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Childhood ‘bronchitis’ and respiratory outcomes in middle-age: a prospective cohort study from age 7 to 53 years


ABSTRACT

Background Chronic bronchitis in childhood is associated with a diagnosis of asthma and/or bronchiectasis a few years later, however, consequences into middle-age are unknown.

Objective To investigate the relationship between childhood bronchitis and respiratory-related health outcomes in middle-age.

Design Cohort study from age 7 to 53 years.

Setting General population of European descent from Tasmania, Australia.

Participants 3202 participants of the age 53-year follow-up (mean age 53, range 51–55) of the Tasmanian Longitudinal Health Study cohort who were born in 1961 and first investigated at age 7 were included in our analysis.

Statistical methods Multivariable linear and logistic regression. The association between parent reported childhood bronchitis up to age 7 and age 53-year lung conditions (n=3202) and lung function (n=2379) were investigated.

Results Among 3202 participants, 47.5% had one or more episodes of childhood bronchitis, classified according to severity based on the number of episodes and duration as: ‘non-recurrent bronchitis’ (28.1%); ‘recurrent non-protracted bronchitis’ (18.1%) and ‘recurrent-protracted bronchitis’ (1.3%). Age 53 prevalence of doctor-diagnosed asthma and pneumonia (p-trend <0.001) and chronic bronchitis (p-trend=0.07) increased in accordance with childhood bronchitis severities. At age 53, ‘recurrent-protracted bronchitis’ (the most severe subgroup in childhood) was associated with doctor-diagnosed current asthma (OR 4.54, 95% CI 2.31 to 8.91) doctor-diagnosed pneumonia (OR=2.18 (95% CI 1.00 to 4.74)) and, paradoxically, increased transfer factor for carbon monoxide (z-score +0.51 SD (0.15–0.88)), when compared with no childhood bronchitis.

Conclusion In this cohort born in 1961, one or more episodes of childhood bronchitis was a frequent occurrence. ‘Recurrence-protracted bronchitis’, while uncommon, was especially linked to multiple respiratory outcomes almost five decades later, including asthma, pneumonia and raised lung gas transfer. These findings provide insights into the natural history of childhood ‘bronchitis’ into middle-age.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Severe early childhood bronchitis manifested by recurrent episodes of protracted wet cough is associated with asthma and bronchiectasis in later childhood.

WHAT THIS STUDY ADDS

⇒ This is the first very long-term prospective study that has examined the relationship between childhood bronchitis severity with adult lung health outcomes. ‘Recurrent-protracted bronchitis’ in childhood, while uncommon, was associated with multiple respiratory outcomes in middle-age including asthma, pneumonia and raised lung gas transfer on lung function measurement.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ This study’s findings support the need for increased vigilance in monitoring young children who have multiple episodes of protracted bronchitis for potential asthma, pneumonia and bronchiectasis up to mid-adult life, confirmed with objective testing.

INTRODUCTION

‘Bronchitis’ implies airway inflammation. However, historically, the term bronchitis in childhood has been applied broadly to bouts of coughing without implying a specific cause or diagnosis, for example, asthma or bacterial bronchitis. Clinicians have previously believed ‘wheezy bronchitis’ or the other hand, signifies asthma. However, the terminology and understanding of the causes of paediatric cough has since evolved significantly and the paradigm has changed. It is now recognised and accepted that ‘chronic cough’ in children, that is, cough lasting >4 weeks, can be caused by a range of pathologies including protracted bacterial bronchitis (PBB), bronchiectasis, asthma and tracheo/
bronchomalacia. Furthermore, wheeze and cough can be common to all of these conditions.\(^3\)\(^4\)

PBB, also known as chronic bacterial bronchitis, is recognised as a discrete diagnostic entity by Respiratory Societies across Europe,\(^3\) the USA\(^5\) and Australia/New Zealand. PBB is defined as presence of a chronic ‘wet’ cough that lasts 1 month or more and resolves with 2–4 weeks of appropriate antibiotic therapy, in the absence of indicators to suggest another cause for the cough.\(^7\)\(^8\)

Prospective paediatric cohort studies have described a link between PBB and both bronchiectasis and asthma, with 27% of children with PBB having an asthma phenotype 5 years later\(^9\) and 8%–10% having bronchiectasis within 2–5 years.\(^9\)\(^10\) Whether chronic bronchitis (CB) in childhood is associated with poor lung health in adulthood is unknown and represents an important research priority, with potential to improve outcomes through earlier recognition and management.\(^5\)

Longitudinal cohort studies from early life to adulthood have provided important insights into lung disease development\(^11\) and are closing the gap in understanding between paediatric and adult respiratory medicine.\(^12\)

While several studies have supported the role of early life exposures in adult lung function deficits and chronic obstructive pulmonary disease (COPD),\(^13\)\(^–\)\(^18\) the early origins of adult chronic productive cough (or CB) remain poorly understood and sparsely studied.\(^19\)

Using population-based data from our Tasmanian Longitudinal Health Study (TAHS) longitudinal cohort, we aimed to investigate trends and associations between bronchitis severity at age 7 in childhood and respiratory health outcomes of asthma, CB, pneumonia and lung function in middle-age at age 53.

**METHODS**

**Study design and population**

Our study sample included participants of the TAHS cohort (1968–2016) who took part in the original assessments at age 7 and were followed up at the mean age of 53 years (details published elsewhere\(^18\)\(^–\)\(^22\)). Tasmania is an island State of Australia located 240 km to the south of the Australian mainland, which is the least populated and marginally the poorest state by gross product per capita, with relatively high rates of smoking and historically, less accessible healthcare facilities for a developed country. Briefly, this population-based cohort of participants essentially from European descent were born in 1961 and first studied including retrospective questionnaire data in 1968 (aged 6–7 years, n=8583), was retraced (n=7312) and resurveyed by a postal survey questionnaire in 2004 at mean age 43 years (n=5729) with further clinical testing. Subsequently, 6127 (71.4%) of the full original cohort were retraced and invited to participate in a clinical follow-up between 2012 and 2016. At mean age=53, 3609 (58.9%) respondents completed the questionnaire and 2719 (43.9%) underwent lung function testing including prebronchodilator/postbronchodilator spirometry and lung gas transfer measurements, on average 46 years later (figure 1). To minimise lost to follow-up, methods of tracing included computer linkage to the National Health Index, Commonwealth Electoral Roll, Medicare database, Tasmanian marriage records,\(^23\) and via siblings and parents who were also part of the original 1968 survey, and multiple attempts at contacting participants may have been required. Over 70% of the original participants still resided in Tasmania, with migration mainly to the East Coast of Australia and fewer than 0.5% now living overseas.
Data collection methods
Details of lung function testing have been described and summarised in online supplemental methods E1a. Lung function testing was standardised across testing sites in accordance with the 2005 American Thoracic Society/European Respiratory Society (ATS/ERS) standards. For this analysis, lung function data at age 7 and 53 years were converted to z-scores (ie, SD or SD units) using established standard reference values. Airflow obstruction was defined by forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) <lower limit of normal (LLN), and spirometric restriction by post-BD FVC <LLN and FEV₁/FVC ≥ LLN.

Definition
Exposure
Childhood bronchitis (or ‘wet’ cough as current clinical definitions) was defined by an affirmative response by parents/guardian to the 1968 survey question by age 7: ‘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)’? Based on the number of episodes and duration of attacks, those with childhood bronchitis was divided into three severity groups based on predetermined categories at the time of the 1968 survey: the non-recurrent subgroup had between one and five episodes only of any duration; the recurrent group had ≥6 episodes lasting <1 month on average; and the recurrent-protracted subgroup had either ‘continuous’ symptoms or ≥6 episodes each lasting an average of a month or more.

Outcomes
Adult lung conditions, current CB, which was a subset of those reporting ever-CB, was defined by the presence of a ‘usual’ cough with sputum (phlegm) for at least 3 months for the last two consecutive years at age 53. Asthma—current at age 53 was defined by a past doctor diagnosis of asthma associated with asthma-like symptoms, asthma medication use and/or related healthcare utilisation within 12 months prior to testing.

