of participants at age 26y.	To examine the individual and combined effects of time to reach tptef/te and $\dot{V}$maxFRC in infancy on risk for asthma and abnormalities of airway structure into mid-adult life.	After adjustment for covariates, a 1-SD decrease in infant tptef/te and $\dot{V}$maxFRC was associated with a 70% ($P = 0.001$) and 55% ($P = 0.005$) increased risk of active asthma, respectively. These effects were partly independent, and 2 out of 3 infants who were in the lowest tertile for both tptef/te and $\dot{V}$maxFRC developed active asthma by mid-adult life. Infant $\dot{V}$maxFRC predicted reduced airflow and infant tptef/te reduced HRCT airway calibre at age 26y.	Findings underscore the long-lasting effects of the foetal origins of asthma, support independent contributions by infant tptef/te and $\dot{V}$maxFRC to development of asthma, and link deficits at birth in tptef/te with HRCT-assessed structural airway abnormalities in adult life.	Findings highlight the importance of considering infant lung function in the context of assessing the impact childhood respiratory illnesses on adult health.
Haider [16], 2022, United Kingdom	Pooled data from multiple cohorts and extending the time frame across childhood.	Included 7,719 participants from 5 birth cohorts with complete report of wheeze at 5 time periods.	Derive multi-dimensional variables of wheezing spells from birth to adolescence (including duration,	Identified 5spell-based wheeze phenotypes with a high degree of certainty: never (54.1%), early-transient (ETW) (23.7%), late-onset (LOW) (6.9%), persistent (PEW) (8.3%), and a novel phenotype, intermittent wheeze (INT) (6.9%). FEV_1/FVC was lower in PEW and INT compared with ETW and LOW and declined from age 8y to adulthood in INT. 17q12-21 and CDHR3 polymorphisms were associated with higher odds	Identified a novel intermittent wheeze phenotype associated with lung function decline to	Using multidimensiona l spell variables may better capture wheeze development and provide a more robust input for

			temporal sequencing, and the extent of persistence/recurrence).	of PEW and INT, but not ETW or LOW. Latent class analysis and spell-based phenotypes appeared similar, but within-phenotype individual trajectories and phenotype allocation differed substantially. The spell-based approach was much more robust in dealing with missing data, and the derived clusters were more stable and internally homogeneous.	early adulthood.	phenotype derivation.
Horak [17], 2003Australia	Prosp cohort study	In 1964, random selection of 7y old metropolitan Melbourne children. n=401 (asthma=295, controls=106) from total of 30,000, plus further 83 children with severe asthma from the same cohort in 1967, at age 10y	Describe outcome of children with asthma at age 42y	"Pattern of asthma during childhood predicts outcome. Most children with persistent asthma had continuing symptoms into adult life and reduced lung function. Children who had intermittent symptoms associated with respiratory tract infections generally had complete resolution of symptoms in adult life"	Importance of childhood asthma on future asthma trajectory as adults	
Jenkins [18], 1994, Australia^	Prosp Tasmanian Longitudinal Health Study over 25y of a birth cohort initially studied at aged 7y.	1494 men and women surveyed in 1991-3 when aged 29 to 32y (75% of a random stratified sample from the 1968 Tasmanian asthma survey of children born in 1961 and at school in Tasmania).	Determine which factors measured in childhood predict asthma in adult life.	Of the subjects with asthma or wheezy breathing by the age of 7y, as reported by their parents 25.6% (190/741) reported current asthma as an adult compared with 10.8% (81/753) of subjects without parent reported childhood asthma ($p<0.001$). Factors measured at the age of 7y that independently predicted current asthma as an adult were being female (OR 1.57 [95%CI 1.19, 2.08]); having a history of eczema (1.45 [1.04, 2.03]); having a low $FEF_{25\%–75\%}$ (OR 1.40 [1.15, 1.71]); having a mother or father with a history of asthma (1.74 [1.23, 2.47] and 1.68 [1.18, 2.38]), respectively); and having childhood asthma (1.59 [1.10, 2.29]) and, if so, having the first attack after the age of 2y (1.66 [1.17, 2.36]) or having had >10 attacks (1.70 [1.17, 2.48]).	Reducing the severity of childhood asthma, especially if it is developed after the age of 2y and is associated with poor lung function, is important to reduce the persistence of asthma into adulthood.	Severity of childhood asthma facilitates persistence into adulthood.
Odling [19], 2021, Sweden	Prosp cohort study (BAMSE) followed up over 22y.	Included 4089 participants who provided information at 8 time points	Identify and characterise trajectories of asthma from infancy	A 4-class solution of asthma trajectories was identified: never/infrequent (n=3291 [80.4%]), early-onset transient (n=307 [7.5%]), adolescent-onset (n=261 [6.4%]), and persistent asthma (n=230 [5.6%]). Uncontrolled asthma was equally	Adolescent-onset and persistent asthma trajectory	This unbiased approach highlights the need of identifying

			to young adulthood, and their associations with lung function and inflammatory and respiratory markers in adolescence and young adulthood.	prevalent in the adolescent-onset and persistent asthma trajectory groups, at both age 16 (41.7% vs 42.4%; p=0.90) and 24y (53.7% vs 52.4%; p=0.81). The persistent asthma trajectory group had a higher proportion of eosinophil counts $\geq$0.3 x 10^9 cells/L at age 24y compared with the adolescent-onset trajectory group (31.0% vs 18.5%; p<0.01).	groups had equal burdens of asthma control in adolescence-young adulthood. Persistent asthma trajectory group showed more signs of T2 inflammation than the adolescent-onset trajectory group.	patients with adolescent asthma to optimise care, because they suffer the same lack of asthma control as those with persistent asthma.
Oskel [20], 2019, United Kingdom	Pooling data from multiple cohorts and extending the time frame across childhood	Included 7,719 participants from 5 birth cohorts with complete report of wheeze at 5-time periods.	Analyse wheezing patterns from early childhood to adolescence using combined data from 5birth cohorts.	Identified 5 phenotypes: never/infrequent wheeze (52.1%), early onset preschool remitting (23.9%), early onset mid childhood remitting (9%), persistent (7.9%), and late-onset wheeze (7.1%). Compared with the never/infrequent wheeze, all phenotypes had higher odds of asthma and lower FEV_1 and FEV_1/FVC in adolescence. The association with asthma was strongest for persistent wheeze (OR_{adj}, 56.54 [95%CI 43.75, 73.06]). Observed considerable within-class heterogeneity at the individual level, with 913 (12%) children having low membership probability (<0.60) of any phenotype. Class membership certainty was highest in persistent and never/infrequent, and lowest in late-onset wheeze (with 51% of participants having membership probabilities <0.80). Individual wheezing patterns were particularly heterogeneous in late-onset wheeze, whereas many children assigned to early onset preschool remitting class reported wheezing at later time	All wheeze phenotypes had significantly diminished lung function in school-age children, suggesting that the notion that early life episodic wheeze has a benign prognosis may not be true for a proportion of transient wheezers.	

