Parental smoke exposure before age 15 years and offspring asthma trajectories from ages 7 to 53 years

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Paternal smoke exposure before 15 years of age was linked to offspring early-onset asthma, associated with midlife COPD. The maternal link was shown with additional offspring childhood passive smoke. Avoiding smoking near children may lower their asthma risk. https://bit.ly/3V7JGiA

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Abstract

Background and objective Paternal passive smoke exposure before 15 years of age was associated with offspring childhood asthma, but its association with asthma beyond childhood had not been investigated. We aimed to investigate such long-term association.

Methods Data were from 1078 father–offspring and 1537 mother–offspring pairs from the Tasmanian Longitudinal Health Study. Offspring (probands of the original cohort) completed asthma surveys at age 7, 13, 18, 30, 43, 50 and 53 years. Life-course asthma trajectories were developed using group-based trajectory modelling. Parents self-reported their own passive smoke exposure before 15 years of age. Multinomial logistic regressions assessed associations between parental passive smoke exposure and offspring asthma trajectories. Active parental smoking, offspring sex, childhood respiratory illnesses and subsequent active smoking were evaluated for mediations and interactions.

Results Paternal passive smoke exposure before 15 years of age was associated with an early-onset adult-remitting asthma trajectory (adjusted multinomial odds ratio (aMOR) 2.53, 95% CI 1.09–5.85) in offspring, but not persistent asthma trajectories. Maternal passive smoke exposure before 15 years of age was associated with an early-onset adult-remitting asthma trajectory in offspring who were also exposed to childhood passive smoke (aMOR 4.30, 95% CI 1.01–18.40; p-interaction=0.044). The observed associations were partly mediated through active parental smoking or offspring childhood respiratory illnesses (each <10%).

Conclusions This study identified a novel association between parental passive smoke exposure before 15 years of age and an early-onset adult-remitting asthma trajectory in offspring, which is related to subsequent COPD. These findings suggest that in parents inevitably exposed to passive smoke during childhood/puberty, asthma risk in future generations associated with such exposure may be lower if parents avoid smoking around children.

Introduction

Asthma is a significant public health issue with substantial burden globally. Asthma affected 262 million people in 2019 [1], causing 461 000 deaths and 22 million disability-adjusted life-years [2]. Its global prevalence is estimated to reach 275 million by 2050 [3]. Importantly, asthma is the most common noncommunicable disease in children [4].

While early-life asthma risk factors are well studied, evidence for intrauterine and childhood interventions remains inconclusive. Specifically, a review of over 40 randomised controlled trials evaluating various intervention strategies targeting some major risk factors revealed insufficient evidence of their effectiveness [5]. The most common interventions evaluated in these trials included nutritional supplements during maternal pregnancy, allergen avoidance from intrauterine life to age 5 years in offspring and avoiding exposure to passive (second-hand) smoke from the birth of offspring [5]. The limited effectiveness of most intrauterine and childhood intervention trails suggests that asthma may partly originate from adverse exposures occurring before conception. To date, this hypothesis has been supported by emerging evidence suggesting the pre-conception origin of respiratory diseases [6].

Among adverse preconception exposures, active and passive smoking before completing puberty in previous generations are likely to have detrimental impact on respiratory health of future generations [7, 8]. Active paternal smoking before 15 years of age has been associated with an increased risk of offspring asthma before 10 years of age [9]. Besides active smoking, passive smoke exposure during puberty is particularly concerning, given its much higher prevalence compared to active smoking in that period (63% *versus* 7%) [10, 11]. In a preliminary analysis, paternal passive smoke exposure before 15 years of age was associated with offspring asthma by 7 years of age [12]. However, the long-term association between parental passive smoke exposure before 15 years of age and offspring asthma later in life had not been investigated. The Tasmanian Longitudinal Health Study (TAHS) has captured dynamic patterns of asthma progression in probands, identifying their asthma trajectories from ages 7 to 53 years [13]. This provides a unique opportunity to investigate associations between longitudinal asthma trajectories and their potential risk factors, including parental passive smoke exposure before 15 years of age. These investigations may clarify asthma pathophysiology and reveal critical windows for prevention.