Online supplemental methods E1b provides further details for the exposure, other outcomes, confounders and effect modifier/s.

Statistical methods
Analyses were carried out using Stata (V.16, Stata). Our exposure, CB, included four categories as defined above, that is, no CB, non-recurrent bronchitis, recurrent non-protracted bronchitis, and recurrent-protracted bronchitis. Univariable trends of continuous/categorical respiratory outcomes were examined across these ordered categories (non-parametric trend tests (nptrend) / univariable logistic regression, respectively). This latter trend estimate approach assumes the relationship between the exposure expressed as an ordered variable attached to numerical values is linearly related to the outcome.

Using complete cases, multivariable linear and logistic regression were used to examine associations between CB and with continuous and categorical respiratory outcomes respectively. For the lung function outcomes, the regression coefficients represented the associations between exposure categories and lung function values expressed as z-scores (SD units) which accounted for age, sex and height (online supplemental methods E2a).

We chose ‘no childhood bronchitis’ as the reference exposure category so differences between categories of childhood bronchitis severity were only relative to the reference group and not compared directly. To interpret differences between childhood bronchitis categories, the absolute numbers of participants estimated to have the lung condition at age 53 were calculated using the ‘margins’ command following the syntax for the separate multivariable regression analyses.

Informed by conceptualising the models using a directed acyclic graph, regression models were adjusted for paternal occupation, parental bronchitis, rurality of primary school, number of siblings and parental smoking when participants were aged 7, plus male/female for the non-lung function analyses (online supplemental methods E1b and E2b).

Childhood asthma, pneumonia-pleurisy and pre-BD FEV₁ at 7 years (ie, non-discriminatory for obstructive and restrictive lung function deficits) partly mediated relationships of corresponding adult outcomes as per causal mediation analyses (online supplemental methods E2c, table E1), thus were not included as model covariates. Mediation by FEV₁/FVC was possible but was not additionally performed. As childhood asthma/wheezeing, ever-smoking and participant sex could plausibly strengthen the exposure/outcome relationships, corresponding interaction terms were used for the following reasons: to exclude the possibility that adult asthma was only related to participants who also wheezed in childhood; to assess whether the association with adult CB was related to adult cigarette smoking; and, because of known sex differences in lung function and asthma development. Sensitivity analyses that excluded participants who self-recalled asthma-ever and doctor-diagnosed pneumonia-ever before age 7 were performed (referred to as ‘recalled’ asthma and pneumonia, respectively).

A cut-off of p<0.10 for interactions was used to assess for effect modification as this was a low powered statistical test. A z-score of >0.5 SD and absolute increase in FEV₁ of 200 mL and 12% post-BD were considered clinically significant.

Patient and public involvement
Patients, TAHS participants or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.
RESULTS
Childhood sociodemographic and clinical characteristics
Among 3202 participants who had complete questionnaire data when aged 53, 47.5% had one or more episodes of childhood bronchitis (Table 1). The prevalence of non-recurrent and recurrent but non-protracted bronchitis was 28.1% (95% CI 26.6% to 29.7%) and 18.1% (95% CI 16.7% to 19.4%), respectively. The prevalence of 1.31% (95% CI 0.94% to 1.77%) for recurrent-protracted bronchitis was similar to that of the 2379 participants with complete lung function data (1.18% (95% CI 0.78% to 1.70%), online supplemental table E2) and the original 1968 cohort (1.21% (95% CI 0.98% to 1.47%), where n=101 of n=8583 = 1.18%).

Minor differences in baseline characteristics at age 7 for those who did not participate in the subsequent follow-up and/or who had missing data at age 53 were seen, namely males of lower socioeconomic status were less likely to have data available (online supplemental results E1, table E2a). The differences between exposure groups and subsequent participation were also only modest, especially for the recurrent-protracted subgroup for which the percentages participating and not participating varied between 1.2% and 1.3%. There was little difference in the prevalence of doctor-diagnosed asthma as a proxy outcome at mean age 43 years, and the reduced participation by those with self-reported CB was not significant (online supplemental table E2b).

At age 7, participants with recurrent childhood bronchitis, with or without protracted episodes, were more likely to be male (Table 1). Children with a history of bronchitis trended to have fewer siblings and fewer
mothers of the recurrent-protracted group smoked regularly. Positive trends were seen across the childhood bronchitis severity subgroups with regard to an increasing prevalence of parental bronchitis and/or symptoms, coexistent asthma/wheezeing (ever and recurrent) and doctor-diagnosed pneumonia and/or pleurisy (p-trend <0.001, table 1).

Middle-age sociodemographic and clinical characteristics
Similar positive trends across the childhood bronchitis severity subgroups were observed between and the actual and estimated prevalence of asthma-ever, current asthma and pneumonia-ever by middle-age (p-trend <0.001, tables 2 and 3, respectively). While the proportions of usual cough, usual phlegm at age 53 were higher in the recurrent-protracted group, trends did not attain statistical significance. Nevertheless, the prevalence for current CB was 2.4-fold higher in this severe compared with the no childhood bronchitis subgroup (12.0% compared with 5.0%, respectively, p-trend=0.07).

The prevalence of current smoking in individuals at age 53 was similar across childhood subgroups (~17%), although a disproportionately high percentage of participants in the recurrent-protracted group had ever-smoked (83% compared with ≤60%, table 2). Clear positive trends across childhood bronchitis severity subgroups were also seen for transfer factor of the lung for carbon monoxide (TLco) and its coefficient (Kco) with a modest inverse trend for alveolar volume. There were similar trends for lower pre- and post-bronchodilator FEV1 and FEV1/FVC at age 53 (p-trend between 0.005 and 0.042, table 2). These trends were somewhat stronger when participants underwent spirometry when aged 7 (pre-BD FEV1 p-trend=0.004; FEV1/FVC p-trend <0.001).

Main associations
Using multivariable regression, compared with no childhood bronchitis, all three childhood bronchitis (non-recurrent, recurrent non-protracted and recurrent-protracted) subgroups were associated with both doctor-diagnosed current and ever-asthma in middle-age. These associations increased in strength in a dose response manner as severity increased (table 4). Compared with no bronchitis, increasing childhood bronchitis severity was associated with recalled doctor-diagnosed pneumonia after 7 years (p=0.032, p<0.001, p=0.05, respectively).

For spirometry outcomes at age 53, compared with no childhood bronchitis, associations were observed for the recurrent (non-protracted) childhood bronchitis subgroup with regards to a significant association with pre-BD airflow obstruction and lower post-BD FEV1/FVC taken as a continuous variable and paradoxically, a borderline association with spirometric restriction (table 5). Recurrent-protracted childhood bronchitis was associated with significantly higher levels of Tlco and Kco but not alveolar volume in middle-age.

Effect modification
Among those without childhood asthma/wheezeing, the odds for current asthma at age 53 were higher for participants with recurrent-protracted childhood bronchitis (OR 4.29 (95% CI 1.45 to 12.6), p=0.008), p-interaction=0.063, online supplemental table E3) although case numbers in the recurrent-protracted subgroup were relatively few (5-10 cases).

To contrast the above-mentioned finding, interactions were consistently seen between childhood bronchitis and childhood asthma/wheezeing with regards to lung function measures used as continuous variables in middle-age, namely pre-BD FEV1, change in FEV1, post-BD, pre-BD FEV1/FVC, and post-BD FEV1/FVC (p-interaction <0.1, online supplemental results E2, table E4). When the analysis was stratified by presence of childhood asthma/wheezeing, compared with no childhood bronchitis, only participants with 1–5 episodes of any duration (ie, non-recurrent group) had non-obstructive lung function changes: reduced post-BD FVC (z-score –0.42 SD (95% CI –0.72 to –0.12), p=0.006), increased pre-BD FEV1/FVC (+0.43 (95% CI +0.11 to +0.74), p=0.008) and post-BD FEV1/FVC (+0.33 (95% CI +0.01 to +0.66), p=0.043) despite an increased pre-BD FEV1. There was also an associated threefold decrease in the odds for pre-BD airflow obstruction (OR 0.34 (95% CI +0.14 to +0.87), p=0.024), but there were too few cases to assess spirometric restriction as the outcome.