				points.		
Owens [21], 2017, Australia	Prosp Perth Infant Asthma Follow-up Study (PIAF) of a birth cohort initially studied at brth	253 subjects enrolled antenatally with lung function assessments at 1, 6 and 12 mo (V′maxFRC), and 6, 11, 18 and 24y (spirometry) of age.	To assess whether this link persists into adulthood and whether infant lung function can predict the remission of asthma symptoms in young adults.	Infants with V′maxFRC in the lowest quartile at 1 mo had an OR of 5.1 (95%CI: 2, 13, *P* = 0.001) for asthma at 24y. Subjects with asthma at 24y had a mean V′maxFRC at 1 mo of 69% predicted (48, 90) versus 110% (101, 119) in non-asthmatic patients (*P*=0.001). Subjects with current versus resolved asthma symptoms at 24y had a mean V′maxFRC at 1 mo of 69% predicted (53, 84) versus 105% (88, 123), respectively (*P*=0.003). Subjects with current asthma at 24y had persistently lower lung function from infancy with a mean reduction of 16.2% (8.1, 24.3, *P*<0.0001).	Reduced lung function in early infancy is predictive of persistent asthma in young adults and a persistent reduction in lung function, suggesting abnormal lung development and growth in utero or very early in life.	These findings highlight the importance of considering infant lung function in the context of assessing the impact childhood respiratory illnesses on adult health.
Owora [22], 2021, Global	Systematic review and meta-analyses of wheezing illness.	Included 13 cohort studies conducted in 11 high-income countries with the length of FU ranging from 3 to 18y.	Systematically review childhood wheeze trajectory studies to identify childhood wheeze trajectory group-specific risk factors among children from birth through to adolescence.	5 distinct latent wheeze trajectory groups were identified: Never/Infrequent, Early-Transient, Early-Persistent, Intermediate-Onset, and Late-Onset. Moderate-to-strong evidence that family history of asthma predicted persistent childhood wheezing among male children but with lower risk among first-born children. There was weak-to-moderate evidence for childhood atopy, male sex, short duration of breastfeeding, tobacco exposure, day care attendance, and having siblings as risk factors for Early-Transient wheezing; except for breastfeeding, these factors were also associated with intermediate and Late-Onset wheezing with varying effect sizes in high-risk vs general population cohorts.	With the exception of the relationship b/w a family history of asthma and persistent childhood wheeze, commonly suspected wheeze risk factors (childhood atopy, male sex, short duration of breastfeeding, tobacco exposure, daycare	Delineation of time-varying risk factor effects may be critical to the specificity of wheeze trajectory group prediction to better inform prognosis and targeted early preventive intervention among at-risk children.

					attendance, and having siblings) are not trajectory-specific and have varying effects in high-risk vs general population cohorts.	
Sears [23], 2003, New Zealand	Prosp study over 26y of a birth cohort initially investigated at the age of 3y.	613 study members with complete respiratory investigations from age 9 to 26y were included.	Describe the outcome of childhood asthma in adults in a population-based study and investigate the risk factors for persistence and relapse.	By age 26y, 51.4% of 613 participants with complete respiratory data had reported wheezing at more than 1assessment. 89 study members (14.5%) had wheezing that persisted from childhood to 26y of age, whereas 168 (27.4%) had remission, but 76 (12.4%) subsequently relapsed by the age of 26y. Sensitisation to house dust mites predicted the persistence of wheezing (OR 2.41; p=0.001) and relapse (OR 2.18; p=0.01), as did airway hyperresponsiveness (OR for persistence, 3.00; p<0.001; OR for relapse, 3.03; p<0.001). Female sex predicted the persistence of wheezing (OR 1.71; p=0.03), as did smoking at the age of 21y (OR 1.84; p=0.01). The earlier the age at onset, the greater the risk of relapse (OR 0.89 per year of increase in the age at onset; p<0.001).	Outcomes in adult asthma may be determined primarily in early childhood	Persistence of asthma into and relapse of asthma in young adulthood is influenced by early life sensitisation and bronchial hyperreactivity and active smoking by age 21y.
Strachan [24], 1996, United Kingdom	Prosp cohort study over 25y of a birth cohort initially studied at the age of 7y.	5801 (31%) contributed information at ages 7, 11, 16, 23, and 33y.	Describe the incidence and prognosis of wheezing illness from birth to age 33y and the relation of incidence to perinatal, medical, social,	The cumulative incidence of wheezing illness was 18% by age 7y, 24% by age 16y, and 43% by age 33y. Incidence during childhood was strongly and independently associated with pneumonia, hay fever, and eczema. There were weaker independent associations with male sex, third trimester antepartum haemorrhage, whooping cough, recurrent abdominal pain, and migraine. Incidence from age 17 to 33y associated strongly with active cigarette smoking and a history of hay fever. There were weaker independent associations with female sex, maternal albuminuria during pregnancy, and histories of	Importance of addressing specific risk factors to reduce the risk of incidence and recurrence of wheezing.	Most of the childhood wheeze/asthma developed by age 7y remits by age 33y. Relapse after long remission by age 33y was common

			environmental, and lifestyle factors.	eczema and migraine. Maternal smoking during pregnancy was weakly and inconsistently related to childhood wheezing but was a stronger and significant independent predictor of incidence after age 16y. Among 880 subjects who developed asthma or wheezy bronchitis from birth to age 7y, 50% had attacks in the previous year at age 7y; 18% at 11, 10% at 16y, 10% at 23y, and 27% at 33y. Relapse at 33y after prolonged remission of childhood wheezing was more common.		
Tan [25], 2023, Australia^	Prosp Tasmanian Longitudinal Health Study over 46y of a birth cohort initially studied at the age of 7y.	Included 1506 participants who reported asthma at least in 1 of the 7 follow-up reviews.	Characterise the longitudinal phenotypes of asthma between the 1st and 6th decades of life in a population-based cohort study.	5 longitudinal asthma phenotypes were identified: early-onset adolescent-remitting (40%), early-onset adult-remitting (11%), early-onset persistent (9%), late-onset remitting (13%), and late-onset persistent (27%). All phenotypes were associated with COPD at age 53y, except for late-onset remitting asthma (OR: early-onset adolescent-remitting, 2.00 [95%CI 1.13, 3.56]; early-onset adult-remitting, 3.61 [1.30, 10.02]; early-onset persistent, 8.73 [4.10, 18.55]; and late-onset persistent, 6.69 [3.81, 11.73]). Late-onset persistent asthma was associated with the greatest comorbidity at age 53y, with increased risk of mental health disorders and CVD risk factors.	5 longitudinal asthma phenotypes identified b/w 1st to 6th decades of life, including 2 novel remitting phenotypes. Identified differential effects of these phenotypes on risk of COPD and non-respiratory comorbidities in middle age.	
Weber [26], 2022, Brazil	Longitudinal birth cohort followed over 22y	Inc 3350 who provided information at 5 time points	Identify wheezing trajectories and investigate their relation with pulmonary function and asthma-related	4 trajectories were identified: never/infrequent, transient-early, late-onset and persistent wheeze. After adjustments, wheezing trajectories remained associated with lower post-bronchodilator values of pulmonary function. Individuals in the persistent wheeze trajectory had a markedly poorer pulmonary function and also showed greater odds of asthma-related outcomes compared to other trajectories groups. Those following this trajectory had on average -109 ml (95%CI -188, -35), -1.80% points (-2.7, -0.87)	Wheezing trajectories, especially the persistent wheeze trajectory, were related to lower pulmonary function values and	

			outcomes at 22y of age.	and -316 ml/s (-482, -150) lower FEV_1, FEV_1/FVC ratio and $FEF_{25-75\%}$ respectively; higher odds of self-reported medical diagnosis of allergy (OR 6.18 [3.59, 10.61]) and asthma (OR 12.88 [8.91, 18.61]) and asthma medication use (OR 9.42 [5.27, 16.87]) compared to the never/infrequent group.	increased risk of asthma and allergy diagnosis in early adulthood.	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)						
Bui [27], 2017, Australia^	Population-based longitudinal cohort of children born in 1961 and attending school in Tasmania, in 1968 (N=8583 recruited).	Cohort resurveyed at 45y, and a selected subsample (n=1,389) underwent prebronchodilator and post-bronchodilator spirometry.	Investigate the role of childhood lung function in adult COPD phenotypes.	The lowest quartile of FEV_1/FVC ratio at 7y was associated with asthma-COPD overlap syndrome (OR 16.3 [95%CI 4.7, 55.9]) and COPD (OR 5.76 [1.9, 17.4]), but not asthma alone.	Screening of lung function in school age children may identify a high-risk group. Need to understand possible modifiers & develop interventions for children with impaired lung function.	Being in the lowest quartile for lung function at age 7y may have long-term consequences for the development of COPD and asthma-COPD overlap syndrome by middle age.
Bui [28], 2018, Australia^	Population-based longitudinal cohort of children born in 1961 and attending school in Tasmania, in 1968 (N=8583 recruited).	FU at 53y (N=2689). Post-bronchodilator spirometry measured. Asthma information collected at 7y.	Identify childhood risk factor profiles and their influence on lung function and COPD in middle age.	A risk profile characterised by frequent asthma, bronchitis and allergy at 7y was most strongly associated with risk of COPD (OR 4.9 [95%CI 2.1, 11.0]) at 53y. The effect of this on COPD was largely mediated by adult active asthma (62.5%) and reduced childhood lung function (26.5%) and was stronger in smokers.	Interventions targeting active asthma in both childhood and adulthood, as well as smoking, might reduce adverse effects in this group.	Children with frequent asthma attacks and allergies, especially if they also become adult smokers, are at particular risk of developing COPD.
Bui [29], 2018, Australia^	Population-based longitudinal cohort of children born in 1961 and attending	Respiratory questionnaires were first collected when participants were aged	Identify predictors of lung function trajectories	Six trajectories identified. Frequent asthma at 7y associated with persistently low lung function and increased risk of spirometrically defined COPD at 53y.	Benefit of optimal asthma control should be	Frequent childhood asthma associated with