To address the knowledge gap, this study aimed to investigate 1) the associations between passive smoke exposure before 15 years of age from either parent and asthma trajectories from childhood to middle age in their offspring, and 2) whether these associations were mediated or modified by other known factors in parents and offspring.

Methods

Study design

This study was conducted using data from the TAHS. The TAHS commenced in 1968 (baseline) and gathered comprehensive respiratory health data from probands (referred to as “offspring” in this paper), from childhood until the sixth decade of life [14]. Briefly, the baseline survey was carried out to assess the respiratory illnesses of 8583 offspring born in 1961, who were attending schools in Tasmania, Australia, in 1968. The parents completed the baseline survey for their offspring and provided information about their own history of respiratory illnesses and demographic characteristics. Follow-up studies were performed when the offspring were at mean ages of 13, 18, 30, 43, 50 and 53 years. Thereafter, in 2010, among the 7243 parents who were still alive and could be located, 5111 (70.6%) participated in the TAHS Parents Postal Survey. From 5097 parents with valid data, 2096 were fathers and 3001 were mothers.

Exposure: parental passive smoke exposure before 15 years of age

In the 2010 TAHS Parents Postal Survey, information on parental passive smoke exposure before 15 years of age was collected. Parents of the offspring were asked to recall their own fathers’ and mothers’ (offspring’s grandparents) active smoking habits before the parents reached puberty completion using the questions “Did your father smoke when you were less than 5 years?”, “Did your father smoke when you were aged 5–15 years?”, “Did your mother smoke when you were less than 5 years?” and “Did your mother smoke when you were aged 5–15 years?”. Fathers or mothers of the offspring were classified as exposed to passive smoke before age 15 years if they responded affirmatively to passive smoke exposure during either of these periods from either of their own parents.

Outcomes: offspring asthma trajectories from childhood to middle age

Offspring asthma was assessed at ages 7, 13, 18, 30, 43, 50 and 53 years. Based on the longitudinal asthma data, asthma trajectories from ages 7 to 53 years were previously modelled using group-based

trajectory modelling (supplementary methods S1) [13]. Six asthma trajectories were identified in the TAHS population with distinct patterns of age of onset and remission, including 1) never asthma, 2) early-onset adolescent-remitting, 3) early-onset adult-remitting, 4) early-onset persistent, 5) late-onset remitting and 6) late-onset persistent (figure S1).

Statistical analyses

Multinomial logistic regressions assessed associations between passive smoke exposure before 15 years from either parent and asthma trajectories in their offspring. A directed acyclic graph model [15] based on *a priori* knowledge was developed to guide selection of potential confounders (methods S2 and figure S2). Model 1 was adjusted for socioeconomic indexes for area – the index of relative socioeconomic disadvantage (SEIFA-IRSD) scores of parents, as a proxy for parental socioeconomic status (methods S3). Moreover, paternal and maternal lifetime history of asthma/wheeze and their baseline age in 1968 were adjusted for in model 2 in respective father–offspring and mother–offspring categories [9, 16]. Results were presented as multinomial odds ratios (MORs) and, when adjusted, as aMORs.

Likelihood ratio tests [17] assessed potential effect modifications for active parental smoking, offspring sex at birth, respiratory illnesses (hay fever, bronchitis, food allergy and pneumonia/pleurisy) and passive smoke exposure related to active parental smoking during childhood (by 7 years of age) and subsequent active smoking by middle age (53 years) (methods S4). Statistical significance for associations and interactions were defined as p-values less than 0.05 and 0.10, respectively.

Causal mediation analysis using the *medeff* program individually quantified the proportion mediated by each mediator, providing standard errors and 95% confidence intervals for the indirect effect [18–20]. Potential mediators assessed included active parental smoking, offspring preterm birth, low birthweight, childhood respiratory illnesses and passive smoke exposure, and subsequent active smoking by middle age. Mediation was considered significant if the 95% confidence interval excluded 0%.

To assess potential selection bias, a comparison of the demographics was performed between included and excluded parent-offspring pairs in this analysis. Definitions of potential confounders, effect modifiers and mediators were provided in methods S5. All analyses were performed using STATA version 18 (StataCorp, College Station, TX, USA).

