Childhood respiratory risk factor profiles, their interactions and mediators, and middle-age lung function: a prospective cohort study from the 1st to 6th decade

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**AT A GLANCE COMMENTARY**

**Scientific Knowledge on the Subject**

Childhood factors may have long-term implications for adult lung function and development of Chronic Obstructive Pulmonary Disease (COPD). A systematic approach to investigating profiles of childhood respiratory risk factors as predictors of middle-age lung function and risk of COPD, and their pathways has not been previously undertaken.

**What This Study Adds to the Field**

Using an objective categorizing approach to establish patterns, we identified distinct childhood respiratory risk profiles in a large cohort. We found that specific risk profiles have different effects on middle-age lung function and COPD and that their effects have different pathways. Children with frequent asthma attacks and multiple allergies were found to be most at risk of developing COPD and lung function deficits in middle-age. This link was largely transmitted through active asthma in adulthood and to a lesser degree through reduced lung function in childhood. This highlights the importance of lifetime asthma control. The finding that subsequent personal smoking markedly increased the long-term risk for some risk profiles highlights an opportunity for targeted prevention. Our findings suggest that childhood risk factor profiles are useful to predict long-term lung health.

This article has an online data supplement, which is accessible from this issue's table of content online at [www.atsjournals.org](http://www.atsjournals.org)
Abstract

Rationale:
Childhood risk factors for long-term lung health often co-exist and their specific patterns may affect subsequent lung function differently.

Objectives:
To identify childhood risk factor profiles, their influence on lung function and chronic obstructive pulmonary disease (COPD) in middle-age and potential pathways.

Methods:
Profiles of 11 childhood respiratory risk factors, documented at age 7, were identified in 8352 participants from the Tasmanian Longitudinal Health Study using latent class analysis. We investigated: associations between risk profiles and post bronchodilator lung function, and COPD at age 53; mediation by childhood lung function and adult asthma; and interaction with personal smoking.

Results:
Six risk profiles were identified: 1 “unexposed or least exposed” (49%), 2 “parental smoking” (21.5%), 3 “allergy” (10%), 4 “frequent asthma, bronchitis” (8.7%), 5 “Infrequent asthma, bronchitis” (8.3%) and 6 “frequent asthma, bronchitis, allergy” (2.6%). Profile 6 was most strongly associated with lower FEV₁ (-261; 95%CI: -373,-148 mL); lower FEV₁/FVC: (-3.4; -4.8,-1.9%) and increased COPD risk (OR: 4.9; 2.1,11.0) at age 53. The effect of profile 6 on COPD was largely mediated by adult active asthma (62.5%) and reduced childhood lung function (26.5%). Profiles 2 and 4 had smaller adverse effects than profile 6. Notably effects of profiles 2 and 6 were synergistically stronger for smokers.

Conclusions:
Profiles of childhood respiratory risk factors predict middle-age lung function levels and COPD risk. Specifically, children with frequent asthma attacks and allergies, especially if they also become adult smokers, are the most vulnerable group. Targeting active asthma in adulthood (i.e. a dominant mediator) and smoking (i.e. an effect modifier) may block causal pathways and lessen the effect of such established early-life exposures.

Word count: 250
Introduction

Impaired adult lung function and chronic obstructive pulmonary disease (COPD) are significant public health concerns. These lung conditions are traditionally thought due to accelerated lung function decline associated with adulthood exposures, particularly smoking. There is emerging evidence that childhood exposures may also have adverse effects on adult lung function and COPD in later life (1-6), possibly by reducing lung growth before early adulthood (7, 8) or by accelerating lung function decline in adulthood (6, 9).

The co-existence of multiple risk factors in childhood is common, and their interplay could take the form of additive or multiplicative effects, mediation and confounding. This complex interplay may determine long-term outcomes. Previous studies have investigated only a few childhood factors, either individually or in simple combinations, and have not addressed the complex interplay between co-existing factors. For example, each of maternal asthma, childhood asthma, pneumonia, parental smoking, as well as an increasing count of these childhood risk factors were found to be associated with reduced lung function and increased risk of COPD in adults, but the way in which these factors aggregated with each other was not considered (6). It is important to identify patterns/profiles of these factors and elucidate specific profiles to describe those at most risk for adult lung function deficits and COPD. It is even more important to disentangle the causal pathways involving mediators and effect modifiers for each profile in order to provide targets for intervention and lessen the adverse effects of established early life factors. To date, such a comprehensive investigation has not been reported.