	school in Tasmania, in 1968 (N=8583 recruited).	7y (baseline) and subsequently in FU studies conducted at ages 13, 18, 30, 43, 50, and 53y. Asthma defined by questionnaire report; repeat lung function measures obtained (post-bronchodilator at 53y). N=2438 with 2+ waves of lung function data at 7 and 53y.	and future COPD risk.		investigated in future trials.	increased COPD risk.
Dharmage [30], 2023, Australia^	Population-based longitudinal cohort of children born in 1961 and attending school in Tasmania, in 1968 (N=8583 recruited).	Spirometry measured at 7, 13,18, 45, 53y. Trajectory modelling identified six FEV_1/FVC trajectories (N=2422).	Investigate lifetime lung function trajectories of FEV_1/FVC and their consequences.	The prevalence of COPD at 53y was highest in the mixed obstructive/restrictive pattern (low FEV1/FVC ratio and low FVC) followed by the obstructive pattern.	Mixed and obstructive only patterns indicate those who might benefit most from early COPD interventions.	Mixed and obstructive only lifetime patterns associated with highest risk of COPD.
McGeachie [31], 2016, USA	Longitudinal FU of CAMP RCT. Inc: children with chronic asthma and airway hyper-responsiveness.	N=1041 children aged 5-12y, enrolled in an RCT in 1993-95 who were followed up. Primary analysis limited to n=684 with at least 1 FEV1 measurement at 23-30y	Characterise patterns of growth and decline in lung function in children with persistent asthma	Children were classified according to 4 characteristic patterns of lung-function growth and decline on repeated measures of FEV1 from childhood. At the last spirometric measurement (mean age 26y), 73 participants (11%) had spirometrically defined COPD; they were more likely to have a reduced pattern of growth than a normal pattern.	Early and serial FEV1 monitoring could identify children and young adults at risk of COPD, although further research is needed to identify interventions which can modify the outcome.	Children with persistent asthma and reduced growth of lung function are at increased risk for fixed airflow obstruction and possibly COPD in early adulthood.
Tagiyeva [32], 2016,	Population-based longitudinal cohort	Followed up in 1989, 1995, and 2001, and	To investigate	Childhood asthma was associated with an increased risk of COPD (OR 6.37 [95%CI 3.73,		Children with asthma were

United Kingdom	recruited in 1964 at age 10-15y. Random sample (N=2511).	again in 2014 when at age 60 to 65y (N=330). Post-bronchodilator spirometry performed.	whether childhood wheezy bronchitis and asthma increase the risk of COPD in the seventh decade.	10.94]).		more likely to develop COPD from the 4th decade as a consequence of reduced FEV_1 from childhood, not an increased rate of FEV_1 decline.
Tai [33], 2014, Australia	Longitudinal cohort. Inc: Primary school children born in Melbourne in 1957 and recruited at 7y. All children with a history of asthma/wheezy bronchitis; 1 in 2 with mild wheezy bronchitis; 1 in 20 controls (N=401). 83 extra children at age 10y with severe asthma.	Followed up at 50y and post-bronchodilator lung function measured (N=346).	Evaluate association between childhood asthma and adult COPD.	Compared to children without symptoms of wheeze by the age of 7y (non-asthmatics), children with severe asthma had an adjusted 32 times higher risk of developing spirometrically-defined COPD (95%CI 3.4, 269); nearly half of the COPD group had never smoked.		Highlights children with severe asthma, but not milder asthma, are at increased risk of developing COPD.
Tan [25], 2023, Australia^	Population-based longitudinal cohort of children born in 1961 and attending school in Tasmania, in 1968 (N=8583 recruited).	Respiratory questionnaires were first collected when participants were aged 7y (baseline) and subsequently in FU studies at ages 13, 18, 30, 43, 50 and 53y. Asthma defined by questionnaire report; repeat lung function measures obtained (post-bronchodilator at 53y). N= 3,249 with asthma defined at 3+	Characterise the longitudinal phenotypes of asthma between the 1^{st} and 6^{th} decades.	5 longitudinal asthma phenotypes identified. 4 of these associated with spirometrically-defined COPD at 53y, especially the 2 persistent phenotypes.	Future research should determine whether long-term preventive treatment can alter disease trajectory and improve outcomes for asthma patients.	Differential effects of asthma phenotypes on risk of COPD in middle age.

		time points.				
Zhang [34], 2024, New Zealand	Population-based longitudinal cohort of children born in Dunedin in 1972/73; recruited at 3y (N=1037).	Followed up 12 more times; lung function measured from 8y; post-bronchodilator spirometry at 45y. Airway hyper-responsiveness measured in childhood. Childhood asthma based on report plus symptoms/medication in last year. Analysis included 865 participants with 6+ spirometry measures from 9-45y.	Document lung function trajectories from childhood to mid-adult life.	10 trajectories for FEV_1 and for FEV_1/FVC identified. Asthma and airway hyper-responsiveness associated with persistently low FEV_1/FVC lung function trajectory, which in turn contributed to spirometrically defined COPD at 45y.	Strategies needed to maximise lung growth but unclear whether better management of childhood asthma would achieve this.	Highlights asthma and airways hyper-responsiveness associated with life course persistent adverse lung function trajectory and COPD.
BRONCHIECTASIS (BE)						
King [35], 2006, Australia	Cross-sectional study. Inc: Adults newly diagnosed with BE seen at a respiratory clinic b/w 1980-2001. BE confirmed by chest CT or bronchogram. Exc: Previously diagnosed BE.	Adults presenting to a tertiary referral hospital with newly diagnosed BE. N=103, mean age 56y (SD 14), females=63%.	Characterise the onset and presenting clinical features of adults at their first presentation of BE.	>80% had chronic respiratory symptoms from childhood. Typical profile of adults first diagnosed with BE are "longstanding productive cough, rhinosinusitis and fatigue in non-smokers with crackles on chest auscultation".		Highlights many adults with BE could have been diagnosed in childhood and the importance of early diagnosis
King [36], 2009, Australia	Cross-sectional. Inc: Adults with chest CT-confirmed BE. Exc: Absence of history of chronic productive cough (defined as productive cough on	Seen in a hospital clinic (Monash Medical Centre) 1998 to 2007. Assessed when clinically stable (no exacerbations for at least one mo). N=182, mean age=58y, females=64%.	Assess if adults with BE can be differentiated into 2 phenotypes (child- and adult-onset) based on the	Those with child-onset (before aged 16y) symptoms have more severe BE (poorer lung function, worse CT scores, more exacerbations, more rhinosinus disease). Lung function inversely related to duration of chronic cough (r=-0.44 [95%CI] -0.59, -0.29; $p<0.001$) FEV_1 % predicted per y of chronic cough; relationship stronger in non-smokers (r=-0.51) than smokers. Onset of chronic productive cough rare b/w the ages of 16–		Highlights importance of chronic wet or productive cough, many adults with BE could have been diagnosed in childhood and

