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**Childhood measles contributes to post-bronchodilator airflow obstruction in middle aged adults: A cohort study**

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## Summary at a glance

Childhood measles infection as a potential early-life respiratory insult is not linked to COPD in adult-life by itself. However, this prospective study found childhood measles increased the risk of post-bronchodilator airflow obstruction for middle aged adults through its interaction with the combined effects of current adult asthma and smoking.

## Abstract:

Background and objective: COPD has potential origins in childhood but an association between childhood measles and post-bronchodilator (BD) airflow obstruction has not yet been shown. We investigated whether childhood measles contributed to post-BD airflow obstruction through interactions with asthma and/or smoking in a non-immunized middle-aged population.

Methods: The population-based Tasmanian Longitudinal Health Study (TAHS) cohort born in 1961 (n=8,583), underwent spirometry in 1968 before immunization was introduced. A history of childhood measles infection was obtained from school medical records. During the 5<sup>th</sup> decade follow-up (n=5,729 responses), a subgroup underwent further lung function measurements (n=1,389). Relevant main associations and interactions by asthma and/or smoking on post-bronchodilator FEV<sub>1</sub>/FVC (continuous variable) and airflow obstruction (FEV<sub>1</sub>/FVC < lower limit of normal) were estimated by multiple regression.

Results: 69% (n=950) had a history of childhood measles. Childhood measles augmented the combined adverse effect of current clinical asthma and smoking at least ten pack-years on post-bronchodilator FEV<sub>1</sub>/FVC ratio in middle-age [z-score -0.70 (95%CI: -1.1 to -0.3)]

versus  $-1.36$  ( $-1.6$  to  $-1.1$ ), three-way-interaction:  $p=0.009$ ], especially for those with childhood-onset asthma. For never and ever-smokers of  $<10$  pack-years who had current asthma symptoms, compared with those without childhood measles, paradoxically, the odds for post-BD airflow obstruction was not significant in the presence of childhood measles [OR  $12.0$  (95%CI:  $3.4-42$ ) versus  $2.17$  ( $0.9-5.3$ )].

Conclusion: Childhood measles infection appears to compound the associations between smoking, current asthma and post-BD airflow obstruction. Differences between asthma subgroups provides further insight into the complex aetiology of obstructive lung diseases for middle-aged adults.

**Short title:** Mid-adult airflow obstruction & measles

**Key words:** measles, asthma, smoking, interaction, airflow obstruction, COPD, epidemiology

## Introduction

Early life factors have been implicated in the development of chronic obstructive pulmonary disease (COPD),<sup>1,2</sup> primarily through slowing of lung function growth during childhood.<sup>3</sup> This effectively reduces peak lung function which is attained by late adolescence/early adulthood.<sup>4</sup> Theoretically, early life factors that lead to airway narrowing have the potential to predispose individuals to exhibit overt respiratory manifestations of asthma. Childhood respiratory infections have been known to predispose to airflow obstruction and reduced peak lung function,<sup>5</sup> and therefore have the potential to contribute to the severity of COPD later in life.<sup>3</sup> Specifically, early childhood viral infections such as respiratory syncytial virus have been linked to asthma and airflow limitation in older children.<sup>6,7</sup> The long-term lung function consequences of the measles virus have not yet been established.

Three *prospective* population-based studies have examined the relationship between early childhood measles and post-bronchodilator (BD) spirometry in adults, all of which recruited participants born in the pre-antibiotic and pre-measles immunization era.<sup>8-10</sup> Although pneumonia is the most common severe acute complication of measles,<sup>11</sup> none of these studies reported main associations between

childhood measles and adult post-BD airflow obstruction. Shaheen and colleagues examined for effect modification by personal smoking in one cohort, but with insufficient power (n=239).<sup>10</sup> Furthermore, none of the mentioned studies assessed associations with other measures of lung function related to COPD such as gas transfer factor and measures of gas trapping. We hypothesized that childhood measles contributed to reduced lung function in adult life, either by modifying the potential obstructive airway effects of adult asthma and/or smoking,<sup>12, 13</sup> or by contributing to lung parenchymal changes.