The co-existence of multiple risk factors in childhood is common, and their interplay could take the form of additive or multiplicative effects, mediation and confounding. Therefore, long term risks should be assessed based on a full risk profile, but previous studies have addressed only a few childhood factors; investigated either individually or in simple combinations. For example, each of maternal asthma, childhood asthma/wheeze, pneumonia, parental smoking, as well as an increasing number of these childhood risk factors have been found to be associated with reduced lung function and increased risk of COPD in adults (6). Additionally, potential mediators or effect modifiers of these associations have seldom been investigated, which is critical to identifying high risk groups and developing potential preventive strategies. Given the increasing interest in precision
The ability to predict long-term lung health based on childhood characteristics is an area that needs to advance substantially. We hypothesised that grouping childhood risk factors in a novel way using advanced statistical methods might better define prognostic risk profiles for poor adult lung function. Using data from the Tasmanian Longitudinal Health Study (TAHS) we aimed to: (1) identify patterns of exposure to childhood factors (risk factor profiles) in a population-based cohort, (2) investigate the impact of these profiles on lung function and risk of COPD in middle age, and (3) determine potential mediation and interaction by plausible childhood and adult factors.

Some of the results of this study have been previously reported in the form of an abstract (10).

METHODS

Study design and data collection
We used data from the TAHS, collected at ages 7 and 53 years (Figure 1). The study methodology has been reported in detail elsewhere (11). In brief, TAHS began in 1968 when 8583 Tasmanian children born in 1961 and attending school in Tasmania were enrolled in a respiratory health study. Parents completed a questionnaire for the child who then underwent a clinical examination and pre-bronchodilator (BD) spirometry. In 2012, surviving participants (mean age 53 years) from the original cohort with contact details (n=6128, 71% of the original cohort) were invited to attend a clinical study. Between 2012 and 2016, 3609 participated (58.9% of those invited). Of those, 2689 participants (74.5%) both completed the questionnaire and performed pre- and post-BD spirometry while 920 participants (25.4%) only completed the questionnaire.

Definition of variables (details in supplement)
Early-life/childhood risk factors were defined using the information provided by parents in the 1968 survey when the children were 7 years old. Adult variables were defined using information provided by participants at 53 years of age. COPD was defined as post-BD FEV₁/FVC< lower limit of normal (LLN) derived from Global Lung Initiative (GLI) reference equations for Caucasian ethnicity (12) plus at least one of the key indicators (shortness of breath at rest or after exercise, chronic cough or chronic...
sputum production; a history of smoking ≥10 packyears; occupational exposure to
vapour/gas/dust/fumes; a family history of COPD) (13). COPD was further classified into the
phenotypes of “COPD with current asthma and COPD without current asthma. A solely
spirometric definition of COPD (only post-BD FEV₁/FVC<LLN) was also used as the second
definition for comparison.

Statistical analysis

Identification of risk factor profiles (latent classes) (details in supplement)

Eleven childhood factors were finally included to identify risk factor profiles using latent
class analysis (LCA). They included childhood asthma (three categories: never, infrequent
attacks and frequent attacks), bronchitis (the same three categories), eczema, hay fever,
food allergy, “hives”, lung infections, maternal smoking, paternal smoking, maternal asthma
and paternal asthma. In LCA, two sets of variables were estimated: conditional probabilities
(i.e., probability of having each indicator factor within a known class) and posterior
probabilities (i.e. probability of membership of each class for a given participant). Models
with an increasing number of classes were fitted to determine the best fit model, using
Bayesian information criteria. Individuals were subsequently assigned to the latent class for
which they had the highest probability of membership.

Associations between risk profiles and lung function and COPD at age 53 years

Multivariable linear and logistic regressions were performed to investigate associations
between the identified risk factor profiles with lung function and COPD at 53 years.
Interactions between risk factor profiles and personal smoking were tested using the
likelihood ratio test and strata specific estimates were reported if p for interaction <0.1.
Mediation analysis, using a general decomposition method developed by Karlson (14), was
performed to identify potential mediators of the association between each risk profile and
adult lung function/COPD. Investigation of interaction and mediation analyses were
conducted separately. Multinomial regressions were used to assess the effect of risk profiles
on COPD phenotypes.

All analyses were performed using Stata 13.0 (Stata Corp, College Station, TX, USA) with the
LCA plug-in (15).
Study participants

Data on the eleven childhood risk factors collected at age 7 years, available for 8352 participants, were used to identify childhood risk factor profiles. Of those, lung function data at 53 years were available for 2689 participants. This group had a slightly higher prevalence of childhood eczema and bronchitis, but lower prevalences of childhood “hives” and parental smoking compared with the remainder of the original cohort (Table E1). They were also more likely female and of higher socio-economic status in childhood.