Despite few case numbers for the recurrent-protracted childhood bronchitis subgroup, associations with pneumonia-ever by age 53 were still seen for females (online supplemental results E3, table E5) and with current CB for middle-aged non-smokers (online supplemental results E4, table E6).

DISCUSSION
Using data from our whole-of-community cohort of European descent born in 1961, parent-reported childhood ‘bronchitis’ (and/or coughing phlegm, or ‘loose or rattly’ cough) was associated with consequential lung outcomes in middle-age, with significant trends for doctor-diagnosed asthma and pneumonia across the spectrum of cough-severity. Associations with doctor-diagnosed asthma and pneumonia were especially evident for the most severe subgroup termed ‘recurrent-protracted childhood bronchitis’. The findings of a low prevalence of CB and substantially higher lung gas transfer in mid-adult life for this subgroup have not previously been described. Similarly, the main association with a mixed obstructive/restrictive lung function pattern of modest magnitude for the subgroup with non-recurrent bronchitis episodes was also unexpected and probably not clinically important. Overall, we provide evidence to support childhood bronchitis as a contributor to clinical lung disease in mid-adult life, especially when chronic, recurrent and protracted.

Unexpectedly, a history of recurrent-protracted bronchitis in childhood was not strongly associated with CB in middle-age. Therefore, we postulate that only a relatively small subgroup at most may have had persistent productive cough episodes spanning childhood to mid-adult life, with adult CB mainly influenced by two age-related factors. Analogous to asthma remission that is common in later childhood and adolescence, most children seem to ‘grow out of’ bronchitis during their late childhood or early adolescent years\(^9\)\(^{32}\) that could be in part explained by...
by immune system maturation. Equally, CB most commonly develops during the productive working years of an adult resulting from environmental exposures e.g. cigarette smoking and/or air pollutants in the workplace, which is in keeping with CB-onset in adulthood.

Interestingly, among those most affected by childhood bronchitis, we found associations with current asthma in middle-age which were evident even for participants without a history of childhood asthma/wheezeing at age 7. This suggests that a predisposition to multiple and protracted episodes of childhood bronchitis could lead to damaged airways, and that a degree of airway narrowing from remodelling could impair normal airway development to manifest as symptomatic asthma in later life. As we were unable to tease out the precise overlaps between PBB, virus-associated wheeze and classic allergic asthma with regard to childhood wheezing, this prompted us to perform the analysis within strata of childhood asthma/wheezeing. In this interaction analysis, we were still able to detect a significant association between the severe recurrent-protracted bronchitis subgroup and adult asthma for those who did not have parent-reported asthma and/or wheezing in childhood, suggesting the observed association could be independent of childhood asthma.

In contrast, we also found lung function deficits, for example, decrease in the odds for airflow obstruction for the subgroup with non-recurrent bronchitis episodes and coexistent childhood asthma/wheezeing, but there was limited power to detect coexistent spirometric restriction. While we cannot draw firm conclusions, these findings are consistent with the Tucson Children’s Respiratory Study (TCRS). The TCRS accurately defined ‘other lower respiratory illnesses (LRIs) by age 3’ after excluding radiologically confirmed pneumonia and found a main association with active wheeze but not physician-diagnosed asthma by age 30 (n=738), however, did not stratify analyses by childhood asthma/wheeze status. These authors also found consistent reductions in FEV, FVC of around 120mL prebronchodilator and postbronchodilator in those with LRIs in early life, which could predispose individuals to COPD with a normal age-related decline if peak lung function was not attained from impaired lung function growth due to adverse exposures in utero and early childhood. The latter lung function finding is also consistent with our previous study that investigated the long-term outcomes of doctor-diagnosed childhood pneumonia and/or pleurisy and showed a restrictive lung function pattern on measures of static lung volumes in middle-age.

The observed ‘physiologically relevant’ elevations in lung transfer factor levels in the absence of increased alveolar volume for the severe recurrent-protracted subgroup could plausibly relate to the high observed prevalence of coexistent asthma/wheezeing in childhood and adulthood. However, this finding also raises the possibility of a vascular mechanism like that seen in bronchiectasis in which broncho-pulmonary anastomoses derived from an expansion of a collateral and high-pressure bronchial artery network diverts pulmonary artery blood flow away from diseased parts to better supply the normal lung, although the increase in bronchitic symptoms was only modest. Interestingly, lung transfer factor (T,co) can be high for adult patients at their first clinical presentation with bronchiectasis, which could be a feature prior to an accelerated decline which typically accompanies disease progression.

Our detailed questioning of parents of the 7-year-old children from a whole-of-community population allowed us to identify a severe subgroup that probably resembles PBB as closely as was possible without having data on antibiotic therapy and its response, given PBB was not
### Table 4  Multivariable main associations between increasing childhood bronchitis severity by age 7 and various lung conditions at age 53 years

<table>
<thead>
<tr>
<th>Lung condition at age 53</th>
<th>Cases (N)</th>
<th>Model N</th>
<th>Childhood bronchitis severity at age 7 (N=3202)†‡</th>
<th>Non-recurrent (n=902) Case (n) OR (95% CI)</th>
<th>Recurrent, non-protracted (n=578) Case (n) OR (95% CI)</th>
<th>Recurrent-protracted (n=42) Case (n) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB-current</td>
<td>158</td>
<td>3062</td>
<td>Case (n)</td>
<td>40 0.90 (0.67 to 1.22)</td>
<td>32 1.07 (0.76 to 1.50)</td>
<td>5 1.75 (0.75 to 4.08)</td>
</tr>
<tr>
<td>CB-ever</td>
<td>275</td>
<td>3085</td>
<td>Case (n)</td>
<td>72 0.84 (0.56 to 1.25)</td>
<td>59 0.93 (0.60 to 1.45)</td>
<td>7 1.94 (0.72 to 5.21)</td>
</tr>
<tr>
<td>Asthma-current</td>
<td>395</td>
<td>3178</td>
<td>Case (n)</td>
<td>116 1.48 (1.14 to 1.92)**</td>
<td>114 2.44 (1.85, 3.21)***</td>
<td>14 4.54 (2.31 to 8.91)***</td>
</tr>
<tr>
<td>Asthma-ever</td>
<td>804</td>
<td>3196</td>
<td>Case (n)</td>
<td>221 1.33 (1.11 to 1.57)**</td>
<td>238 2.75 (2.28 to 3.31)***</td>
<td>28 6.49 (3.44 to 12.2)***</td>
</tr>
<tr>
<td>≥7 years§</td>
<td>783</td>
<td>3196</td>
<td>Case (n)</td>
<td>221 1.41 (1.16 to 1.72)**</td>
<td>218 2.74 (2.21 to 3.41)***</td>
<td>28 8.19 (4.22 to 15.9)**</td>
</tr>
<tr>
<td>Pneumonia-ever</td>
<td>574</td>
<td>3188</td>
<td>Case (n)</td>
<td>174 1.43 (1.15 to 1.78)**</td>
<td>146 2.02 (1.58 to 2.57)***</td>
<td>15 3.19 (1.66 to 6.14)**</td>
</tr>
<tr>
<td>≥7 years§</td>
<td>460</td>
<td>3188</td>
<td>Case (n)</td>
<td>135 1.30 (1.02 to 1.65)*</td>
<td>111 1.79 (1.37 to 2.33)***</td>
<td>9 2.18 (1.00 to 4.74)†</td>
</tr>
<tr>
<td>&lt;7 years</td>
<td>114</td>
<td>3188</td>
<td>Case (n)</td>
<td>39 2.21 (1.38 to 3.56)**</td>
<td>35 3.39 (2.05 to 5.60)***</td>
<td>6 9.80 (3.70 to 25.9)**</td>
</tr>
</tbody>
</table>