Using a prospective cohort study spanning five decades, we aimed to investigate the consequences of childhood measles with regards to post-bronchodilator lung function measures in middle-age, and to investigate potential interactions with asthma and smoking. This manuscript is novel but complements a previous publication.<sup>12</sup>

## Methods

### *Study Design and Population*

Participants were from the 5<sup>th</sup> decade follow-up of the Tasmanian Longitudinal Health Study (TAHS 1968-2008), and details have been

published,<sup>12, 14-18</sup> including the TAHS cohort profile paper.<sup>18</sup> Briefly, this population-based cohort born in 1961 (n=8,583) and studied with spirometry in 1968 was retraced (n=7,312),<sup>17</sup> and resurveyed (n=5,729 responses) between 2002 and 2005. Parent-completed school medical records which included history of childhood infections and immunizations were accessed. Those who participated at multiple time points (1974 clinical study and/or 1992 follow-up visit), and those with either adult asthma and/or chronic bronchitis based on the 2004 postal survey, were invited to participate in a clinical study (n=2,373)(Figure 1).<sup>2</sup> Of these, 1405 laboratory attendees underwent testing including post-BD spirometry (n=1,389), gas transfer factor and static lung volumes measurements. Fifteen percent (n=354) only completed the telephone administered questionnaire.

This study was approved by Human Ethics Review Committees at The Universities of Melbourne (approval number 040375), Tasmania (040375.1) and New South Wales (08094), the Alfred (1118/04), and Royal Brisbane & Women's Hospital Health Service District (2006/037). Written informed consent was obtained from all participants.

### *Data Collection Methods*

Details of complex lung function testing have been described,<sup>12</sup> and are summarized in Supplementary Appendix S1. The measurements of lung function were standardized across testing sites following American Thoracic Society (ATS) and European Respiratory Society (ERS) standards.<sup>19-21</sup> For this analysis, lung function data from the baseline survey (1968) and laboratory study (2006-2008) were converted to z-scores.<sup>12, 22-24</sup>

### *Clinical Definitions*

A history of childhood measles was defined by an affirmative response by parents to a specific question recorded by the Tasmanian school medical service. Childhood current asthma was defined by the presence of asthma or “wheezing breathing” within 2 years of lung function testing when participants were aged 6–7 years. Current clinical asthma was defined by a history of adult asthma and at least one of asthma symptoms, medication use, and/or health care utilization for asthma within 12 months preceding the laboratory study visit. Additional definitions are covered in Supplementary Appendix S2.

Post-bronchodilator (BD) airflow obstruction (AO) (or post-BD AO) was defined by  $FEV_1/FVC < 5^{\text{th}}$  percentile of normal predicted values (z-score  $< -1.645$ ) following 200  $\mu\text{g}$  of salbutamol administered via spacer, and its severity assessed.<sup>25</sup> Post-BD AO has been used synonymously with spirometrically-defined COPD.

### *Statistical analysis*

All analyses were carried out using Stata (release 12, Stata Corporation, College Station, Texas, USA). Multivariable linear and logistic regression was used to examine associations between childhood measles, post-BD AO and other lung function outcomes. Sampling weights, being the inverse of the probability of being included in the sample, were included in all prevalence estimates and regression models. Models were adjusted for *a priori* confounders and additionally adjusted for covariates that changed estimates of association by at least 10% (Supplementary Appendix S3). Biologically plausible interactions (or multiplicative effects) were investigated and results were stratified if an interaction was present. A conventional cut-off of  $p < 0.05$  was used to determine statistical significance.

## Results

### *Demographic and clinical features*

Clinical characteristics and lung function data for the laboratory study participants have been published.<sup>12</sup> Briefly, the mean age (standard deviation [SD]) was 44.9 [0.85] years and 51% were male. As mentioned, our laboratory sample was intentionally enriched for ever having asthma and/or wheezing breathing 67% (n=925), of whom 36% (n=335) had current clinical asthma. Over half were ever-smokers (57%, n=804), of whom 59% (n=457) had smoked at least ten pack-years. The criterion for post-BD AO for the present analysis was met by 9.25% (n=123) of participants, of whom the majority had mild AO (n=95, 77% of this physiological group).