Prevalence and characteristics of childhood risk factor profiles identified by LCA

The best fit LCA model delineated six latent classes, each representing one childhood risk factor profile (Figure 2, E1). They were labelled for their increased probability of the defining risk factors as: “unexposed or least exposed” (n=4090, 49%), “parental smoking” (n=1792, 21.5%), “allergy” (n=836, 10%), “frequent asthma, bronchitis” (n=727, 8.7%), “infrequent asthma, bronchitis” (n=694, 8.3%) and “frequent asthma, bronchitis, allergy” (n=213, 2.6%) (details in supplement). “Unexposed or least exposed” group was used as the reference group in all analyses. Prevalence of risk profiles among participants with lung function data at 53 years was similar to those in the entire original cohort. Characteristics of risk profiles are presented in Table 1.

Childhood risk factor profiles and lung function at 53 years

Compared with the unexposed/least exposed reference profile, all other profiles except for the “allergy” profile were associated with reduction in adult post-BD FEV$_1$ (Table 2). The highest reduction was seen for the “frequent asthma, bronchitis, allergy” profile (-261 mL; 95%CI: -373, -148 mL), followed by the “frequent asthma, bronchitis” profile (-136 mL; 95%CI: -206, -67 mL). Smaller post-BD FEV$_1$ reductions were seen for the “infrequent asthma, bronchitis” profile (-91 mL; 95%CI: -161, -20 mL) and “parental smoking” profile (-84 mL; 95%CI: -135, -33 mL). These estimates of strength of association were independent of personal smoking. For comparison, the effect of current smoking compared with never-smoking on post-BD FEV$_1$ in the same model was -260 mL (95%CI: -313, -206 mL); and the effect of ten packyears was -69 mL (-82, -55 mL). All these risk profiles were also significantly associated with reduced post-BD FEV$_1$/FVC, with the largest reduction seen for the “frequent asthma, bronchitis, allergy” profile.

Results for pre-BD lung function were similar to the post-BD lung function data (Table 2).
Childhood risk factor profiles and COPD at 53 years

The prevalence of COPD in the six risk profiles is presented in Table 1. Compared with the reference profile, the “frequent asthma, bronchitis, allergy”, “frequent asthma, bronchitis” and “parental smoking” profiles were significantly associated with 4.9, 2.2 and 1.7 fold increased risks of COPD, respectively (Table 3). Results were similar when a solely spirometric definition of COPD was used (Table E2).

We further assessed associations between risk profiles and COPD phenotypes (Table E3). Compared with the reference profile, the “frequent asthma, bronchitis, allergy” profile was significantly associated with COPD with current asthma (OR: 26.0) but not with COPD without current asthma. The “frequent asthma, bronchitis” profile was also significantly associated with COPD with current asthma, but to a much lesser extent (OR: 5.8), and again not with COPD without current asthma. The “parental smoking” profile was associated with COPD without current asthma (OR: 2.2) but not with COPD with current asthma.

Direct and indirect pathways: the role of childhood lung function and adult active asthma as mediators

Active asthma at 53 years were examined as a mediator for associations between three childhood asthma related risk profiles and lung function outcomes. Childhood FEV₁ was examined as a mediator for specific associations if there was a significant association between the specific risk profile and the mediator.

As the “frequent asthma, bronchitis, allergy” profile was significantly associated with reduced childhood FEV₁ (Table E4), both childhood FEV₁ and active asthma at 53 years were considered potential mediators of the association between this profile and lung function and COPD at 53 years. Up to 89% of the total effect of the “frequent asthma, bronchitis, allergy” profile on COPD was mediated by the two factors simultaneously with active asthma having a greater effect (62.5%) than childhood lung function (26.5%) (Figure 3, Table E5). Similarly, around 50% of the total effect of this profile on adult lung function parameters was mediated by the two factors simultaneously with active asthma having a greater effect (24.5% - 35%) than childhood lung function (18.7% - 24%) (Figure E2, Table E6).

The “frequent asthma, bronchitis” profile was not significantly associated with reduced childhood FEV₁, thus, only active asthma at 53 years was examined as a mediator for the effect of this profile. Eighty-two percent of the total effect of this profile on COPD was
mediated by adult active asthma (Figure 3). Likewise, one third to one half of the total effect of this profile on lung function parameters was mediated by adult active asthma (Figure E3, Table E7).

Personal smoking was analysed as a mediator of associations between the “parental smoking” profile and lung function and COPD at 53 years. The mediated effects of personal smoking accounted for around one fifth of the total effect and did not reach statistical significance at an alpha level of 0.05 (Table E8).

Active asthma at 53 years was found not to be a significant mediator for the effect of the “infrequent asthma, bronchitis” profile on lung function (Table E9).

**Interaction between risk profiles and personal smoking status**

We observed evidence for overall interactions between risk profiles (as a multi-category variable) and personal smoking on lung function parameters at 53 years: post-BD FEV$_1$ (p-interaction=0.06), pre-BD FEV$_1$ (p=0.07), post-BD FEV$_1$/FVC (p=0.02), and pre-BD FEV$_1$/FVC (p=0.09). Personal smoking increased the adverse effects of two profiles: “frequent asthma, bronchitis, allergy” and “parental smoking” (p for interaction terms<0.05) (Table E10).