*P<0.05, **p<0.01, ***p<0.001.
†Parent-reported bronchitis by age 7 categorised into none (reference=1, not shown), non-recurrent, recurrent (>5 episodes of coughing phlegm or ‘loose, or rattly’ cough lasting <1 month on average), and recurrent-protracted (>5 episodes, ≥1 month average duration).
‡Multivariable models were adjusted for rurality of school, paternal occupation, family history of bronchitis, sibling number, maternal and paternal smoking, and participant sex.
§Doctor-diagnosed asthma | pneumonia recalled after childhood bronchitis was assessed that is, after age 7.
¶P=0.050.
CB, chronic bronchitis.
PBB are complicated by bronchiectasis within the next et al. 9: e001212. doi:10.1136/bmjresp-2022-001212. Notably, 8%–10% of children with pneumonia during an acute respiratory illness could rather have actually been bronchiectasis in our cohort.45 Nonetheless, the awareness of PBB as a treatable condition has ideally been performed to investigate this hypothesis. Although the main strength of our TAHS cohort is the prospective, longitudinal data collection over five decades used to evaluate relationships between childhood respiratory health and long-term respiratory outcomes. The comprehensive questioning allowed us to create severity categories for childhood cough phenotypes that identified some severity–outcome relationships which strengthens the argument for a causal association. Although the severe subgroup with recurrent-protracted childhood bronchitis was small in this general population sample, there was sufficient statistical power to detect significant associations with long-term outcomes enhanced by a large reference group without bronchitis in childhood.

Regarding limitations, our study relied on parental report of their children’s health at age 7 and self-report of doctor-diagnosed conditions at mean age 53. We acknowledge the potential for misclassification of childhood bronchitis (and asthma/wheezing), which could have been overestimated or underreported by parents according to its severity, but this misreporting of information across multiple exposure groups would bias estimates towards the null as such misclassification is more likely to be non-differential. There was also potential for differential misclassification of the self-reported adult lung conditions by exposure status. However, with the 46-year lag between exposure and outcome measures and the likelihood of multiple intervening life events, such differential reporting by participants seemed unlikely. While a typical pattern of attrition was observed for males of lower socioeconomic class, the possibility of collider bias (from inappropriately controlling for a collider variable that is influenced independently by both the exposure

### Table 5 Multivariable main associations between increasing childhood bronchitis severity by age 7 and lung function at age 53 years

<table>
<thead>
<tr>
<th>Lung function† ‡</th>
<th>Case (n)</th>
<th>Model (N)</th>
<th>Non-recurrent (n=686)</th>
<th>Recurrent, non-protracted (n=427)</th>
<th>Recurrent-protracted (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-BD zFEV₁</td>
<td>–</td>
<td>2379</td>
<td>-0.02 (-0.22, +0.17)</td>
<td>-0.15 (-0.39, +0.08)</td>
<td>-0.10 (-0.88, +0.68)</td>
</tr>
<tr>
<td>Post-BD zFEV₁</td>
<td>–</td>
<td>2354</td>
<td>-0.09 (-0.19, +0.01)</td>
<td>-0.16 (-0.28, -0.05)**</td>
<td>-0.09 (-0.47, +0.29)</td>
</tr>
<tr>
<td>BDR Δ FEV₁ (mL)</td>
<td>–</td>
<td>2344</td>
<td>-4.8 (-17, +8)</td>
<td>-0.05 (-15, +15)</td>
<td>-0.10 (-50, +50)</td>
</tr>
<tr>
<td>Pre-BD zFVC</td>
<td>–</td>
<td>2378</td>
<td>-0.02 (-0.18, +0.13)</td>
<td>-0.10 (-0.28, +0.08)</td>
<td>+0.01 (-0.59, +0.62)</td>
</tr>
<tr>
<td>Post-BD zFVC</td>
<td>–</td>
<td>2354</td>
<td>-0.08 (-0.16, +0.01)</td>
<td>-0.09 (-0.19, +0.01)</td>
<td>-0.005 (-0.34, +0.33)</td>
</tr>
<tr>
<td>BDR Δ FVC (mL)</td>
<td>–</td>
<td>2343</td>
<td>-3.3 (-17, +11)</td>
<td>+8.7 (-8.1, +26)</td>
<td>-10 (-66, +46)</td>
</tr>
<tr>
<td>Pre-BD zFEV₁/FVC</td>
<td>–</td>
<td>2378</td>
<td>-0.03 (-0.12, +0.06)</td>
<td>-0.09 (-0.19, +0.02)</td>
<td>-0.19 (-0.54, +0.16)</td>
</tr>
<tr>
<td>Pre-BD airflow obstruction††</td>
<td>191</td>
<td>2378</td>
<td>1.12 (0.79–1.61)</td>
<td>1.64 (1.11–2.40)*</td>
<td>§</td>
</tr>
<tr>
<td>Post-BD zFEV₁/FVC</td>
<td>–</td>
<td>2354</td>
<td>-0.03 (-0.11, +0.06)</td>
<td>-0.12 (-0.22, -0.02)*</td>
<td>-0.15 (-0.49, +0.19)</td>
</tr>
<tr>
<td>Post-BD airflow obstruction**</td>
<td>103</td>
<td>2342</td>
<td>1.16 (0.72–1.87)</td>
<td>1.46 (0.87, 2.47)</td>
<td>§</td>
</tr>
<tr>
<td>Spirometric restriction**</td>
<td>53</td>
<td>2239</td>
<td>1.67 (0.89–3.11)</td>
<td>1.99 (0.97–4.01)††</td>
<td>§</td>
</tr>
<tr>
<td>zTCo</td>
<td>–</td>
<td>2285</td>
<td>+0.03 (-0.06, +0.12)</td>
<td>+0.09 (-0.02, +0.20)</td>
<td>+0.51 (+0.15, +0.88)**</td>
</tr>
<tr>
<td>zKco</td>
<td>–</td>
<td>2285</td>
<td>+0.05 (-0.04, +0.15)</td>
<td>+0.18 (+0.06, +0.29)**</td>
<td>+0.51 (+0.13, +0.89)**</td>
</tr>
<tr>
<td>zVA</td>
<td>–</td>
<td>2285</td>
<td>-0.02 (-0.11, +0.07)</td>
<td>-0.09 (-0.20, +0.02)</td>
<td>+0.06 (-0.30, +0.42)</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01.
†Parent-reported bronchitis by age 7 categorised into none (reference=1), non-recurrent, recurrent (>5 episodes of coughing per month on average), and recurrent-protracted (>5 episodes, >1 month average duration).
‡Multivariable models were adjusted for rurality of school, paternal occupation, family history of bronchitis, sibling number, maternal and paternal smoking, and participant sex.
§Cells that had <5 cases; see table 2 for case numbers.
¶Lung function measured in z-scores, which, by definition, has a mean of 0 and SD of 1.
**ORs: pre-BD airflow obstruction (zFEV₁/FVC <LLN); spirometric restriction (post-BD zFVC <LLN and zFEV₁/FVC ≥LLN).
††P=0.050.
BD, bronchodilator; BDR, bronchodilator response; CB, chronic bronchitis; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; Kco, carbon monoxide transfer coefficient; LLN, lower limit of normal; TCo, carbon monoxide transfer factor of the lung; VA, alveolar volume.

defined until 2016.7 Notably, 8%–10% of children with PBB are complicated by bronchiectasis within the next 5 years, which raises the possibility that some positive auscultatory signs heard by a medical practitioner who diagnosed pneumonia during an acute respiratory illness could rather have actually been bronchiectasis in our most severe subgroup and high resolution CT scans would have ideally been performed to investigate this hypothesis. Nonetheless, the awareness of PBB as a treatable and preventable cause of bronchiectasis is crucial especially for some socially disadvantaged communities, for example, Indigenous Australian populations.