	most days for ≥6 mo).	Child onset n=107 (59%); adult-onset n=75 (41%).	time of onset of their productive cough.	50y.		the importance of early diagnosis.
McCallum [37], 2020, Australia	Prosp longitudinal study. Inc: Indigenous children aged 0.5-9y with CSLD or CT□confirmed BE enrolled in previous prosp studies.[38,39] Exc: Inability to contact participants.	131/180 (72.8%) of original cohort reviewed at single FU visit (Australia, New Zealand, Alaska, [USA]). Global rating based on symptoms, ALRI frequency, examination findings, spirometry. Mean age=12.3y (SD 2.6). Median duration of FU=9.0y [range 5-13]) post-original recruitment.	Determine (a) long□ term clinical characteristics and lung function and, (b) risk factors associated with global clinical status and lung function, of children with BE and CSLD.	Spirometry values mostly within population norms: median FEV_1=90% predicted (IQR 81□ 105); FVC=98% predicted (IQR 85□114). 38.7% reported on-going chronic cough episodes. Global rating: well=20.3%, stable=43.9%, improved=35.8%. Household tobacco exposure and age at first ALRI□episode were independent risk factors associated with lower FVC% predicted values.	With appropriate clinical care, outcomes even in those from populations at high□risk of premature mortality are good. Need for prosp studies that focus on the prevention and management throughout the life course.	Importance of early diagnosis and management and access to standardised modern good medical care.
Pasteur [40], 2000, United Kingdom	Cross-sectional. Inc: Adults with chest CT-confirmed BE. Exc: Those with known causes of BE when referred.	Seen in a hospital clinic (Papworth Hospital, United Kingdom), 1995 to 1998. N=150, female=62.7%, mean age=52.7y (SD 15.2). Median age at onset of symptoms =14y (range 1-80).	Determine causative factors of BE in adults with BE diagnosed with chest CT.	Intensive investigations led to identification of one or more causative factor in 47% with implications for prognosis and treatment in 22/150 (15%). From the figure, ~58% of the patients were symptomatic before aged 20y.		Highlights many adults with BE could have been diagnosed in childhood.
Sibanda [41], 2020, United States	Retro longitudinal. Inc: Yukon Kuskokwim Delta adults aged 20-40y on 31 Dec 2017 with a documented history of childhood BE. Exc: none reported.	People with diagnosis of BE before 18y of age identified from registry. N=31, median age=30y (range 20-40). median age when BE diagnosed=4.5y.	Review the clinical course of Yukon Kuskokwim Delta Alaska Native adults with childhood BE.	4/31 (13%) deceased (2 from BE-related issues), 13% had severe pulmonary impairment and dependent on family or assisted living, additional 35% had persistent pulmonary symptoms and 9.7% cor pulmonale. 18 (62%) patients had no mention of BE in the medical visits/hospitalisations at or after aged 20y, only 5 seen by an adult pulmonologist, and most patients had no ongoing regular medical FU.	Lack of provider continuity, remote location of patients and co-morbidities all contribute to poor transition into	Highlights the need for optimal transitioning of paediatric patients with BE to adult care.

					adult care and increased adult morbidity.	

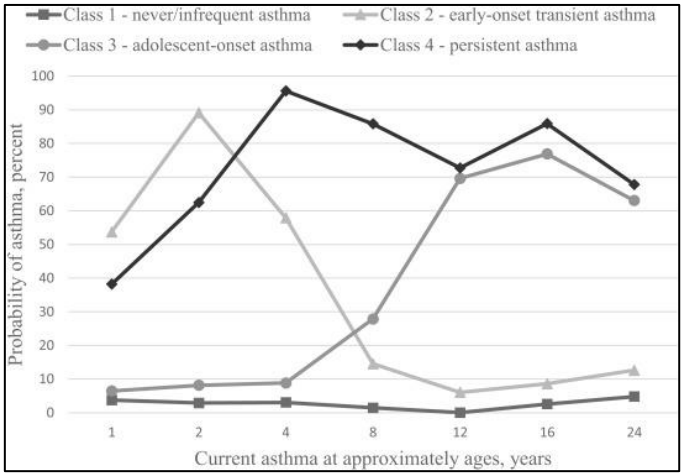
*For children we included studies where follow-up data extends to adolescents (aged ≥12-years);
†When a systematic review had been performed and an individual study included in the systematic review, we did not describe this study in the Table, unless additional information was provided by the original paper.
^Overlapping data as these studies are from the same cohort.
ALRI=acute lower respiratory infection(s), BE=bronchiectasis, BDR=bronchodilator responsiveness, BW=birth weight BPD=broncho-pulmonary dysplasia, b/w=between, CI=confidence interval, COPD=chronic obstructive pulmonary disease, CSLD=chronic suppurative lung disease CT=computed tomography, CVD=cardiovascular disease, CXR=chest x-ray, DLCO=diffusing capacity of the lung for carbon monoxide, EP=extreme preterm <28wk gestation, Exc=exclusion, ELBW=extreme low birthweight <1000g, $FEF_{25\%–75\%}$=forced expiratory flow at 25-75% of FVC, FeNO=fractional exhaled nitric oxide, FEV_1=forced expiratory volume in 1-second, FRC=functional residual capacity, FU=follow-up, FVC=forced vital capacity, g=grammes, HRCT=high-resolution computed-tomography, Inc=inclusion, IQR=interquartile range, kPa=kilopascals, LCI=lung clearance index, mo=months, OR=odds ratio, OR_{adj}=adjusted OR, Prosp=prospective, RCT=randomised controlled trial, Retro=retrospective, RV=residual volume, SD=standard deviation, TLC=total lung capacity, tptef/te=time to reach peak tidal expiratory flow to the total expiratory time, $\dot{V}maxFRC$=maximal expiratory flow at functional residual capacity, VLBW=very low birthweight <1500g, VP=very preterm <32wk gestation, wk=week(s), y=year(s), z=Z-score.

S3

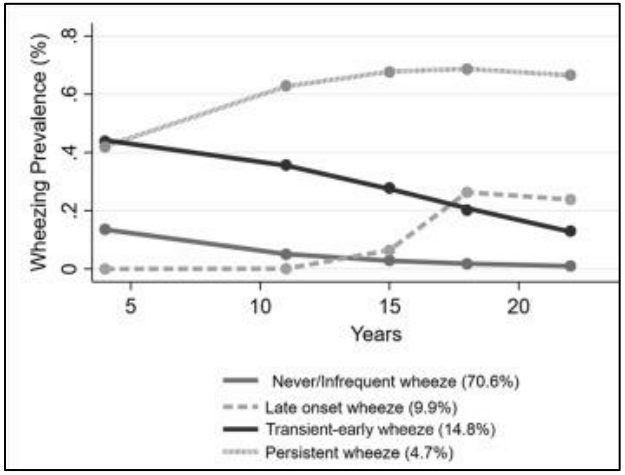
Figure:

Data from the three other studies (in addition to the Tasmanian Longitudinal Study (TAHS)[25], Figure-2) that used data-driven techniques to derive the trajectories of childhood asthma. All figures were obtained from the respective publications and reproduced with permission.