**Discussion**

Using latent class analysis (LCA) to categorize respiratory risk factors in childhood, we identified six profiles in this Australian general population sample. We found that these risk profiles differentially affect lung function and COPD in middle age through different pathways involving mediators and effect modifiers. Importantly, we identified one specific childhood profile with markedly elevated risk of lung function deficits and COPD in middle-age. The “frequent asthma, bronchitis, allergy” profile, although representing a relatively small group, had the lowest lung function and highest risk of COPD, particularly the COPD with current asthma subtype; for comparison, FEV$_1$ deficits associated with this profile were similar to the effect of current smoking. The effects of this profile on COPD and lung function were largely mediated through adult active asthma (62.5% for COPD) and less through childhood lung function (26.5% for COPD). The effect of the “frequent asthma, bronchitis” profile on COPD and lung function was smaller; only significantly mediated by active adult asthma (82% for COPD) but not childhood lung function; and mainly seen for the COPD with current asthma subtype. The effect of the “parental smoking” profile was
dominant for COPD without current asthma and neither childhood lung function nor adult active asthma mediated that effect. Personal smoking accentuated the adverse effects of the “frequent asthma, bronchitis, allergy” and “parental smoking” profiles on lung function. The complex interplay of multiple co-existing respiratory risk factors is likely to be a major determinant of long-term lung health. However, previous studies have mostly investigated the adverse effect of individual early life factors in isolation (4, 5, 9, 16-18). Only one study (6) has contributed to this area through investigating the long-term effect of a childhood disadvantage score created by counting five risk factors but not considering how they aggregate within individuals. Our current paper is the first to identify distinct risk profiles in a general population, using an unbiased data driven approach which better accommodates the unknown interplay between co-existing individual risk factors. Importantly, among identified risk profiles, our findings identify groups with high risk of long-term lung function deficits and COPD. This may be useful for physicians to predict long-term outcomes of paediatric patients and for public health policies and researchers to target interventions to high-risk profiles. Given the adverse long-term impact of our identified high-risk profiles, it is important to address preventive interventions in early-life. However, if these profiles are already established, there may still be opportunities to lessen the impact of early life exposures. Our findings on the role of adult active asthma as a mediator and personal smoking as an effect modifier provide strong evidence that targeting mediators and/or effect modifier may still be a useful option. Our current manuscript brings a novel critical perspective to identifying those at risk of Chronic Obstructive Pulmonary Disease early and it complements our recently published TAHS paper in The Lancet Respiratory Medicine (19). In the LRM paper, we identified three pre-BD FEV1 trajectories with lower lung function in childhood and increased risk of COPD in middle age. Although, the primary aim of the LRM paper was to identify lifetime trajectories of lung function, we also reported the link between some early life factors and the identified lung function trajectories but not with COPD. In the current manuscript, we addressed the unknown complex interplay between co-existing multiple early life factors by identifying distinct risk profiles and how these profiles are associated with subsequent COPD; and attempted to disentangle pathways of risk profile-outcome associations by investigating mediators and effect modifiers. Although, the two papers have clearly different objectives,
their findings together provide critical yet different insights into the origins of COPD. The former suggests an impact of individual early life factors on certain lung function trajectories from childhood while the later identify specific risk profiles at risk of COPD in later life. In support of our findings about the early origins of COPD, Lange et al. (20) followed up three large independent cohorts and found that half of the cases who developed COPD already had lower lung function in early adulthood followed by a normal rate of decline.

Our frequent asthma, bronchitis, allergy profile represents a multiple allergic comorbidity group. The prevalence of this profile is similar to the previously reported prevalences of comorbid allergic diseases (21, 22). Allergic disease comorbidity may be explained by different mechanisms, including direct causal effect and/or shared genetic and environmental factors (23, 24). A systematic review of family data suggested that genetics play a bigger role than environmental factors in the link between eczema and subsequent allergic disorders (23). However, Pinart et al. (22) showed that only 38% of the comorbidity of asthma and allergic diseases was attributable to IgE sensitization and suggested a more important role of additional pathways, including shared environmental factors. Consistent with these conclusions, the probability of parental asthma was modest in the “frequent asthma, bronchitis, allergy” group which showed a strong co-aggregation of asthma, eczema, hay fever and food allergy, suggesting a lesser role for heritability.