The main strength of our TAHS cohort is the prospective, longitudinal data collection over five decades used to evaluate relationships between childhood respiratory health and long-term respiratory outcomes. The comprehensive questioning allowed us to create severity categories for childhood cough phenotypes that identified some severity–outcome relationships which strengthens the argument for a causal association. Although the severe subgroup with recurrent-protracted childhood bronchitis was small in this general population sample,
and outcome) is not likely because the prevalence of proxy outcomes 10 years earlier were largely unaffected and the loss to follow-up was similar between the exposure groups. Although several hypotheses were tested, these were predetermined by their biological plausibility based on previous literature and so we interpreted the general pattern of results rather than focusing on individual p values or using a Bonferroni correction. Finally, the Australian participants included in this study were almost exclusively of European ethnicity and in this era (born 1961) were not routinely immunised against common childhood pathogens, for example, measles, pneumococcus and *Haemophilus influenzae* type B. This may limit the generalisability of our findings to later birth cohorts and other ethnic groups in the vaccination era.

**CONCLUSION**

In summary, our findings suggest associations between childhood ‘bronchitis’ and doctor-diagnosed pneumonia and asthma in adulthood, especially evident for the recurrent-protrated subgroup, with trends across the spectrum of cough severity. The elevation of lung gas transfer in middle-age for this recurrent-protrated group is interesting and may be explained by asthma, chronic vascular changes and/or mild bronchiectasis; where possible, replication in other similar cohorts and further research to establish its clinical significance is warranted. Collectively, these findings provide novel insights into the potential natural history of severe bronchitis in children. Importantly, they support initiatives to enhance awareness among primary care physicians to promote the timely diagnosis and management of protracted episodes of cough in children with close monitoring for subsequent development of asthma and other complications such as bronchiectasis.

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**Contributors**

The authors alone are responsible for the content and writing of the article. SCD, EHW, MJA, JLH, PST, GH, BE, LG and JLP were involved in acquiring funding and/or establishing study directions and protocols. The data was acquired by SCD, EHW, MJA, PST and BRT. JLP led the analysis and interpretation of data with support especially from SCD, DW and ABC, as well as MAR, A.J., C.J., DSB and GB. JLP wrote the initial draft of the manuscript, which was critically revised for important content by all authors, especially DW, ABC and EHW. All authors approved the submission of the manuscript. JLP is acting guarantor who accepts full responsibility for the work and/or conduct of the study, had access to the data, and controlled the decision to publish.

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**Competing interests**

JP, AL, CL, DB, EHW, MJA and SCD have received an investigator-initiated grant from GlaxoSmithKline for unrelated research, and SCD holds a similar grant from AstraZeneca. MJA also holds investigator-initiated grants from Pfizer, Boehringer-Ingelheim and Sanofi for unrelated research; has undertaken an unrelated consultancy and received assistance with conference attendance from Sanofi; and received a speaker’s fee from GlaxoSmithKline. ABC is on independent data safety and monitoring boards for a SRAs-COVID vaccine (Moderna), an unlicensed RSV vaccine (GSK) and monoclonal antibody (AstraZeneca), where the monies are received by her institution. BRT serves on the medical advisory boards of Chiesi Australia and 4D Medical and has received an unrelated consultancy from GlaxoSmithKline and speaker fees from Mundipharma. AL has received investigational product (EpiCeram TM) free of charge from Primus Pharmaceuticals for use in unrelated research. DW has received consultancy fee from MSD for participation on an expert input forum, outside the submitted work.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Ethics approval**

This study was approved by Human Ethics Review Committees at all participating institutions, principally the Universities of Melbourne (040375) and Tasmania (H0012710). Written informed consent was obtained from all participants.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data availability statement**

Data are available on reasonable request. TAHS is a cohort study with data that has been prospectively collected since 1968 and will be an ongoing resource for future epidemiological analyses. Data collection protocols have been detailed in the TAHS cohort profile paper published in 2016 (Matheron et al. 2016 doi: 10.1093/ije/dyw028). The raw data have not been made widely applicable.

**Supplemental material**

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SUPPLEMENTARY INFORMATION

Childhood “bronchitis” and respiratory outcomes in middle-age: a prospective cohort study from age 7 to 53 years


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Methods E1. Data collection and additional clinical definitions

E1a. Spirometry testing

*Pre- and post-BD spirometry* was performed using the EasyOneTM ultrasonic Spirometer (ndd, Medizintechnik, AG, Switzerland). Participants were asked not to smoke for 4-6 hours prior to testing. Each subject was required to perform at least three pre- and three post-BD trials that met American Thoracic Society (ATS) and European Respiratory Society (ERS) acceptability and repeatability criteria [1]. The highest value for FEV₁ and FVC from acceptable and repeatable trials was recorded. Spirometry was repeated ten minutes after the administration of 300μg of salbutamol via spacer.

E1b. Additional clinical definitions

*Exposure at age 7*

*Childhood bronchitis* was defined by an affirmative response by parents/guardian to the 1968 survey question: “Has he/she at any time in his/her life suffered from attacks of bronchitis or attacked of cough with sputum (phlegm) in the chest ("loose" or “rattly” cough)?”. *Childhood bronchitis frequency* was defined by responses to the question: “Since the attacks began, approximately how many has he/she had altogether?”, with the following options: one attack only; 2-5 attacks; 6-10 attacks; 11-20 attacks; and over 20 attacks. *Childhood bronchitis duration* was defined by: “On average (as near as you can say), how long do these attacks usually last (with usual treatment)?”, with the following options: less than 12 hours; a day; a week; a month; “continuous” (never from of loose cough for more than a day or two). The four mutually exclusive groups were defined using these two stem questions (see 4-level definition in the main text). A cut-off of >5 episodes of at least one month duration was used because there were two few participants to conduct the analysis with a single episode as an intermediate category.

Only for the mediation analyses, childhood bronchitis as the exposure was expressed as a binary variable, defined by five or more episodes of any duration by age seven.

*Other outcomes at age 53*

*Chronic bronchitis-ever* was defined by affirmative responses, “Have you, at any time in your life, suffered from with phlegm (sputum) in the chest (with or without a cold)” and “Have you had this cough with phlegm on most days for at least three months and for two years in a row?” at age 53.
Doctor-diagnosed asthma-ever was defined by the self-report of “ever having asthma” that was “confirmed by a doctor” at age 53. Doctor-diagnosed ever-asthma after 7 years was the age of asthma onset recalled by the participant during middle-age (either at mean age of 43 or 53 years).

Doctor-diagnosed pneumonia-ever was defined by the self-report of “ever having pneumonia” that was “confirmed by a doctor” at age 53. Doctor-diagnosed ever-pneumonia occurring ‘before age 7’ and ‘at or after age 7’ was recalled by the participant during middle-age (at mean age 53).

Confounders at age 7
The occupation of the participants’ fathers when they were seven-years old was used as a proxy for socioeconomic class (1968), coded in accordance with the Australian Standard Classification of Occupations (ASCO) four-digit codes [2]. For paternal occupation, these codes were then grouped into five major skill groups: i) Managers/ professionals; ii) Associate professionals; iii) Tradespersons and advanced clerical; iv) Intermediate clerical and production; v) Elementary clerical, labourers, and related workers.

Rurality was assigned to the school attended by the participant at the time of the original 1968 survey. Categories included “inner regional Australia”, “outer regional Australia”, “remote Australia”, and “very remote Australia” [3]. These categories were derived directly from pre-specified options of the questionnaire.

Maternal and paternal smoking were defined by an affirmative response of the respective parent or guardian to the 1968 survey question “Do you smoke every day (or six days out of seven)”; and if yes, then “How much do you smoke?” followed by three options: “more than 20 cigarettes a day; six to 20 cigarettes a day; less than 6 cigarettes a day”. These categories were derived directly from pre-specified options of the questionnaire.

Parental history of bronchitic symptoms was defined by answers to the 1968 survey questions of mothers and fathers (or guardians) separately which included: 1) Do you suffer from chronic bronchitis, or from more than one attack of bronchitis every three years or so? Or, 2) Do you usually have a cough either first thing in the morning or some time during the day? Or, 3) Do you usually clear or bring up some phlegm (sputum) from your chest in the morning or some time during the day, where “usually” means on three or four days in the week, or for three or four months of the year. A positive family history was defined by at least one parent who self-reported at least one of cough, sputum, or bronchitis at the same time as reporting bronchitic episodes for their child who participated in the TAHS study.
Effect modifiers (in addition to sex-differences)

**Childhood asthma/wheezing** was defined by the presence of asthma and/or wheezy breathing within the preceding 12 months in response to the 1968 survey question, “Has he/she at any time in his/her life suffered from attacks of asthma or of wheezy breathing?”