A history of childhood measles infection was reported for 69% (n=950) laboratory participants, and this did not differ by either adult or childhood current asthma status (p=0.130 and p=0.474 respectively, Table 1). Other than the deliberate enrichment for asthma and respiratory symptoms, laboratory study attendees were representative of the original 1968 cohort, especially including the prevalence of childhood measles (Supplementary Table S1).

### *Interactions on adult FEV<sub>1</sub>/FVC ratio*

While we did not find a significant main association between childhood measles and post-BD FEV<sub>1</sub>/FVC ratio taken as a continuous variable [z-score -0.10 to -0.11, p>0.10, Supplementary Table S2], we observed a two-way interaction between the effects of personal smoking and current asthma on post-BD FEV<sub>1</sub>/FVC ratio, but notably only for those with past childhood measles (3-way-interaction: p=0.009, Tables 2 and Supplementary Table S2). Above the sum of individual asthma and smoking estimates, the *excess* reduction in absolute FEV<sub>1</sub>/FVC ratio attributed to childhood measles for ever-smokers with e 10 pack-year history and current clinical asthma was 6.4% of predicted.

This three-way interaction was relevant to those with early-onset current clinical asthma rather than late-onset asthma (3-way-interaction: p=0.011 and 0.198 respectively, data not shown). When restricted to only include participants who had childhood current asthma at mean age (SD) 6.51 (0.28) years, the interaction was still significant despite relatively few regression numbers (n=225, 3-way-interaction: p<0.001).

A measles-related asthma-smoking interaction was also observed when post-BD AO was defined using the lower limit of normal (2-way-interaction:  $p=0.047$ ; 3-way-interaction:  $p=0.012$ ) (Table 3). This analysis differs from the continuous lung function outcome, mainly because the association between current clinical asthma without ten pack-year history and post-BD AO did not differ significantly in the presence and absence of childhood measles, despite similar case numbers [OR 2.23 ( $p=0.077$ ) versus OR 12.0 ( $p<0.001$ ) respectively]. The estimates were relatively imprecise given modest regression numbers of post-BD AO ( $n=95$ ).

### *Population prevalence for adult AO*

Given the observed three-way asthma-smoking-measles interaction on post-BD airflow obstruction, lung function summary statistics and prevalence of post-BD AO taken as the categorical variable have been stratified in Tables 4 and 5 respectively. While the average population prevalence of post-BD AO in the reference group with and without measles was similar (column 2, Table 5), the adjusted post-BD AO prevalence for the asthma-smoking subgroup was significantly greater when there was also childhood measles [19% (95%CI: 4–34) versus 40% (27–52)]. Paradoxically, the prevalence of post-BD AO was significantly less when the asthma-only subgroup was accompanied

by childhood measles [18% (9–27) versus 8.1% (4–13)]. Only 5.7% of laboratory participants had current adult asthma, e 10 pack-years and measles, yet this subgroup represented 19% (95%CI: 13–28%) of post-BD AO cases in the entire TAHS population.

### *Childhood measles and other lung function indices*

No association between childhood measles and [pre-BD] spirometry when participants were seven-years old was seen (Supplementary Table S3). A modest association was seen between childhood measles and reduced  $T_{LCO}$  in middle-age [z-score -0.12 (-0.2 to -0.0005),  $p=0.049$ ,  $n=994$ ], but not for the static lung volume indices (Supplementary Appendix S4).

## Discussion

In this population-based study, childhood measles recorded by school medical report was not found to have an independent influence on post-BD airflow obstruction in middle-aged individuals, but did augment substantially the combined effect of current asthma and smoking at least ten pack-years. This three-way interaction was

apparent from both decreasing post-BD FEV<sub>1</sub>/FVC ratio taken as a continuous variable and by increasing odds of ‘spirometrically-defined COPD’. Of this ‘asthma-smoking-measles’ subgroup comprising 5.7% of laboratory study participants, 40% had co-existent post-BD airflow obstruction, and this profile contributed one-fifth of the total ‘COPD’ burden at this relatively young age. This primarily related to childhood-onset current adult asthma.