It has been shown previously that childhood asthma accompanied by eczema and hay fever was associated with persistently reduced lung function from childhood to adolescence (25). Similarly, we found the profile with asthma and allergic comorbidity to be associated with reduced childhood lung function and with middle-age lung function deficits and increased risk of COPD decades later. Additionally, we found that the profile with asthma and allergic comorbidity was associated with a greater risk than the profile with asthma but not allergic comorbidity. These findings are consistent with our previous results, showing that childhood asthma, eczema and hay fever were synergistically associated with a persistently low lung function trajectory from childhood to middle age (19). Thus, some lung function deficits in relation to childhood asthma plus multiple allergies seem to be evident in childhood and track to adulthood.

Previous studies have indicated that childhood asthma with allergic comorbidity is more likely to persist to adulthood (26-28). Consistent with this, we found that the “frequent asthma, bronchitis, allergy” profile had an increased risk of adult active asthma. Our
mediation analysis showed that the reduced lung function and increased risk of COPD in middle age, associated with the “frequent asthma, bronchitis, allergy” profile, was partly established in childhood with additional effects of active asthma in adulthood. Thus, preventions targeting active asthma in both childhood and adulthood might reduce adverse effects in this group.

A previous analysis of TAHS showed a three-way interaction between active adult asthma, atopy and personal smoking on adult lung function (29). We also found an interaction between the “frequent asthma, bronchitis, allergy” profile and personal smoking on middle-age lung function. Importantly, the effect of this profile on FEV\textsubscript{1} was still significant in never-smokers and was further compounded in smokers. This contradicts previous studies (30) showing that early-life factors, including respiratory infections and home over-crowding, only have adverse effect on adult lung function if compounded by personal smoking. Nevertheless, our findings emphasize the particular importance of avoiding smoking for individuals with allergic comorbidity in childhood and adulthood.

The association between the “parental smoking” profile and middle age lung function and COPD in our study emphasizes that parental smoking in childhood is an important risk factor for long-term lung function deficits and COPD, either through mediation or interaction. Children with parents who smoke are more likely to smoke themselves (31). In our study this group had the highest prevalence of lifetime smoking, suggesting potential mediation by personal smoking on the parental smoking-offspring lung function pathway. On the other hand, personal smoking may modify the effect of parental smoking (9, 32, 33). We found no strong evidence that personal smoking was acting as a mediator. However, we found that personal smoking significantly augmented the adverse effects of the parental smoking profile. This provides even stronger evidence for reducing smoking prevalence, because it not only affects the smoker, but also the long-term lung health of their offspring.

COPD is acknowledged to have diverse phenotypes which may differ in prognosis and response to treatment and prevention strategies. Our findings clearly demonstrate this by showing that different childhood risk profiles are related to different COPD phenotypes. Asthma related profiles showed a pronounced relationship with COPD with current asthma. The role of adult active asthma as a mediator for COPD further explained the pathway for the influence of asthma-related profiles on the COPD with current asthma subtype. While mechanisms of COPD with current asthma are not yet determined (34), this study adds
evidence for a pathway from childhood as well as a direct effect of active asthma in adulthood.

In contrast to asthma related profiles, the “parental smoking” profile was predominantly related to COPD without current asthma. This highlights the long-term adverse effect of smoking exposure in childhood on adult lung function and COPD. There are several different mechanisms for this link. Smoking exposure in childhood may directly affect lung growth with deficits tracking to adulthood (5). Smoking exposure in childhood may increase susceptibility to adult insults such as personal smoking (32). Smoking exposure may also increase the risk of other childhood respiratory conditions such as asthma and infections, which predict further reduced lung function in later life (35). We also found that the probability of parental smoking in asthma-related profiles was relatively high. The “parental smoking” profile may represent children less susceptible to the effects of smoke exposure and not acquiring the additional morbidities seen in other profiles (asthma, bronchitis, respiratory infections).

This study has the strength that we identified risk profiles objectively, using an unsupervised and thus un-biased method. Moreover, our results are applicable at a population level as TAHS is a whole population-based cohort study representing almost the entire population of 7-year olds in 1968 from a single Australian State (Tasmania). A wide range of childhood risk factors, long term follow-up to middle age and post-BD lung function measurements to define COPD are also major strengths. In addition, the prospective nature of the study has allowed us to explore potential mediators.

Our definition of COPD included fixed airflow limitation plus symptoms and/or a history of smoking >10 pack years and was in accordance with the current GOLD strategy document for health care professionals (13). This definition may differ from those previously used for clinical diagnosis of COPD, which required a history of exposure, plus symptoms and fixed airflow limitation. As the population was relatively younger than the age when most COPD patients are diagnosed (usually in their sixties) and symptoms may be under-reported by participants, our definition needed to be sensitive to capture early COPD cases. Whilst our definition may have overestimated the number of COPD participants, this is likely to be random across exposure categories. Therefore, if anything, the associations with childhood risk profiles, may have been under-estimated.
One limitation of this study is the potential attrition bias. There were small differences in some childhood characteristics between participants with lung function measurements in middle-age and the remainder of the cohort. However, the prevalence of childhood risk profiles, our exposure variables of interest, were similar between those two groups. Given that the attrition was not associated with the exposure, it is unlikely that attrition has affected associations between risk profiles and lung function outcomes in our study.