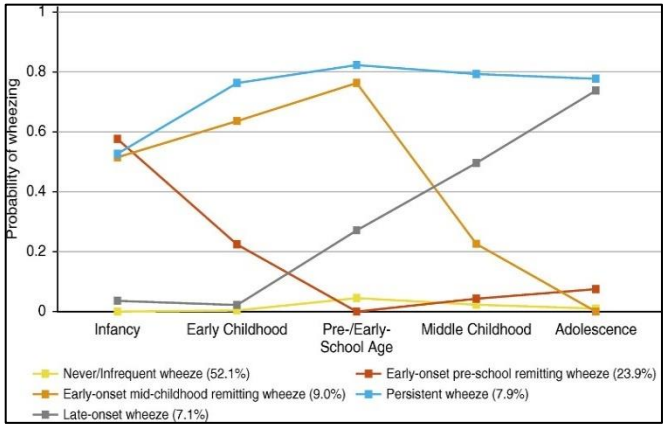
(a) The BAMSE birth cohort[19],

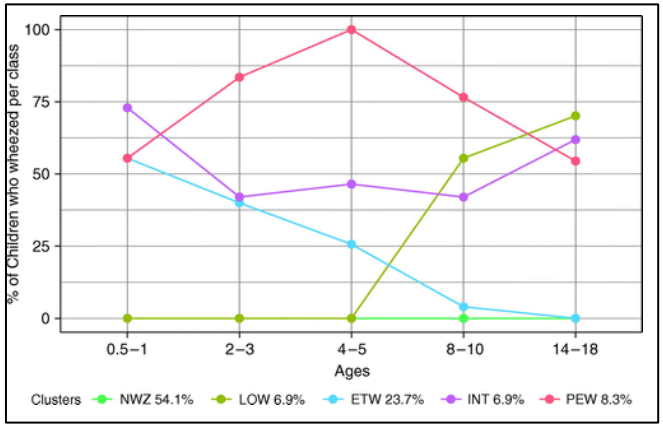


(b) The Pelotas birth cohort[26]



(c) STELLAR consortium[16],





S4

Table: Studies on undifferentiated chronic cough and breathlessness in children and adults and future health outcomes

First author, year	Study type; Inclusion and exclusion criteria	Sampling demographics	Aim of study	Main findings specific to question of this review	Solutions proposed by authors of the paper (if any)	Comments
CHILDREN						
Bui [29], 2018, Australia*	Prosp cohort (Tasmanian Longitudinal Health Study (TAHS), enrolled at 7y in Tasmania, Australia. Inc: Participants of cohort who have at least two lung function data at age 7 and 53y. Exc: Insufficient participant data. Included participants had "similar baseline characteristics to those not included except for more female participants, more participants with eczema, and fewer smoking parents among those included".	Lung function trajectories modelled from data at 7, 13, 18, 45, 50, 53y. Original cohort N=8583, study group n=2438, male n=1180 (48%). Childhood bronchitis defined by Q at aged 7y "Has he/she at any time in his/her life suffered from attacks of bronchitis or attacks of cough with sputum (phlegm) in the chest ('loose' or 'rattly' cough)?" Frequent childhood bronchitis defined as attack frequency ≥1 every 3 mo. Childhood asthma: "Has he/she at any time in his/her life suffered from attacks of asthma or of wheezy breathing?". Frequent asthma: ≥1 attack every 3 mo.	"To (1) characterise population FEV_1 trajectories from the 1st to the 6th decade, (2) investigate their childhood predictors and interaction with adult asthma and personal smoking, and (3) relate trajectories to COPD risk".	Study found 6 potential FEV_1 trajectories based on 7y data: early below average with accelerated decline; persistently low; early low with accelerated growth and normal decline; persistently high; below average; and average. Childhood bronchitis (vs no bronchitis) was an independent risk factor in the 'early below average with accelerated decline' trajectory; infrequent (OR 1.9 [95%CI 1.1, 3.1]) and frequent bronchitis (OR 2.5 [1.3, 4.8). Other significant factors were: maternal heavy smoking (OR 2.5 [1.1, 5.9) but not maternal light-moderate smoking, frequent asthma (OR 4.4 [2.1, 9.1]), past pneumonia/pleurisy (OR 2.0 [1.2, 3.5) and allergic rhinitis (OR 2.0 [1.2, 3.4]).	"Reduction of maternal smoke exposure and personal smoking and encouragement of immunisation are identified as public health targets to prevent adverse lung function trajectories and reduce future COPD burden. Clinicians and patients with asthma should be made aware of the potential long-term implications of non-optimal asthma control throughout life"	Chronic wet cough (chronic bronchitis) was one of the significant independent risk factors associated with future adult accelerated lung function decline.
Perret [42], 2022, Australia*	Prosp cohort (TAHS). Inc: Participants of cohort with relevant data at 53y. Exc: Missing participant data.	Cohort enrolled at age 7y and FU at the mean age of 53y. Original cohort N=8583, study group n=3202, mean age 53y, (range 51-55), male n=1578 (49%). Childhood bronchitis ('wet' cough) defined by Q at aged	"To investigate the relationship b/w childhood bronchitis and respiratory-related health outcomes in	Compared with those with 'no childhood bronchitis' (n=1680), all 3 subgroups of childhood bronchitis (non-recurrent [n=902], recurrent non-protracted [n=578] and recurrent-protracted [n=42]) associated with doctor-diagnosed current and ever-asthma in middle-	"need for increased vigilance in monitoring young children who have multiple episodes of protracted bronchitis for potential asthma,	Childhood bronchitis associated with clinical lung disease in mid-adult life, especially when chronic,

		7y as per Bui et al.[29], Subgroups: 'non-recurrent' subgroup: 1-5 episodes only of any duration; 'recurrent': ≥6 episodes lasting <1 mo on average; 'recurrent-protracted': either continuous symptoms or ≥6 episodes each lasting an average of ≥1 mo.	middle- age".	age, and recalled doctor- diagnosed pneumonia after 7y (p=0.032, p<0.001, p=0.05, respectively). Prevalence for current chronic bronchitis at 53y was 2.4- fold higher in recurrent-protracted childhood bronchitis subgroup (vs no childhood bronchitis) but overall trend was non-significant, (p_{trend} 0.07) but note small group.	pneumonia and bronchiectasis up to mid- adult life, confirmed with objective testing".	recurrent and protracted
Perret [43], 2024, Australia* and USA	Prosp cohorts (TAHS and Coronary Artery Risk Development in Young Adults (CARDIA). TAHS - Inc: Participants at 53y assignable to both a symptom profile and FEV_1/FVC trajectory CARDIA - Inc: those assignable to both a symptom profile and FEV_1/FVC trajectory. Exc: not mentioned.	TAHS cohort description as above. Study group n=2421 of 8583 from original cohort, mean age 53y, (range 51-55), male48%. CARDIA enrolled 5115 healthy individuals from 4 cities in the USA (non-mining areas), aged 18–30 y in 1985-86. Spirometry measurements were collected at mean ages of 25 (baseline), 27, 30, 35, 45, 55y. Study group n=3153 mean age 55.1y, SD 3.6, 43% males.	To identify (a) combinations of symptoms in middle age and investigate relationships with FEV_1/FVC trajectories, and (b) symptom profiles associated with rapidly declining FEV_1/FVC trajectory but without spirometry-defined COPD.	Rapid decline FEV_1/FVC trajectories higher in those with wheeze and bronchitis in TAHS participants aged <14y (54 [20%] of 265 vs 289 [12%] of 2421). By aged 14y, 20% participants with rapid decline trajectories had wheeze and 'usual phlegm' and 10% 'usual phlegm.		See the row of the same study in the adult section
Zhang [44], 2024, Australia*	Prosp cohort (TAHS). Inc: Participants of cohort with any cough at 53y. Exc: Participant categorised as non-coughers at 53y.	Cohort enrolled at age 7y and FU at the mean age of 53y. Original cohort N=8583, study group n=2213, mean age 53y, (range 51-55, SD 1), male n=1065 (48%).	To "explore cough subclasses in a community-based adult cohort" and "identify potential treatable traits	Six distinct cough subclasses: minimal cough n=206 (9.3%), cough with colds only n=1189 (53.7%), cough with allergies n=305 (13.8%), intermittent productive cough n=213 (9.6%), chronic dry cough n=147 (6.6%), and chronic productive cough n=153 (6.9%). "Compared with 'minimal cough' group, those	"Clinical vigilance and close monitoring for potential lung function impairment could provide opportunities for early intervention	Community-based study showed that adults at mid-age (51-55y) who have intermittent or chronic