Measles-related lower respiratory tract involvement can frequently manifest as radiographic lung infiltrates in hospitalised children,<sup>26</sup> and the long-term sequelae of these changes have been poorly characterized. For cases of fatal measles infection, post-mortem studies have identified inflammation of “fine” or smaller airways as a morphological feature distinct from lower lobe collapse and secondary bacterial pneumonia<sup>27</sup>. This raises the possibility that widespread small airways damage, inflammation and remodelling potentially arising from childhood measles, predisposes to symptomatic asthma<sup>24</sup> and increased susceptibility to future respiratory insults like smoking. However, in addition to possible underlying primary structural tissue damage, the pathophysiology has been reported to include sustained measles-related immunological changes such as reductions in adult atopy.<sup>28</sup>

The concept of an asthma-smoking interaction in relation to post-BD airflow obstruction has been reported in our earlier work,<sup>12</sup> but importantly, modification by childhood measles is a novel finding.<sup>29</sup> The measles virus is highly contagious for all non-immunized individuals who have not had the disease,<sup>30</sup> and so was highly prevalent in this pre-immunization era group, but we found no independent effect of measles on its own. This suggests that from an epidemiological viewpoint, childhood measles might contribute towards causing disease together with other component causes, but is not sufficient to cause disease on its own.<sup>31</sup>

In this prospective cohort, earlier findings showed a significant temporal relationship between childhood measles and subsequent asthma development in adolescence.<sup>16</sup> For middle-aged non-smokers and those smoking <10 pack-years, our data suggests the link between current clinical asthma and post-BD AO differed by childhood measles status, which paradoxically seemed to protect against post-BD AO for those reporting measles by age seven (Table 3). This is difficult to explain or even speculate but raises the possibility for measles-associated current adult asthma to be an asthma phenotype that is distinct from adult asthma *without* a measles history, given its

lack of association with post-BD AO. Furthermore, the adverse obstructive smoking effect is so augmented in the presence of a substantial history, and required the co-presence of current adult asthma to see this. This potential for an infection to augment the influence of personal smoking seems quite similar to the clinical experience in tuberculosis.<sup>32</sup>

We acknowledge that post-BD FEV<sub>1</sub>/FVC was only measured at one time-point so longitudinal decline was not assessed. However, the complex interplay between smoking, active asthma by age-of-onset and childhood measles might in part explain why the TAHS has previously found a positive asthma-smoking interaction on post-BD AO while the Dunedin cohort study that was born *after* the widespread availability of measles immunization, found a negative one.<sup>33-35</sup>

While only a relatively small proportion of our middle-aged population comprised the asthma-smoking-measles subgroup, the magnitude of the lung function deficits and contribution to post-BD airflow obstruction were considerable. For the era prior to measles immunization, this interaction might in part explain the previously

observed heterogeneity of lung function loss for a given age, sex and pack-year history. This analysis raises the possibility that childhood measles might have a role in influencing the development of post-BD airflow obstruction, especially for those with current asthma who may be less likely to progress to the ‘asthma-COPD overlap (ACO)’.<sup>36</sup> If this is accurate, the introduction of measles immunization might well lessen the burden of post-BD airflow obstruction for Australians born after 1970, which in the context of the marked drop off in smoking rates, has the potential for modifying future demographics of COPD in immunized communities.

### *Strengths and limitations*

Our study has two main strengths: First, TAHS has collected data prospectively over five decades, from the age of seven until mid-adult life, with lung function measures that included static lung volumes and gas transfer factor. As TAHS participants were not immunized against measles and more than two-thirds had natural infection as young children, sufficient case numbers allowed us to investigate complex interactions although some estimates were relatively imprecise. Second, while the ‘healthy survivor effect’ might have

underestimated our observations, the older (pre-antibiotic) cohorts<sup>8-10</sup> would have been more susceptible to this form of bias.

In terms of limitations, it is acknowledged that it was not feasible to confirm the cases of childhood measles by serological testing.

However, the TAHS school medical health records were completed through by face-to-face interview by highly experienced trained staff at a time when this childhood disease was highly prevalent and skilled clinical acuity was standard practice. As infections by measles may be more easily recalled if its occurrence was more recent and/or severe, our findings may not reflect milder and subclinical disease. While the lack of objective testing and diagnosis by a doctor may contribute to exposure misclassification, this most likely biases associations towards the null. Also, our analyses did not account for potential long-term obstructive lung effects from other infections such as respiratory syncytial virus,<sup>6,7</sup> as this information was not collected, but again, this tends to weaken the signals.