We did not have information on birth weight and gestational age that may be associated with lower lung function in very early life, which may track over time and lead to childhood respiratory symptoms (36, 37). However, in a subsample with data available (32% of the study sample), we found that birth weight of the risk profiles was not significantly different from the reference profile. Hence, in our study birth weight is unlikely to be a confounder of the associations between risk profiles and adult lung function. However, this finding should be interpreted cautiously given the small size of this subsample.

The distinction between childhood asthma and bronchitis can be difficult in some children. However, in our study, prevalences of childhood asthma and bronchitis were markedly different (16% vs 47%). Moreover, our definition of childhood asthma has been validated against bronchial hyper-responsiveness and physician diagnosis (38). Thus, although there is still a possibility of misclassification, it is less likely to have significantly affected our results.

We acknowledge that the question used to define pneumonia was not highly specific as it encompassed both pneumonia and pleurisy, and the latter symptom may be present without an accompanying pneumonia. This may have overestimated the prevalence of pneumonia in our study but such misclassification is likely to be random between our outcomes and is unlikely to influence observed associations.

The sample size of the “frequent asthma, bronchitis, allergy” profile was relatively small which may have limited the power to detect associations. However, despite this, we still found significant effects of this profile on middle-age lung function and COPD. As we are the first to characterize childhood risk profiles in a general population, investigating these risk profiles in independent cohorts is needed before we draw firm conclusions.

Conclusions
This is the first study to identify distinct childhood risk profiles, report their different associations with middle-aged lung function and COPD and untangle mediators involved in pathways and effect modifiers. Although these observational associations do not prove causality given that the potential for residual confounding by perinatal factors cannot be entirely ruled out, our findings suggest that childhood risk factor profiles are useful to predict long-term lung function and COPD. Our findings can inform potential risk prediction tools to identify those at high risk and interventions to reduce the burden of long-term lung health impairment. One particular group, children with frequent asthma attacks and multiple allergic comorbidities, are the most vulnerable and require targeted prevention strategies. We found that active adult asthma mediates 63% - 82% of the total effects of two childhood asthma-related profiles on middle-age COPD. Although not directly tested, our findings raise the possibility that optimal asthma control throughout life may lessen the adverse effect of these childhood asthma-related profiles, and this should be investigated in future intervention studies. The synergistic interaction between personal smoking and risk profiles emphasizes the importance of preventing smoking in children with such childhood exposures.

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Table 1. Characteristics of risk profiles

<table>
<thead>
<tr>
<th>Risk factor profiles</th>
<th>Unexposed or least exposed</th>
<th>Infrequent asthma, bronchitis</th>
<th>Frequent asthma, bronchitis</th>
<th>Frequent asthma, bronchitis, allergy</th>
<th>Parental smoking</th>
<th>Allergy</th>
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<td></td>
<td>N=4090 (49%)</td>
<td>N=694 (8.3%)</td>
<td>N=727 (8.7%)</td>
<td>N=213 (2.6%)</td>
<td>N=1792 (21.5%)</td>
<td>N=836 (10%)</td>
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**Male sex**

49.3 (2017)

55.8 (387) 56 (407) 63.4 (135) 49.8 (892) 52.6 (440)

**Childhood characteristics**

**Asthma**

Infrequent

1 (41) 76 (525) 2.6 (19) 13.6 (19) 1.3 (2.3) 2.9 (24)

Frequent

0.3 (12) 0 70.6 (512) 86 (183) 0.2 (4) 3.2 (27)

**Eczema**

6 (245) 21 (145) 9 (63) 85 (180) 3 (54) 32 (268)

**Food allergy**

1.1 (43) 10.5 (72) 4.6 (33) 49 (100) 2.9 (24)

**Hay fever**

1.9 (75) 24 (164) 34 (240) 83 (173) 40 (333)

**Hives**

12 (475) 25 (170) 32 (232) 36 (73) 47 (389)

**Bronchitis**

Infrequent

21 (859) 78 (542) 7 (51) 8.5 (18) 22 (403) 26 (217)

Frequent

7.7 (313) 20 (136) 90 (656) 89 (189) 11 (195) 46 (381)

**Pneumonia/pleurisy**

5.5 (221) 38 (257) 42 (299) 37 (78) 11 (193) 16 (129)

**Maternal asthma**

6.2 (238) 25 (161) 25 (174) 38 (78) 7.2 (127) 12.3 (98)