**Ever-smoking** was defined by self-reporting the equivalent of smoking 100 cigarettes during their lifetime. A distinction between current and past smoking was not relevant to the interaction analysis.

Methods E2. Additional statistical methods

E2a. Derivation of lung function variables

Raw lung function values (measured in mL or as a ratio) were converted into z-scores using established reference values [4], with lung function expressed as difference from the expected mean, in standard deviation units, based on the individuals age, sex, height and ethnicity. The z-score values for each participant were then used as the outcome in linear regression models. As such, the coefficients represent the associations between exposures and lung function values expressed as z-scores (standard deviation units); i.e. the coefficient represents the change in z-score for each continuous lung function outcome for the exposed category compared with the reference category.

E2b. Selection of confounder variables

Regression models were adjusted for potential confounders of the bronchitis-respiratory outcome relationship including paternal occupational class [2], parental history of bronchitic episodes and symptoms that was prospectively-collected, rurality of primary school, sibling number and sex for the non-lung function analyses. These were informed via a directed acyclic graph drawn in Daggity [http://www.dagitty.net/](http://www.dagitty.net/) (see figure below).

Parental smoking at age seven was included in models, although its true temporality with childhood bronchitis could not be confirmed. Linearity when the sibling number variable was expressed as quintiles was confirmed using the fp command in Stata (data not shown).
Figure: Directed acyclic graph
E2c. Mediation analyses

Childhood asthma, pneumonia-pleurisy FEV$_1$ at seven years were considered as potential confounders for corresponding adult outcomes, however, these factors were confirmed to be intermediaries and/or mediators of the relationship via causal mediation analysis using the medeff command in Stata [6, 7]. Therefore, the analyses of asthma and lung function outcomes were stratified by childhood asthma/wheezy breathing.

Table E1. Mediation of the childhood bronchitis-adult lung outcome relationships by the corresponding pneumonia/asthma/lung function feature at age 7

<table>
<thead>
<tr>
<th>Lung outcome in middle-age</th>
<th>Mediation analysis effect [% (95%CI)] †‡</th>
<th>% of total effect mediated §</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indirect effect</td>
<td>Direct effect</td>
</tr>
<tr>
<td>Dr-diagnosed pneumonia-ever</td>
<td>+2.45 (1.3-4.7)</td>
<td>+4.98 (1.5-8.8)</td>
</tr>
<tr>
<td>Dr-diagnosed asthma-ever</td>
<td>+13.25 (9.4-16.8)</td>
<td>+8.32 (4.4-12.5)</td>
</tr>
<tr>
<td>Current asthma</td>
<td>-3.13 (-7.3, +0.6)</td>
<td>-5.30 (-29, +17)</td>
</tr>
<tr>
<td>Pre-BD FEV$_1$</td>
<td>+2.16 (-1.8, +6.1)</td>
<td>-6.47 (-25, +11)</td>
</tr>
<tr>
<td>Pre-BD FVC</td>
<td>-7.40 (-11, -4.3)</td>
<td>+2.28 (-7.6, +11)</td>
</tr>
<tr>
<td>Post-BD FEV$_1$/FVC</td>
<td>-3.38 (-7.3, +0.3)</td>
<td>-2.19 (-13, +7.7)</td>
</tr>
<tr>
<td>Post-BD FVC</td>
<td>+1.92 (-2.2, +5.8)</td>
<td>-3.02 (-12, +5.3)</td>
</tr>
<tr>
<td>Post-BD FEV$_1$/FVC</td>
<td>-7.81 (-11, -4.6)</td>
<td>-0.45 (-10, +8.6)</td>
</tr>
</tbody>
</table>

Definitions of Abbreviations: BD, bronchodilator; FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity
† Of the two ‘average causal mediation effects’, the lowest indirect effect estimate was used
‡ Adjusted for sex, paternal occupation, family history bronchitis, rurality of school, parental smoking, sibling number, and childhood asthma for the adult asthma outcomes
§ % mediated of total effect was not estimated for analyses in which there were opposing direct and indirect effects

Main findings from the mediation analyses:

- childhood asthma/wheeze was a partial mediator of the child bronchitis and adult asthma outcomes
- childhood pneumonia/pleurisy was a partial mediator of the child bronchitis and adult pneumonia outcome
• childhood FEV₁ was a stronger mediator of the child bronchitis and adult spirometry outcomes

Causal Mediation Analysis [6, 7] was used to determine the extent to which the total ‘effect’ of childhood bronchitis taken as a binary variable (≤5 and >5 episodes) on selected lung function outcomes was mediated by their corresponding childhood feature. Specifically, this relates to the relationship between childhood bronchitis and adult pneumonia-ever (mediated by childhood pneumonia-pleurisy); adult asthma (mediated by childhood asthma); and continuous adult lung function (mediated by childhood lung function, pre-bronchodilator). This analysis partitions the total effect into an indirect effect of childhood bronchitis on adult lung outcomes (childhood bronchitis acting through the mediator and then the mediator acting on the adult lung outcome) and a direct effect of childhood bronchitis on adult lung outcomes (that does not act through changes in the mediator induced by childhood bronchitis).

Notably, there was substantial mediation of relationships between childhood bronchitis and adverse lung outcomes in middle-age. For adult doctor-diagnosed pneumonia recalled in middle-age, the percent of the total effect mediated by childhood pneumonia/pleurisy was 31.1%. For adult doctor-diagnosed asthma, this was mediated by childhood asthma/wheezing by approx. 61%. Mediation for continuous lung function outcomes by childhood spirometry were variable, but the percent of total effect mediated for post-BD FEV₁/FVC levels was estimated to be as high as 94.6%.
### Results E1. Missing data

**Table E2a. Missing data from childhood in the entire TAHS cohort**

<table>
<thead>
<tr>
<th>Clinical feature in childhood N=8,583</th>
<th>Lung conditions reported at age 53 [n(%)]</th>
<th>Lung function measured at age 53 [n(%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete cases (n=3202)</td>
<td>Missing data (n=5381)</td>
</tr>
<tr>
<td>Childhood bronchitis</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>None</td>
<td>1680 (52)</td>
<td>2850 (55)</td>
</tr>
<tr>
<td>Non-recurrent (1-5 episodes, any duration)</td>
<td>902 (28)</td>
<td>1429 (28)</td>
</tr>
<tr>
<td>Recurrent (≥5 episodes), non-protracted</td>
<td>598 (18)</td>
<td>800 (16)</td>
</tr>
<tr>
<td>Recurrent, protracted</td>
<td>42 (1.3)</td>
<td>59 (1.2)</td>
</tr>
<tr>
<td>Age [years (SD)]</td>
<td>6.50 (0.3)</td>
<td>6.51 (0.3)</td>
</tr>
<tr>
<td>Sex [% male]</td>
<td>1576 (49)</td>
<td>2817 (52)</td>
</tr>
<tr>
<td>Rurality of School [n(%)]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Inner city</td>
<td>1868 (58)</td>
<td>3137 (60)</td>
</tr>
<tr>
<td>Outer regional</td>
<td>1238 (39)</td>
<td>1934 (37)</td>
</tr>
<tr>
<td>Remote</td>
<td>96 (3.0)</td>
<td>173 (3.3)</td>
</tr>
<tr>
<td>Paternal occupation [n(%)]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Managers/ professionals (highest)</td>
<td>795 (25)</td>
<td>875 (18)</td>
</tr>
<tr>
<td>Elementary clerical/ labour/ other (lowest)</td>
<td>379 (12)</td>
<td>779 (16)</td>
</tr>
<tr>
<td>Familial bronchitis [n(%)]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>One parent</td>
<td>1026 (32)</td>
<td>1650 (36)</td>
</tr>
<tr>
<td>Both parents</td>
<td>122 (3.8)</td>
<td>215 (4.7)</td>
</tr>
<tr>
<td>Mother’s smoking [n(%)]</td>
<td>1080 (34)</td>
<td>1953 (40)</td>
</tr>
<tr>
<td>Father’s smoking [n(%)]</td>
<td>1879 (59)</td>
<td>3006 (65)</td>
</tr>
<tr>
<td>Sibling number [mean (SD)]</td>
<td>2.6 (1.6)</td>
<td>2.4 (1.9)</td>
</tr>
<tr>
<td>Spirometry at age 7 (z-score)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>zFEV₁ [mean (SD)]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>zFVC [mean (SD)]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>zFEV₁/FVC [mean (SD)]</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: IQR, interquartile range, SD, standard deviation
† Chi-squared and nptrend tests were used to derive p-values*
For the present analysis, 45.1% (n=3,202) of the 7,099 participants of the original cohort who had complete childhood bronchitis data also had complete outcome and confounder data. While there was some variation in the prevalence of childhood bronchitis subgroups by missing data categories, there was little difference between the percentages missing for the main exposure subgroup of “recurrent-protracted” childhood bronchitis (1.2-1.3%).