While analyses were adjusted for sampling weights, it is possible that selection bias may not be entirely eliminated. Finally, as participants were essentially of European descent and unvaccinated for measles,

this may limit the generalizability of our findings to non-Causasian populations and adults born after 1970 in high-income countries.<sup>33</sup>

In conclusion, we have found a novel interaction between the effects of childhood measles and the combination of current clinical asthma and smoking on a key diagnostic criterion for COPD in middle-aged adults. The lack of investigation into these interactions is likely to have resulted in null findings in previous studies. While we did not find measles to have an independent effect on its own, our stratification has raised the possibility of a measles-related adult asthma phenotype, that most likely originated in childhood. These findings, if replicated by others, may give rise to opportunities for ‘personalized prevention’, especially for developing countries which have high personal smoking rates,<sup>37</sup> and are home to the majority of the world’s unvaccinated children.<sup>38</sup> For observational population-based cohorts, childhood measles infection and timing of immunization are considerations when studying the natural history of asthma and COPD.

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**Disclosure statement**

CFM has participated in Advisory Boards for Novartis and Pfizer, has received speaker fees from GlaxoSmithKline, and speaker fees to her institution from Menarini; EHW has received an honorarium from GlaxoSmithKline for giving lectures and an investigator-initiated research grant from Boehringer Ingelheim; MJA has received investigator initiated grants for unrelated research from Pfizer and Boehringer-Ingelheim and conference support from Sanofi; BRT has received speaker fees from Mundipharma Australia and Astra Zeneca; and PST has received payment for consultancy from Astra Zeneca.

## Figure legend

### **FIGURE 1: TAHS FLOW DIAGRAM 1968–2008**

The derivation of TAHS participants from 1968 to 2006–2008 has been included in a figure already published.<sup>2</sup> The present figure specifies how the subset of 1,258 participants emerged from 1,405 participating in the laboratory study (without reference to supplementary data).

**TABLE 1: LABORATORY ATTENDEE CHARACTERISTICS, BY CHILDHOOD MEASLES INFECTION**

Participant characteristic	TAHS laboratory participants [N=1,389] *	
	Childhood measles status [N=1,369]	
	No [n=419 (31%)]	Yes [n=950 (69%)]
Age [years (SD)]	44.9 (0.9)	44.8 (0.8)
Sex (% male)	219 (52)	478 (50)
Smoking status [n(%)]		
Never smoked	186 (44)	389 (41)
Past smoker	130 (31)	280 (30)
Current smoker	103 (26)	279 (29)
Smoking $\geq 10$ pack-years [n(%)]	132 (32)	316 (34)
Childhood current asthma age 7 [n(%)]	109 (26)	213 (22)
Adult current asthma at age 45 [n(%)]	105 (25)	225 (24)
Atopic sensitization at age 45 [n(%)] †	249 (60)	507 (54)
Socioeconomic status [n(%)] ‡		
1 (highest)	120 (29)	271 (29)
2	50 (12)	11 (12)
3	90 (22)	187 (20)
4	69 (17)	176 (19)
5 (lowest)	87 (21)	198 (21)
Childhood spirometry at age 7 (SD)		
FEV <sub>1</sub> [L]	1.35 (0.2)	1.33 (0.2)
Vital capacity [L]	1.47 (0.2)	1.46 (0.2)
Post-BD lung function at age 45 (SD) §		
FEV <sub>1</sub> [L]	3.47 (0.8)	3.39 (0.7)
FVC [L]	4.42 (1.0)	4.32 (0.9)
FEV <sub>1</sub> /FVC ratio	78.9 (7)	78.6 (7)
T <sub>L</sub> CO [mL/min/mmHg]	27.7 (7)	26.8 (7)
TLC [L]	6.54 (1.4)	6.40 (1.2)
FRC [L]	3.17 (0.8)	3.07 (0.8)
RV [L]	1.96 (0.6)	1.9 (0.5)
RV/ TLC ratio	29.8 (6)	29.8 (6)