			of the identified subclasses by describing their clinical characteristics from childhood to adulthood".	with intermittent productive cough and chronic productive cough subclasses had worse lung function trajectories (FEV_1 persistent low trajectory 2.9%, 6.4%, and 16.1%; p=0.0011, p<0.0001; FEV_1/FVC early low–rapid decline trajectory 2.9%, 12.1%, and 13.0%; p=0.012, p=0.0007) and a higher prevalence of cough (age 53y 0.0%, 32.4% [26.1–38.7], and 50.3% [42·5–58·2]) and asthma (age 53y 6.3% [3.7–10.6], 26·9% [21.3–33.3], and 41.7% [24.1–49.7]) from age 7y to age 53y".	or prevention. Lung function should be assessed routinely when evaluating or managing adults with productive cough, including in primary care".	productive cough have often coughed from childhood and have worse outcomes compared to those with minimal cough.
ADULTS						
Backman [45], 2023, Sweden	Prosp, population-based case-referrent study including repeated lung function testing across more than 10y of FU.	Prosp cohorts recruited in 1985, 1992, 1993, and 1996 from OLIN (Obstructive Lung Disease Study in Northern Sweden). Study population of n=1,986 constituted the longitudinal OLIN COPD study and has since 2005 been invited to annual exams including spirometry	Identify FEV_1 trajectories and their determinants based on annual spirometry among individuals with and without airway obstruction and to assess mortality in relation to trajectories.	Data-driven analyses identified 3 lung function trajectories with clinically different outcomes in terms of FEV_1 decline and mortality amount those with airway obstruction, while 2 trajectories among the non-obstructed referents. Rapid decline in lung function and low normal lung function with normal decline led to increased mortality.	Future studies may reveal tools for both preventive measures and new treatable traits.	Did not tease out effects of symptoms and did not specify whether mortality was cardiovascular or all-cause, etc.
Carpenter[46], 1989, United	Prosp cohort study	Setting: 92 General Practices. A nationally representative sample of 1,532 British men and women aged 40-64y.	Assess mortality over 27y from 1958 to 1985 from	Breathlessness was the only symptom significantly associated with excess mortality from CVD.	It is no longer thought to be appropriate to consider productive	FU was performed by using the routine system for

Kingdom		Subjects interviewed regarding respiratory symptoms including cough, phlegm, breathlessness and wheeze using Medical Research Council's questionnaire	all causes, CVD, lung cancer, and chronic bronchitis		cough and exertional breathlessness to be symptoms of the same disease.	reporting mortality in the UK; therefore, some deaths may have been missed. No lung function testing.
Cheng [47], 2021, China	Data were analysed from 4 prosp cohorts	Subjects with at least 2 lung function tests were included. Rates of decline in FEV_1 and FVC for each subject were calculated and categorized into quartiles The final sample comprised 12,899 subjects. Mean age 48.58y; 43.61 % males.	Determine the association of longitudinal change in lung function and subsequent CV risks. CV events=composite of CHD, chronic heart failure, stroke, and any CV death over 14.8y.	There was a graded relationship between quartiles of lung function decline and CV risks. The faster the decline in FEV_1 and FVC, the greater the CV events.	These findings emphasise the value of periodic evaluation of lung function and open new opportunities for disease prevention.	Did not focus on symptoms
Cuttica, [48], 2015, USA	Used the Coronary Artery Risk Development in Young Adults (CARDIA) study to explore the development of heart-lung interactions. CARDIA is a prosp cohort study of the evolution of CVD risk factors in young adults recruited b/w age 18-30y.	Analysed cardiac structural and functional measurements determined by echocardiography at Y25 and measures of pulmonary function over 20y in 3,000 subjects. Lung function (FVC and FEV_1) was measured at Y0, 2, 5, and 10 and at Y20. Only FVC and FEV_1/FVC ratio were reported. At Y25, LV end-diastolic volume, end-systolic volume, LV ejection fraction, LV posterior wall thickness, interventricular septal thickness, LV fractional shortening, LV stroke volume, cardiac output and LV mass were measured.	Understand the preclinical history of how lung diseases are associated with CVD and how they evolve to inform prevention strategies for common heart-lung conditions.	Decline in FEV_1/FVC ratio was associated with underfilling of the left heart and low cardiac output. Decline in FVC with preserved FEV_1/FVC ratio was associated with left ventricular hypertrophy and diastolic dysfunction. Lastly, cardiopulmonary interactions apparent with common complex heart and lung diseases evolve concurrently from early adulthood.	"This study provided a window into the preclinical evolution of heart-lung interactions as they evolve from health in young adults to disease in middle age. This has wide ranging implications for gaining insight into understanding the strong association of comorbid heart and lung disease seen later in life."	Did not focus on symptoms such as breathlessness or cough.

Epi-Kryston [49], 1988 United Kingdom	Analysis of prospectively collected data from the Whitehall study. In 1967-1969, 18,403 male civil servants aged 40-64y were examined and questioned.	This analysis was undertaken after completion of the main study. N=17,717 men; smokers of pipes or cigars only and men of unknown smoking habits were excluded. The Central Registry of the National Health Service provided death certificates. Mortality rates for all causes of death, CVD and chronic respiratory diseases excluding other diseases of the upper respiratory tract and lung cancer were reported for 10y of FU. The questionnaire (London School of Hygiene CV questionnaire and other standardised questions), was self-administered. 4 questions about common respiratory symptoms taken from MRC bronchitis questionnaire. Mean FEV_1, FVC measured.	To clarify relationships btw mortality and chronic phlegm production, breathlessness, and impaired pulmonary function	Breathlessness was significantly associated with respiratory, CV and all cause mortality. While chronic phlegm production was significantly associated with all-cause and respiratory mortality, these associations did not persist after controlling for breathlessness or FEV_1 percent predicted. While FEV_1 <65% predicted was significantly associated with mortality from respiratory, CVD and all causes, the association for the latter 2 was not as high as those for breathlessness.	"This study population offered an opportunity to assess different measures of respiratory impairment while controlling for covariates such as age and smoking habits." Because mortality among men reporting breathlessness remained high over 10y of followup, "if confirmed, breathlessness should be considered an independent predictor of mortality from cardiorespiratory disease."	This study suggested that breathlessness might be a greater risk for CV and all-cause mortality than lung function decline.
Feng [50], 2022, data from a United States study (authors from China)	Prosp cohort study involving participants from the Coronary Artery Risk Development in Young Adults Study (CARDIA).	Enrolment of 4,621 participants aged 18-30y. Chronic respiratory symptoms were identified through respiratory symptom questionnaires in 2 consecutive examinations. Incident CVD and all-causes mortality were adjudicated over a 30y FU. During an average of 30.9y, there were 284 CVD events and 378 deaths.	Assess if chronic respiratory symptoms in young adulthood are associated with CVD and all-cause mortality in later life	After multivariable adjustments for demographic characteristics, CV risk factors, smoking and lung function, hazard ratios for CVD events were 1.51 for any respiratory symptom, 1.57 for cough or phlegm, 1.31 for wheeze, 1.73 for shortness of breath, and 1.32 for chest illness. Similar findings were observed for all-cause mortality. Chronic respiratory symptoms in young adulthood were associated with an increased risk of CVD and all-cause mortality in midlife independent of established CV risk factors, smoking and lung	"Identifying chronic respiratory symptoms in young adulthood may help provide prognostic information regarding future cardiovascular health."	Hazard ratio for CVD for all respiratory symptoms was greatest for shortness of breath, followed by chronic productive cough