Missing data of the confounding variables included 1.6% for rurality; 6.9% for occupation; 6.4% mother’s smoking; 8.6% father’s smoking and 8.8% familial bronchitis, and this was somewhat greater for male participants of lower socio-economic status with a familial history of bronchitis and parental smoking. However, for the recurrent-protracted childhood bronchitis group, this missing confounder data reduced the number of cases from 44 to 42 only.

Table E2b. Missing data and an earlier follow-up in middle-age (with some selection)

<table>
<thead>
<tr>
<th>Clinical feature at mean age 43 years (10 years prior to outcomes at age 53)</th>
<th>Lung conditions reported at age 53 [n(%)]</th>
<th>Lung function measured at age 53 [n(%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete cases (n=2957)</td>
<td>Missing data (n=2766)</td>
</tr>
<tr>
<td>Doctor-diagnosed asthma-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ever [n(%)]</td>
<td>654 (22)</td>
<td>591 (21)</td>
</tr>
<tr>
<td>Self-reported chronic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bronchitis [n(%)]</td>
<td>165 (5.6)</td>
<td>185 (6.8)</td>
</tr>
</tbody>
</table>

† Chi-squared tests were used to derive p-values

The differences in corresponding outcomes of doctor-diagnosed asthma-ever at an earlier time-point in middle-age as a proxy for the outcome at mean age 53 years, approx. 10 years later was not significant, and did not reach the p<0.05 threshold for self-reported chronic bronchitis.

Overall, substantial collider bias seems unlikely as participation was minimally associated with the exposure, or proxies of the outcome.
Results E2. Effect modification by childhood asthma/wheezing

Table E3: Interactions between the effects of childhood bronchitis on lung conditions in middle-age, by childhood asthma-wheezing status

<table>
<thead>
<tr>
<th>Lung condition at age 53</th>
<th>Cases (n)</th>
<th>No childhood asthma (n=2,652)</th>
<th>Childhood asthma (n=550)</th>
<th>p-int value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-recurrent (n=735)</td>
<td>Recurrent bronchitis (n=310)</td>
<td>Recurrent and protracted (n=17)</td>
</tr>
<tr>
<td>CB-current</td>
<td>158</td>
<td>0.85 (0.55–1.32)</td>
<td>0.79 (0.43–1.46)</td>
<td>§</td>
</tr>
<tr>
<td>CB-ever</td>
<td>275</td>
<td>0.84 (0.60–1.18)</td>
<td>0.86 (0.54–1.37)</td>
<td>§</td>
</tr>
<tr>
<td>Asthma-current</td>
<td>395</td>
<td>1.34 (1.00–1.82)</td>
<td>0.99 (0.63, 1.57)</td>
<td>4.29 (1.45–12.6) **</td>
</tr>
<tr>
<td>Asthma-ever</td>
<td>804</td>
<td>1.19 (0.98–1.44)</td>
<td>1.25 (0.96–1.63)</td>
<td>2.58 (1.07–6.21) *</td>
</tr>
<tr>
<td>From ≥ 7 years</td>
<td>783</td>
<td>1.21 (0.99–1.47)</td>
<td>1.26 (0.96–1.65)</td>
<td>2.67 (1.11–6.43) *</td>
</tr>
<tr>
<td>Pneumonia-ever</td>
<td>574</td>
<td>1.42 (1.12–1.81) **</td>
<td>1.71 (1.25–2.34) **</td>
<td>4.01 (1.49–10.8) **</td>
</tr>
<tr>
<td>From ≥ 7 years</td>
<td>460</td>
<td>1.30 (1.00–1.68) ^</td>
<td>1.67 (1.19–2.33) **</td>
<td>1.96 (0.53–7.25)</td>
</tr>
</tbody>
</table>

Definitions of abbreviations: BD, bronchodilator; CB, chronic bronchitis; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; OR, odds ratio; T̵co, carbon monoxide transfer factor of the lung

* p<0.06  ** p<0.05  *** p<0.01  **** p<0.001
† Parent-reported bronchitis by age 7 categorized into none (reference = 1, not shown), non-recurrent, recurrent (>5 episodes of “loose, or rattly” or chesty cough lasting <1 month on average), and recurrent-protracted (>5 episodes, ≥1 month average duration)
‡ Multivariable models were adjusted for rurality of school, paternal occupation, family history of bronchitis, sibling number, maternal and paternal smoking, and participant sex
§ Cells that had <5 cases and negative findings

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### Table E4: Interactions between the effects of childhood bronchitis on lung function in middle-age, by childhood asthma-wheezing status

<table>
<thead>
<tr>
<th>Lung function at age 53 §</th>
<th>Model (N)</th>
<th>No childhood asthma (n=1,983)</th>
<th>Childhood asthma (n=396)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-recurrent (n=559)</td>
<td>Recurrent bronchitis (n=233)</td>
</tr>
<tr>
<td>Pre-BD zFEV₁</td>
<td>2379</td>
<td>-0.11 (-0.28, +0.07)</td>
<td>-0.01 (-0.26, +0.23)</td>
</tr>
<tr>
<td>Post-BD zFEV₁</td>
<td>2354</td>
<td>-0.07 (-0.17, +0.03)</td>
<td>-0.03 (-0.17, +0.11)</td>
</tr>
<tr>
<td>BDR ΔFEV₁ (ml)</td>
<td>2344</td>
<td>-2.54 (-15.9, +10.8)</td>
<td>-10.48 (-29.1, +8.19)</td>
</tr>
<tr>
<td>Pre-BD zFVC</td>
<td>2378</td>
<td>-0.07 (-0.20, +0.07)</td>
<td>-0.03 (-0.22, +0.16)</td>
</tr>
<tr>
<td>Post-BD zFVC</td>
<td>2354</td>
<td>-0.05 (-0.14, +0.04)</td>
<td>-0.05 (-0.17, +0.08)</td>
</tr>
<tr>
<td>BDR ΔFVC (ml)</td>
<td>2343</td>
<td>-2.85 (-17.7, +12.0)</td>
<td>-9.39 (-30.2, +11.4)</td>
</tr>
<tr>
<td>Pre-BD zFEV₁/FVC</td>
<td>2378</td>
<td>-0.06 (-0.15, +0.03)</td>
<td>+0.03 (-0.10, +0.16)</td>
</tr>
<tr>
<td>Pre-BD airflow obstruction □</td>
<td>2378</td>
<td>1.28 (0.86–1.90)</td>
<td>1.19 (0.69–2.07)</td>
</tr>
</tbody>
</table>