*Definition of Abbreviations:* AO, airflow obstruction; BD, bronchodilator; CI, confidence interval; FEV<sub>1</sub>, forced vital capacity in one second; FRC, functional residual capacity; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; T<sub>L</sub>CO, transfer factor of the lung for carbon monoxide

\* Missing data for childhood measles status, n=20

† p = 0.052 (Chi-squared test)

‡ Socioeconomic status based on participant occupation

§ Technically acceptable lung function data available for post-BD spirometry (n=1,311); T<sub>L</sub>CO corrected for haemoglobin and carboxyhaemoglobin (n=1,222) and static lung volumes (n=1,198)

**TABLE 2: INTERACTION BETWEEN THE EFFECTS OF CHILDHOOD MEASLES, CURRENT ASTHMA AND SMOKING ON POST-BRONCHODILATOR FEV<sub>1</sub>/FVC IN MIDDLE-AGE †‡**

Asthma pattern	Personal smoking (pack-years)	Post-BD forced expiratory ratio at age 45 (N = 1002)			
		Childhood measles infection §			
		No (N = 328)		Yes (N = 674)	
		n (%)	z-scores [95%CI] ††	n (%)	z-scores [95%CI] ††
No or remitted asthma	< 10	158 (48)	Ref	351 (52)	Ref
	≥10	86 (26)	-0.50 [-0.7 to -0.2] ***	166 (25)	-0.30 [-0.5 to -0.1] ***
Current clinical asthma (any age of onset)	< 10	62 (19)	-0.37 [-0.7 to -0.1] *	106 (16)	-0.45 [-0.6 to -0.3] ***
	≥10	22 (7)	-0.70 [-1.1 to -0.3] **	51 (8)	-1.36 [-1.6 to -1.1] ***
Asthma-smoking interaction			p = 0.520	p < 0.001	
Asthma-smoking-measles interaction (3-way)			p = 0.009		

*Definitions of Abbreviations:* BD, bronchodilator; CI, confidence interval; FEV<sub>1</sub>/FVC, the ratio between forced expiratory volume in one second and forced vital capacity; ref, reference group

\*p<0.05 \*\*p<0.01 \*\*\*p<0.001

† Reference group = those without current asthma who smoked less than a ten pack-year history

‡ Multivariable adjusted model includes sampling weights, sex, paternal occupation, familial and/or parental history of COPD/asthma, pre-BD FEV<sub>1</sub>/VC at age 7 years (continuous), maternal smoking, current asthma at age 7, adult atopy, plus the interaction term personal smoking\*current asthma at age 45, stratified by measles infection

§ No main effect for childhood measles infection per se on post-BD FEV<sub>1</sub>/FVC (Supplementary Table S2)

†† A z-score is the deviation from the mean predicted value, where 95% of normally distributed data lies between -1.96 SD and +1.96 SD

**TABLE 3: MULTIVARIABLE INTERACTION BETWEEN THE EFFECTS OF CHILDHOOD MEASLES, CURRENT ASTHMA AND SMOKING ON POST-BRONCHODILATOR AIRFLOW OBSTRUCTION IN MIDDLE-AGE †‡**

Asthma pattern	Personal smoking (pack-years)	Post-BD airflow obstruction at age 45 (n=95)			
		Childhood measles infection (N = 1026)			
		No (N = 334)		Yes (N = 692)	
		% (n/N) §	OR [95%CI]	% (n/N) §	OR [95%CI]
No or remitted asthma	< 10	2 (4/162)	Ref	4 (13/361)	Ref
	≥10	11 (10/87)	5.14 [1.5, 18] **	9 (15/169)	2.34 [1.1, 5.1] *
Current clinical asthma (any age of onset)	< 10	23 (14/62)	12.0 [3.4, 42] ***	10 (11/109)	2.17 [0.9, 5.3]
	≥10	26 (6/23)	15.4 [3.5, 65] ***	42 (22/53)	17.2 [7.3, 40] ***
Asthma-smoking interaction			p = 0.109	p = 0.042	
Asthma-smoking-measles interaction			p = 0.012		