**Paternal asthma**

7.8 (295) 24 (151) 25 (164) 47 (94) 1.8 (32) 5 (38)

**Maternal smoking**

9.3 (356) 43.9 (288) 54.5 (379) 35.3 (72) 100 (1781) 15.9 (127)

**Paternal smoking**

46.8 (1771)

62.6 (400) 72.6 (481) 55.3 (109) 100 (1695) 39.5 (310)

**Childhood SES**

1st and 2nd classes (highest)

30 (1159) 27 (174) 22 (144) 31 (59) 20 (334) 34 (263)

3rd class

30 (1500) 25 (162) 32 (214) 32 (61) 30 (486) 31 (243)

4th and 5th classes

40 (1549) 48 (309) 46 (303) 38 (72) 50 (824) 35 (276)

**Adult characteristics**

N=1322 †

N=205 †

N=215 †

N=75 †

N=488 †

N=301 †

Active asthma

15.3 (202) 27.3 (56) 47.4 (102) 72 (54) 13.5 (66) 20.3 (61)

COPD

3.3 (43) 3.9 (8) 7.9 (17) 12 (9) 6.2 (30) 5 (15)

Smoking status

Never

47.3 (621) 45.1 (92) 46.9 (99) 46.7 (35) 42.6 (206) 46.5 (139)

Past

37.7 (495) 40.7 (83) 38.9 (82) 38.7 (29) 37 (179) 41.5 (124)

Current

14.7 (11) 14.2 (29) 14.2 (30) 14.7 (11) 20.5 (99) 12 (36)

Pack-years, median (IQR)

0.06 (0-12) 0.05 (0-15) 0.23 (0-12) 0.02 (0-11) 0.52 (0-18) 0.13 (0-12)

**Adult SES**

1st and 2nd classes (highest)

51.3 (670) 51.2 (104) 43.9 (93) 45.3 (34) 46.1 (221) 54.7 (163)

3rd class

31.7 (413) 31.5 (64) 36.8 (78) 32 (24) 37.8 (181) 30.2 (90)

4th and 5th classes

17 (222) 17.2 (35) 19.3 (41) 22.7 (17) 16 (77) 15.1 (45)

Data presented as % and (number)

† Number (prevalence) of risk factor profiles among participants with lung function data at 53 years
<table>
<thead>
<tr>
<th>Profiles</th>
<th>FEV$_1$ (mL)</th>
<th>FVC (mL)</th>
<th>FEV$_1$/FVC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-BD spirometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexposed/least exposed ¶</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Parental smoking †</td>
<td>-84 (-135, -33)*</td>
<td>-54 (-112, 3)</td>
<td>-0.9 (-1.6, -0.3)*</td>
</tr>
<tr>
<td>Allergy</td>
<td>-18 (-77, 41)</td>
<td>36 (-32, 104)</td>
<td>-0.9 (-1.6, -0.2)*</td>
</tr>
<tr>
<td>Frequent asthma, bronchitis</td>
<td>-136 (-206, -67)**</td>
<td>-73 (-154, 6)</td>
<td>-1.6 (-2.5, -0.7)**</td>
</tr>
<tr>
<td>Infrequent asthma, bronchitis</td>
<td>-91 (-161, -20)*</td>
<td>-55 (-136, 26)</td>
<td>-0.9 (-1.8, -0.1)*</td>
</tr>
<tr>
<td>Frequent asthma, bronchitis, allergy</td>
<td>-261 (-373, -148)**</td>
<td>-150 (-280, -21)*</td>
<td>-3.4 (-4.8, -1.9)**</td>
</tr>
</tbody>
</table>

*For comparison ♦♦♦

Current smoking at 53 years -260 (-313, -306)** -49 (-111, 12) -5.4 (-6.1, -4.7)**

Lifetime smoking, per 10 packyears -69 (-82, -55)** -26 (-41, -10)** -1.2 (-1.4, -1.0)**

Pre-BD spirometry

<table>
<thead>
<tr>
<th>Profiles</th>
<th>FEV$_1$ (mL)</th>
<th>FVC (mL)</th>
<th>FEV$_1$/FVC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed/least exposed ¶</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Parental smoking †</td>
<td>-89 (-141, -37)**</td>
<td>-67 (-127, -7)*</td>
<td>-1.0 (-1.7, -0.3)**</td>
</tr>
<tr>
<td>Allergy</td>
<td>-23 (-85, 37)</td>
<td>7 (-64, 78)</td>
<td>-0.6 (-1.5, 0.2)</td>
</tr>
<tr>
<td>Frequent asthma, bronchitis</td>
<td>-147 (-218, -75)**</td>
<td>-102 (-185, -18)*</td>
<td>-1.7 (-2.6, -0.7)**</td>
</tr>
<tr>
<td>Infrequent asthma, bronchitis</td>
<td>-74 (-146, -4)*</td>
<td>-54 (-137, 28)</td>
<td>-0.8 (-1.7, 0.1)</td>
</tr>
<tr>
<td>Frequent asthma, bronchitis, allergy</td>
<td>-292 (-408, -176)**</td>
<td>-202 (-337, -67)**</td>
<td>-3.5 (-5.0 -1.9)**</td>
</tr>
</tbody>
</table>