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| Post-BD zFEV$_1$/FVC | 2354 | −0.05 (−0.14, +0.04) | +0.01 (−0.11, +0.14) | || +0.33 (+0.01, +0.66)* | +0.01 (−0.29, +0.31) | || 0.033
| Post-BD airflow obstruction □ | 2342 | 1.24 (0.74–2.08) | 1.00 (0.47–2.12) | || 0.45 (0.12–1.69) | 0.85 (0.28–2.60) | || 0.370
| Spirometric restriction □ | 2239 | 1.61 (0.82–3.17) | 1.53 (0.56–4.18) | || || 0.150
| zT$_{co}$ | 2285 | +0.03 (−0.07, +0.13) | +0.02 (−0.12, +0.16) | || −0.13 (−0.44, +0.19) | −0.03 (−0.32, +0.26) | || 0.500
| zKCO | 2285 | +0.05 (−0.06, +0.15) | +0.11 (−0.03, +0.26) | || +0.10 (−0.21, +0.42) | +0.30 (0.000, +0.59)^ | || 0.655
| zVA | 2285 | −0.02 (−0.11, +0.08) | −0.11 (−0.25, +0.02) | || −0.30 (−0.63, +0.04) | −0.40 (−0.71, −0.09)* | || 0.158

**Definitions of abbreviations:** BD, bronchodilator; BDR, bronchodilator response; CB, chronic bronchitis; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; OR, odds ratio; T$_{co}$, transfer factor of the lung for carbon monoxide; zFEV$_1$/FVC<LLN, airflow obstruction

* p<0.05 *p<0.001

† Parent-reported bronchitis by age 7 categorized into none (reference = 1, not shown), non-recurrent, recurrent (>5 episodes of “loose, or rattly” or chesty cough lasting <1 month on average), and recurrent-protracted (>5 episodes, ≥1 month average duration)

‡ Multivariable models were adjusted for rurality of school, paternal occupation, family history of bronchitis, sibling number, maternal and paternal smoking, and participant sex

§ Lung function measured in z-scores which, by definition, has a mean of 0 and standard deviation of 1

▲ Too few cases or residual degrees of freedom to derive point estimates; for Post-BD zFVC<LLN, failure was predicted perfectly for those with childhood asthma/wheezing

For participants with a history of childhood asthma/wheezing only, compared with the reference group of no childhood bronchitis, those with fewer than five episodes of childhood bronchitis of any duration had borderline lung function deficits consistent with a non-obstructed pattern (p-interaction <0.1). A change in lung function was regarded to be significant if the difference was >100 mL and >0.5 SD, so the associations did not quite reach clinical significance and included: reduced post-BD FVC [z-score −0.42 SD (95%CI: −0.72, −0.12), p=0.006], increased pre-BD FEV$_1$/FVC [+0.43 (+0.11, +0.74), p=0.008] and post-
BD FEV₁/FVC [+0.33 (+0.01, +0.66), p=0.043] despite an increased pre-BD FEV₁, as well as an associated 3-fold decrease in the odds for pre-BD airflow obstruction [OR 0.34 (+0.14, +0.87), p=0.024].

Results E3. Sex-differences

Table E5: Interactions between the effects of childhood bronchitis on lung conditions in middle-age, by sex

<table>
<thead>
<tr>
<th>Lung condition at age 53</th>
<th>Cases (n)</th>
<th>Childhood bronchitis severity at age 7 [OR (95% CI), N=3,202] †‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females with childhood bronchitis (n=1,626)</td>
<td>Males with childhood bronchitis (n=1,576)</td>
</tr>
<tr>
<td></td>
<td>Non-recurrent (n=470)</td>
<td>Recurrent, non-protracted (n=252)</td>
</tr>
<tr>
<td>CB-current</td>
<td>158</td>
<td>0.59 (0.31–1.11)</td>
</tr>
<tr>
<td>CB-ever</td>
<td>275</td>
<td>0.80 (0.51–1.23)</td>
</tr>
<tr>
<td>Asthma-current</td>
<td>395</td>
<td>1.29 (0.91–1.84)</td>
</tr>
<tr>
<td>Asthma-ever</td>
<td>804</td>
<td>1.24 (0.99–1.56) ^</td>
</tr>
<tr>
<td>Pneumonia-ever</td>
<td>574</td>
<td>1.67 (1.25–2.22) **</td>
</tr>
<tr>
<td>Aged ≥ 7 years</td>
<td>460</td>
<td>1.61 (1.17–2.20) **</td>
</tr>
<tr>
<td>Aged &lt; 7 years</td>
<td>114</td>
<td>1.96 (1.05–3.65) *</td>
</tr>
</tbody>
</table>

Definitions of abbreviations: BD, bronchodilator; CB, chronic bronchitis; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; OR, odds ratio; T_Lco, carbon monoxide transfer factor of the lung

*p<0.06 **p<0.05 ***p<0.001
†Parent-reported bronchitis by age 7 categorized into none (reference = 1, not shown), non-recurrent, recurrent (>5 episodes of “loose, or rattly” or chesty cough lasting <1 month on average), and recurrent-protracted (>5 episodes, ≥1 month average duration)
‡Multivariable models were adjusted for rurality of school, paternal occupation, family history of bronchitis, sibling number, maternal and paternal smoking, and participant sex
§Cells that had <5 cases and negative findings

Stratification of the analyses relating to lung conditions as outcomes were limited by few case numbers but found some association between childhood bronchitis and recalled doctor-diagnosed pneumonia-ever for females (p-interaction between 0.097-0.114).

Notably, chronic airway infection such as bronchiectasis unrelated to cystic fibrosis has some predominance in non-smoking females [8, 9], although it is possible that females could report pneumonia-like symptoms more frequently than males, similarly to the increase in dyspnoea reported by females with chronic obstructive pulmonary disease [10]. This potential increase in pneumonia prevalence contrasts the observed increase in severity of community-acquired pneumonia and its related mortality in older males [11, 12].
### Results E4. Potential effect modification by ever-smoking

**Table E6: Interactions between the effects of childhood bronchitis on lung conditions in middle-age, by smoking-ever status**

<table>
<thead>
<tr>
<th>Lung condition at age 53</th>
<th>Cases (n)</th>
<th>Childhood bronchitis severity at age 7 [OR (95% CI), N=3,176] †‡</th>
<th>Ever-smokers by age 53 with childhood bronchitis (n=1,860)</th>
<th>p-int value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-smokers at age 53 with childhood bronchitis (n=1,316)</td>
<td>Ever-smokers by age 53 with childhood bronchitis (n=1,860)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-recurrent (n=377)</td>
<td>Non-recurrent (n=514)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent, non-protracted (n=251)</td>
<td>Recurrent-protracted (n=20)</td>
<td></td>
</tr>
<tr>
<td>CB-current</td>
<td>158</td>
<td>1.16 (0.53–2.51)</td>
<td>5.40 (1.30–22.5) *</td>
<td>0.389</td>
</tr>
<tr>
<td>CB-ever</td>
<td>275</td>
<td>1.21 (0.71–2.05)</td>
<td>§</td>
<td>0.425</td>
</tr>
<tr>
<td>Asthma-current</td>
<td>395</td>
<td>1.19 (0.78–1.85)</td>
<td>3.04 (1.03–8.94) *</td>
<td>0.456</td>
</tr>
<tr>
<td>Asthma-ever</td>
<td>804</td>
<td>1.32 (0.97–1.81)</td>
<td>7.63 (2.93–19.9) ***</td>
<td>0.905</td>
</tr>
<tr>
<td>Pneumonia-ever</td>
<td>574</td>
<td>1.63 (1.13–2.34) **</td>
<td>5.13 (1.98–13.3) **</td>
<td>0.509</td>
</tr>
</tbody>
</table>

*Definitions of abbreviations:* BD, bronchodilator; CB, chronic bronchitis; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; OR, odds ratio; T, co, carbon monoxide transfer factor of the lung

†Parent-reported bronchitis by age 7 categorized into none (reference = 1, not shown), non-recurrent, recurrent (>5 episodes of “loose, or rattly” or chesty cough lasting <1 month on average), and recurrent-protracted (>5 episodes, ≥1 month average duration)

‡ Multivariable models were adjusted for rurality of school, paternal occupation, family history of bronchitis, sibling number, maternal and paternal smoking, and participant sex

§ Cells that had <5 cases and negative findings

^p=0.051 *p<0.05 **p<0.01 ***p<0.001
References