*Definitions of Abbreviations:* BD, bronchodilator; CI, confidence interval; FEV<sub>1</sub>/FVC, the ratio between forced expiratory volume in one second and forced vital capacity; LLN5; lower limit of normal at the 5<sup>th</sup> percentile; n, number with post-BD AO; N, number in the subgroup; OR, odds ratio; ref, reference group

\*p<0.05 \*\*p<0.01 \*\*\*p<0.001

† Reference group = those without current asthma who smoked less than a ten pack-year history

‡ Multivariable adjusted model includes sampling weights, sex, paternal occupation, familial and/or parental history of COPD/asthma, current asthma at age 7, pre-BD FEV<sub>1</sub>/VC at age 7 years (binary), plus the three-way interaction term personal smoking\*current asthma\*childhood measles

§ This column refers to the number of post-BD AO cases (n) within individual subgroups (N), expressed as a percentage

**TABLE 4: LUNG FUNCTION AND ASTHMA-SMOKING-MEASLES SUBGROUPS**

Subgroups related to measles, current asthma, and/or smoking at least ten pack-years	Post-BD spirometry at age 45 years (N=1,258) *‡				
	N= (%)	FEV <sub>1</sub> , L raw value	FEV <sub>1</sub> z-score §	FEV <sub>1</sub> /FVC raw value	FEV <sub>1</sub> /FVC z-score §
No childhood measles infection					
Neither asthma nor smoking	193 (15)	3.7 (0.7)	+0.23 (0.9)	80 (4)	+0.02 (0.8)
Asthma only	74 (6)	3.2 (0.7)	-0.31 (1.2)	78 (8)	-0.39 (1.2)
Smoker only	102 (8)	3.5 (0.7)	-0.30 (0.9)	77 (7)	-0.43 (1.0)
Asthma plus smoking	26 (2)	2.9 (0.8)	-0.89 (1.3)	75 (9)	-0.85 (1.2)
Childhood measles infection					
Measles only	436 (35)	3.5 (0.7)	+0.15 (0.9)	81 (5)	+0.04 (0.9)
Asthma plus measles	135 (11)	3.3 (0.7)	-0.38 (1.0)	77 (7)	-0.49 (1.0)
Smoker plus measles	220 (17)	3.4 (0.6)	-0.32 (1.0)	78 (6)	-0.34 (0.9)
Asthma, smoking plus measles	72 (6)	2.8 (0.7)	-1.14 (1.3)	71 (10)	-1.41 (1.3)

*Definition of Abbreviations:* BD, bronchodilator; FEV<sub>1</sub>, forced expiratory ratio in one second; FEV<sub>1</sub>/FVC, the ratio of FEV<sub>1</sub> over forced vital capacity; SD, standard deviation

\* Asthma and chronic bronchitis enriched population-based sample, excluding those with missing data

‡ Lung function data are expressed as mean (SD), unless otherwise specified

§ A z-score is the deviation from the mean predicted value, where 95% of normally distributed data lies between -1.96 SD and +1.96 SD

**TABLE 5: POPULATION PREVALENCE OF POST-BRONCHODILATOR AIRFLOW OBSTRUCTION IN ASTHMA-SMOKING-MEASLES SUBGROUPS**

Subgroups with measles, current asthma, and/or smoking at least ten pack-years	N= (%)	Population prevalence of post-BD AO, reweighted to the entire TAHS population [% (95%CI)] * ‡ §
No childhood measles infection		
Neither asthma nor smoking	193 (15)	3.1 (0.3, 6)
Asthma only	74 (6)	18 (9, 27)
Smoker only	102 (8)	11 (4, 19)
Asthma plus smoking	26 (2)	19 (4, 34)
Childhood measles infection		
Measles only	436 (35)	2.9 (1, 5)
Asthma plus measles	135 (11)	8.1 (4, 13)
Smoker plus measles	220 (17)	8.0 (4, 12)
Asthma, smoking plus measles	72 (6)	40 (27, 52)

*Definition of Abbreviations:* AO, airflow obstruction; BD, bronchodilator; CI, confidence interval

\* Calculated using sampling weights derived from the 1968, 1974 and 2004 surveys