*For comparison ♦♦♦

Current smoking at 53 years -254 (-309, -199)** -84 (-148, -19)* -4.7 (-5.4, -4.0)**

Lifetime smoking, per 10 packyears -71 (-85, -57)** -37 (-53, -21)** -1.1 (-1.2, -0.9)**

Data show the difference in lung function parameters at 53 years between each risk profile and the reference (Ref) profile from the adjusted regression models (adjusted for age, height, sex, smoking status and childhood SES except indicated). Negative values indicate lower lung function.

† Adjusted for age, height, sex, smoking status and childhood SES
* p<0.05; ** p<0.01; *** p<0.001
The effect of smoking is presented in order to enable comparison with the effect of childhood risk profiles. Estimates for smoking are from the same models with childhood risk profiles.

Values for the reference profile were 3.31 L, 4.15 L and 79.9% for post-BD FEV₁, FVC and FEV₁/FVC respectively; corresponding values for pre-BD parameters were 3.21 L, 4.14 L and 77.7%.
Table 3. Associations between risk factor profiles and COPD at 53 years

<table>
<thead>
<tr>
<th>Profiles</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed or least exposed</td>
<td>Ref</td>
</tr>
<tr>
<td>Parental smoking</td>
<td>1.7 (1.1, 2.8)*</td>
</tr>
<tr>
<td>Allergy</td>
<td>1.5 (0.8, 3.0)</td>
</tr>
<tr>
<td>Frequent asthma, bronchitis</td>
<td>2.2 (1.1, 4.4)*</td>
</tr>
<tr>
<td>Infrequent asthma, bronchitis</td>
<td>1.4 (0.7, 2.8)</td>
</tr>
<tr>
<td>Frequent asthma, bronchitis, allergy</td>
<td>4.9 (2.1, 11.0)***</td>
</tr>
</tbody>
</table>

For comparison †

| Current smoking at 53 years †                | 11.0 (6.5, 19.0)***  |
| Lifetime smoking, per 10 packyears           | 1.5 (1.3, 1.6)***    |

Model was adjusted for sex, childhood socio-economic status and smoking status

*p<0.05; ** p<0.01; *** p<0.001

† The effect of current smoking is for comparison with the effect of risk profiles in the same models.
**1968**: 8583 (99%) of all Tasmania school children aged 7 years were recruited. A questionnaire including respiratory risk factors were completed by parents.

1974 (n=7383), 1981 (n=851), 1991 (n=1723), 2002-2006 (n=5729) and 2010 (n=840) surveys.

**2012**: 6128 (71%) with available contacts were invited. **2012-2016**: 3609 (59%) participated (mean age 53 years).

920 (25%) completed a questionnaire only

2689 (75%) performed pre and post-BD spirometry, and completed a questionnaire.

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*Figure 1. Flow chart of Tasmanian Longitudinal Health Study (TAHS)*
Figure 2. Probability of having each risk factor among six risk factor profiles estimated from the LCA model. 1-Unexposed or least exposed; 2-parental smoking; 3-allergy; 4-Frequent asthma, bronchitis; 5-infrequent asthma, bronchitis; 6-frequent asthma, bronchitis, allergy. Intensity of colour indicates probability (from 0 to 1 or 100%)
Figure 3. Mediated effect by mediators of associations between the three risk profiles and COPD at 53 years
AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Childhood factors may have long-term implications for adult lung function and development of Chronic Obstructive Pulmonary Disease (COPD). A systematic approach to investigating profiles of childhood respiratory risk factors as predictors of middle-age lung function and risk of COPD, and their pathways has not been previously undertaken.

What This Study Adds to the Field

Using an objective categorizing approach to establish patterns, we identified distinct childhood respiratory risk profiles in a large cohort. We found that specific risk profiles have different effects on middle-age lung function and COPD and that their effects have different pathways. Children with frequent asthma attacks and multiple allergies were found to be most at risk of developing COPD and lung function deficits in middle-age. This link was largely transmitted through active asthma in adulthood and to a lesser degree through reduced lung function in childhood. This highlights the importance of lifetime asthma control. The finding that subsequent personal smoking markedly increased the long-term risk for some risk profiles highlights an opportunity for targeted prevention. Our findings suggest that childhood risk factor profiles are useful to predict long-term lung health.