				function. Also, the greater number of chronic respiratory symptoms, the greater the CVD and all-cause mortality.		
Gao[51], 2022, data from a United States study (authors from China).	Prosp cohort study involving participants from the Coronary Artery Risk Development In Young Adults Study (CARDIA)	A total of 2,694 participants (44.7% men) with a mean age of 40.4y were included. The rates of decline in FVC and FEV_1 over a 20y period were calculated for each participant and categorised into quartiles. The primary outcome was CAC.	To assess relationship between lung function decline and CAC progression.	During a FU of 8.9y, 455 (16.9%) participants had CAC progression. After adjusting for traditional CV risk factors, the hazard ratios for CAC progression were higher for participants in the 2^{nd}, 3^{rd}, and highest quartiles (4^{th}) of FVC decline compared with those in the lowest quartile (1^{st}). Similar trends were observed for the association between FEV_1 and CAC progression. A faster decline in FVC and FEV_1 during young adulthood was independently associated with an increased risk of CAC progression in midlife.	Maintaining optimal lung function during your adulthood may improve future CV health.	Respiratory symptoms, especially breathlessness, were not assessed.
Haider[52], 1999, United States	Prosp population-based investigation from the Framingham Heart Study	Since 1948, 5,209 men and women aged 28-62y, were FU at regular intervals. Biennial FU visits were conducted to collect medical history, physical examination, 12-lead ECG, and laboratory tests. Data regarding age, gender, height, weight, CV risk factors, and antihypertension medication use were routinely obtained. Smoking information, LV hypertrophy data, information related to inflammatory mediators, vital capacity, and questionnaire regarding productive and unproductive cough were obtained. First fatal or non-fatal acute myocardial infarction data study's	Assess association of chronic cough with myocardial infarction for 6 consecutive examination cycles (1965-79) among participants without myocardial infarction at baseline. Secondary analysis, plasma fibrinogen levels were measured	In 15,656 person-examinations in 3,637 subjects, there were 291 myocardial infarctions. Chronic cough (productive or non-productive) were significant predictors of acute myocardial infarction; association persisted after adjustment for traditional CVD risk factors. Based upon elevated plasma fibrinogen levels, inflammation was perhaps the mechanism of how cough was associated with myocardial infarction. Chronic cough was the leading risk for myocardial infarction even after adjusting for lung function.	The findings were "consistent with the hypothesis that chronic infections or inflammation lead to myocardial infarction and that fibrinogen may be a mediator of the process".	Breathlessness was not assessed.

		endpoint.	during cycle 10 (1965-67) in a subgroup of 1,288.			
Jousilahti[53], 1966, Finland	Prosp cohort study of randomly selected eastern Finnish men and women born between 1913 and 1947 and examined in either 1972 or 1977.	The data reported were from a 13y FU of 19,444 participants. From this group, a random sample of 6.6% of the population b/w 1913-1947 were drawn. Total of participants n=9342 men and 10,102 women; mean age 42.3y and 43.7 respectively. A self-administered questionnaire included questions about medical history, symptoms of diseases, smoking history, socioeconomic background and health behaviour. A respiratory questionnaire focused on symptoms of productive cough and chronicity. Other assessments: blood pressure and blood cholesterol. CHD incidence and mortality were end-points. The FU time of each participant in the present analysis was 13y or until the end-point occurred.	To assess how chronic respiratory infection using the definition of chronic bronchitis as a surrogate marker of infection predicts coronary disease.	Long-lasting productive cough (meeting definitions of chronic bronchitis), predicted CHD (e.g., 1st myocardial infarction and CV death) in men and women independent of known major cardiovascular risk factors.	"Whether the association we found is causal can only be answered by studies where more specific measurements of infections are done."	Non-productive cough, breathlessness or lung function were not assessed.
Leivseth [54], 2014, Norway	Prosp cohort HUNT2 (Nord-Trondelag Health Study) that enrolled subjects between August 1995 and June 1997. The original group was 65,237 participants from which a 5% random sample were invited to participate.	After excluding participants because of missing data and identifying those with CVD at baseline, the study cohort included 10,491 subjects for the current study. Information about lifestyle, complaints, diseases and demographics were collected as well as	To assess if respiratory symptoms are associated with mortality independent of lung function.	Lung function was inversely associated with all-cause and CV mortality, and dyspnoea when walking was associated with all-cause mortality independent of lung function. Of the respiratory symptoms, only dyspnoea when walking remained associated with all-cause mortality after controlling	On the basis that lung function decline was associated with CV as well as all- cause mortality and dyspnoea on exertion was only associated with all-	The take home message for the reader is that assessing breathlessness as well as lung function are equally important.

		filling out a lung specific questionnaire and an interview and performed flow-volume spirometry from which FEV_1, FVC information was calculated. Questionnaires were completed regarding cough with phlegm, wheeze, shortness of breath at rest and with exertion. Participants FU from the date of attendance in HUNT2 to the date of death or until the end of FU, December 31, 2009 or 14 yrs, whichever came first. Primary endpoints: all-cause and CV death.		for lung function.	cause mortality, the authors speculated that objectively measuring lung function is superior to subjectively reported reporting respiratory symptoms in mortality studies.	
Perret [43], 2024, Australia* and USA	Prosp cohorts (TAHS and Coronary Artery Risk Development in Young Adults (CARDIA). TAHS - Inc: Participants at 53y assignable to both a symptom profile and FEV_1/FVC trajectory CARDIA - Inc: those assignable to both a symptom profile and FEV_1/FVC trajectory. Exc: not mentioned.	TAHS cohort description as above. Study group n=2421 of 8583 from original cohort, mean age 53y (range 51-55), male 48%. CARDIA enrolled 5115 healthy individuals from 4 cities in the USA (non-mining areas), aged 18–30 y in 1985-86. Spirometry measurements were collected at mean ages of 25 (baseline), 27, 30, 35, 45, 55y. Study group n=3153 mean age 55.1y, SD 3.6, 43% males.	To identify (a) combinations of symptoms in middle age and investigate relationships with FEV_1/FVC trajectories, and (b) symptom profiles associated with rapidly declining FEV_1/FVC trajectory but without spirometry-defined COPD.	People in rapid decline trajectories (vs normal decline) had the following factors: self-reported smoking, asthma, inhaler use, occupational exposures and respiratory symptoms. The most impaired early low, rapid decline trajectory in TAHS and low peak, persistent rapid decline trajectory in CARDIA associated with the following symptom profiles: predominant productive cough (TAHS multinomial OR 3.00 [95%CI 1.53, 5.85]; CARDIA 6.17 [2.26–16.8]); predominant dry cough (TAHS 2.32 [1.26, 4.31]); some chesty colds (CARDIA 3.11 [1.22, 7.93], TAHS 2.55 [1.24, 5.23]). In CARDIA only, the second-most and third-most impaired trajectories were also associated with predominant productive cough. In rapid decline trajectories, for TAHS, by aged 14y, 20% have wheeze and ‘usual phlegm’ and 10% ‘usual phlegm’. In	Presence of respiratory symptoms, esp. wheeze, should prompt clinicians to undertake lung functions tests.	In people on impaired FEV_1/FVC trajectories, respiratory symptoms common and many developed early-onset or young COPD by the middle age (53-55y). However, unclear how repeatable is reported wheeze and the type of wheeze

				CARDIA respective numbers were 25% and 7% by aged 18-30y. Dyspnoea was not a dominant feature.		
Rosengren [55], 2015, USA	Prosp population study (The multifactor primary prevention trial started in Goteborg in 1970) free of clinical angina pectoris and prior myocardial infarction. Exc: Prior myocardial infarction or angina, incomplete data on breathlessness, smoking or serum cholesterol.	Population was originally an intervention trial comprising all the men in the city born b/w 1915-1925, except those born in 1923. The present study dealt with the intervention group which was a random third of the men, or 10,000 men. 10y after entry, 20% random subsamples of the intervention and one of the control groups were again examined. A first screening examination took place b/w January1970 and March 1973. In the present study, data were used from the 2nd screening, which started in 1974, completed in 1977. All surviving men who still lived in Goteborg (n=9411) invited for screening. The response rate was 76%. N=6442. Data on breathlessness with exertion, cough with phlegm, chest pain, smoking habits, leisure time, physical activity, diabetes and family history of myocardial infarction were collected. At screening exams, blood pressure and serum cholesterol were obtained. All subjects FU until 31 December 1993 (mean 16y). The Swedish National Register on deaths was matched against a	To assess the relation between respiratory symptoms and mortality from CV causes, cancer and all causes	After adjustment for age, smoking habits and other risk factors, the relative risks associated with effort related breathlessness of dying from CVD, cancer, and from any cause were all increased. After adjustments described above, men with cough and phlegm, without breathlessness, did not have an elevated risk of dying from CVD and cancer. In conclusion, "a positive response to a simple question about effort related breathlessness predicted subsequent mortality from several causes during a FU period of 16y, independently of smoking and other risk factors."	"The best way to look at breathlessness is as a risk indicator, and as an added incentive to correct other risk factors such as smoking or hypercholesterolemia. However, more studies are needed which combine objective measurements and respiratory symptoms."	Lung function was not assessed.