‡ Prevalence of post-BD AO for all subgroups = 9.46% (119/1,258) as defined by GLI2012 equations, z-scores, and lower limit of normal at the 5<sup>th</sup> percentile

§The sum of the prevalence/ proportion between AO and 'no AO' subgroups equals 100 (latter not shown)

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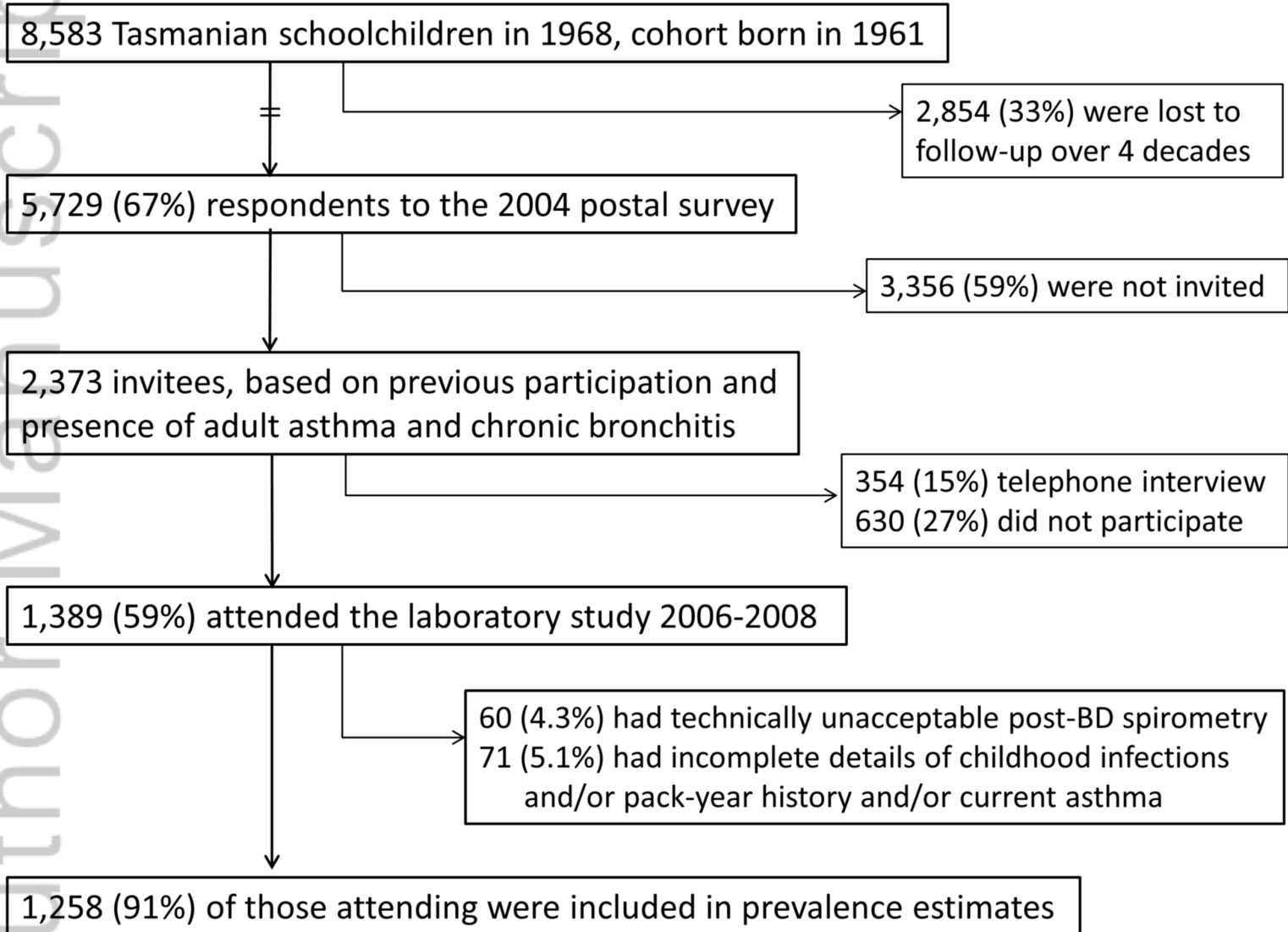
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