		computer file of the men in the study.				
Sethi[56], 2023, United Kingdom	Systematic review and meta-analysis	Medline, CINAHL, and EMCARE were searched for the terms breathlessness and survival or mortality on January 24, 2023. Of 1,993 studies identified, 21 were eligible for inclusion in the systematic review and 19 for the meta-analysis.	Examine the relationship of breathlessness with mortality in healthy adults in a general population.	Near unanimous finding in the studies identifying a significant relationship btw the presence of breathlessness and increased mortality. Estimated pooled effect size: presence of breathlessness increased the risk of mortality by 43%. As breathlessness severity increased from mild to severe, mortality increased by 30%. Most studies adjusted for significant confounders such as age, gender, body mass, lung function, smoking, etc.	Breathlessness and mortality may be causally related in the following way: "Breathlessness initiates or perpetuates a negative spiral of deconditioning, loss of fitness and frailty, leading to increased mortality."	Did not specify which mortality is associated. Mechanism underlying this is unclear and may reflect the "ubiquity of breathlessness as a symptom of many diseases."
Stavem [57], 2006, Norway	Prosp occupational cohort study. Inc: Free from known or suspected heart disease, drug-treated hypertension, diabetes mellitus, malignancy, advanced pulmonary, renal and liver diseases, any severe locomotor activity limitation. Exc: chronic drug regimens. Additional 40 were excluded on the day of the examination because of recent morbidity and the remaining declined to participate.	In 1972, all healthy males aged 40-59y from 5 companies in Oslo, Norway invited to a CV screening survey; n=2014 (86%) consented. Between August 1972-March 1975, subjects underwent: detailed case history, chest x-ray, measurement of resting heart rate and blood pressure, spirometry, a symptom limited exercise ECG, fasting blood tests including cholesterol and respiratory symptoms Q using a British MRC to assess productive cough (and chronicity) and dyspnoea (breathlessness with effort). Smoking habits were assessed. Mortality data obtained from Statistics Norway, Oslo.	To assess the association of breathlessness and productive cough with CV and all-cause mortality over 26y.	Phlegm, breathlessness and combinations of them were associated with all-cause mortality, even after adjusting for physical fitness, known CV and other risk factors such as smoking and lung function. In contrast, none of the 6 respiratory symptoms individually or in combination were associated with CV mortality in multivariable analysis.	"The present study could not confirm an association between respiratory symptoms and CV mortality in contrast to some other studies. This difference might again be explained by inclusion of physical fitness as covariate in the present study."	This study could not separate productive cough from breathlessness as risk factors for all-cause mortality.
Stavem [58], 2022,	Prosp Study of a pooled sample of 4 cohorts of random samples of the	The pooled population included 95,704 participants. A self-administered	To analyse the association between	Overall, 13% of the participants died from CVDs: 33% from acute myocardial infarction, 18% from	"Future studies should examine the most effective	Lung function was not reported.

Norway	Norwegian population	questionnaire included information on smoking, education, occupational exposure to air pollution, respiratory symptoms, as well as additional information about previous heart and lung diseases. The Norwegian Directorate of Health and Social Services provided information on causes of death. A validated questionnaire on respiratory symptoms included 11 questions covering current cough, phlegm, wheezing, periods of cough and/or breathlessness with and without exercise. The questionnaire also included questions on smoking history.	respiratory symptoms and death from CVDs during a 45y FU	ischemic heart disease, 18% from other heart diseases, 20% from cerebrovascular diseases and 9% from other vascular diseases. "Breathlessness on effort [shortness of breath on exertion on level ground at ordinary pace] [but not attacks of shortness of breath] was a robust indicator of early deaths from all subgroups of CVDs. The severity of breathlessness increased the risk for such deaths." The adjusted hazard ratios for CV deaths was elevated in men and women for breathlessness when walking on level ground at an ordinary pace. The associations between CV deaths and breathlessness were also present in never smokers. Positive answers to questions on cough, phlegm, wheezing and attacks of breathlessness were not associated with early CV deaths after adjustments.	approach to diagnose and how to treat people with self-reported breathlessness on effort."	
Tockman [59], 1995, USA	Prosp cohort White male Baltimore Longitudinal Study of Aging (BLSA).	White male participants without CHD clinically evaluation at 2y intervals; 883 had satisfactory pulmonary and lipid studies and returned for a least 1 visit. Lung function, serum cholesterol, blood pressure, cigarette smoking, and body mass index obtained from BLSA database. 79 CHD deaths, 804 survivors during an average of 17.4y FU.	Determine whether rate of FEV_1 loss independently predicts CHD mortality in apparently healthy men.	After adjustment for age, initial FEV_1% predicted, common CHD risk factors (e.g., smoking status, hypertension, and cholesterol), a time-dependent proportional hazards model showed that cardiac mortality, but not all cause mortality, generally increased with increasing quintile of FEV_1 decline for the entire cohort and separately for the subset of never-smokers. Thus, excess CHD mortality follows a large decline in FEV_1.	"periodic spirometric re-evaluation may be appropriate as part of the standard health maintenance examination to detect individuals at higher risk for CHD."	Respiratory symptoms, especially breathlessness with exertion were not assessed.
Zhang [44], 2024,	Prosp cohort (TAHS). Inc: Participants of cohort with any cough at 53y.	Cohort enrolled at age 7y and FU at the mean age of 53y. Original cohort N=8583, study	"Explore cough subclasses in a	6 distinct cough subclasses: minimal cough n=206 (9.3%), cough with colds only n=1189 (53.7%), cough	"Clinical vigilance and close monitoring for	Community-based study showed that

Australia	Exc: Participant categorised as non-coughers at 53y.	group n=2213, mean age 53y, (range 51-55, SD 1), male n=1065 (48%).	community-based adult cohort" and "identify potential treatable traits of the identified subclasses by describing their clinical characteristics from childhood to adulthood".	with allergies n=305 (13.8%), intermittent productive cough n=213 (9.6%), chronic dry cough n=147 (6.6%), and chronic productive cough n=153 (6.9%). "Compared with 'minimal cough' group, those with intermittent productive cough and chronic productive cough subclasses had worse lung function trajectories (FEV_1 persistent low trajectory 2.9%, 6.4%, and 16.1%; p=0.0011, p<0.0001; FEV_1/FVC early low–rapid decline trajectory 2.9%, 12.1%, and 13.0%; p=0.012, p=0.0007) and a higher prevalence of cough (age 53y 0.0%, 32.4% [26.1–38.7], and 50.3% [42·5–58·2]) and asthma (age 53y 6.3% [3.7–10.6], 26·9% [21.3–33.3], and 41.7% [24.1–49.7]) from age 7 to 53y".	potential lung function impairment could provide opportunities for early intervention or prevention. Lung function should be assessed routinely when evaluating or managing adults with productive cough, including in primary care".	adults at mid-age (51-55y) who have intermittent or chronic productive cough have often coughed from childhood and have worse outcomes compared to those with minimal cough.

*Overlapping data as these studies are from the same cohort.

b/w=between, CAC=coronary artery calcium, CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease, CV=cardiovascular, CVD=cardiovascular disease, ECG=electrocardiogram, Exc=exclusion, FEV_1=forced expiratory volume in 1-second, FU=follow-up, FVC=forced vital capacity, Inc=inclusion, mo=months, LV=left ventricular, MRC=Medical Research Council, Prosp=prospective, SD=standard deviation, TAHS=Tasmanian Longitudinal Health Study, y=year(s).

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