Results

This analysis included 1078 father–offspring pairs and 1537 mother–offspring pairs who had data on paternal or maternal passive smoke exposure before 15 years of age and offspring asthma trajectories (figure S3). Of fathers and mothers, 69.0% and 72.9% respectively reported exposure to passive smoke before 15 years of age. Regarding their offspring, approximately 60% of them were exposed to passive smoke during childhood. More than 50% of offspring had a history of active smoking by middle age (table 1). Compared to those excluded, the included offspring had a lower proportion of males and reported lower prevalence of childhood passive smoke exposure and subsequent active smoking. Their parents were younger and more socioeconomically advantaged (table S1).

Associations between paternal passive smoke exposure before 15 years of age and offspring asthma trajectories

Paternal passive smoke exposure before 15 years of age was associated with increased odds of their offspring belonging to the early-onset adult-remitting asthma trajectory (aMOR 2.53, 95% CI 1.09–5.85) (table 2). This asthma trajectory included those offspring with asthma onset early in childhood and adolescence that gradually remitted during adulthood. No evidence of associations was found with the other asthma trajectories.

The statistical evidence for interactions did not meet our prespecified threshold of a p-interaction<0.1 in father–offspring pairs (table S2). The percentages of mediations by potential mediators are shown in table S3. Active paternal smoking, offspring childhood passive smoke exposure and active smoking by middle age, and childhood pneumonia/pleurisy modestly mediated the association between paternal passive smoke exposure before 15 years of age and the early-onset adult-remitting asthma trajectory in offspring. Specifically, the mediated proportions were 5.8% (95% CI 3.0–24.1%) for paternal smoking, 2.9% (95% CI 1.5–11.3%) for childhood passive smoke exposure, 1.1% (95% CI 0.5–4.5%) for active smoking by middle age and 0.7% (95% CI 0.3–3.1%) for pneumonia/pleurisy. Other mediators, including offspring preterm birth, low birthweight, hay fever, bronchitis and food allergy, did not show significant mediation.

TABLE 1 Characteristics of the offspring and their parents

Characteristic	Offspring of fathers (n=1078)	Offspring of mothers (n=1537)
Birthweight (kg), mean±SD	3.3±0.5	3.3±0.5
Missing, n	242	244
Height at age 53 years (cm), mean±SD	170.1±9.4	170.2±9.3
Missing, n	8	13
Weight at age 53 years (kg), mean±SD	81.8±17.2	82.0±17.0
Missing, n	6	11
Preterm birth, n (%)	119 (15.0)	202 (16.3)
Missing, n	282	298
Small for gestational age, n (%)	124 (18.0)	177 (16.2)
Missing, n	387	444
Sex at birth, male, n (%)	512 (47.5)	742 (48.3)
Birthplace		
Tasmania, Australia, n (%)	967 (90.2)	1395 (91.1)
Other Australian state or territory, n (%)	60 (5.6)	84 (5.5)
UK, NZ, SA, Canada or USA, n (%)	36 (3.4)	40 (2.6)
Other overseas country, n (%)	9 (0.8)	13 (0.9)
Missing, n	6	5
Passive smoke exposure by age 7 years, n (%)	615 (57.4)	952 (62.8)
Missing, n	6	22
Active smoking by age 53 years, n (%)	550 (51.0)	844 (55.1)
Missing, n	0	4
	Fathers (n=1078)	**Mothers (n=1537)**
Age at baseline when offspring aged 7 years (years), mean±SD	34.7±5.2	32.5±5.2
Missing, n	15	21
SEIFA-IRSD (scores), mean±SD	995.9±46.8	995.7±47.5
Missing, n	14	19
Passive smoke exposure before age 15 years, n (%)	744 (69.0)	1120 (72.9)
Active smoking		
Never smoked, n (%)	421 (39.7)	976 (64.1)
Smoking commenced before age 15 years, n (%)	141 (13.3)	36 (2.4)
Smoking commenced after age 15 years, n (%)	498 (47.0)	510 (33.5)
Missing, n	18	15
Lifetime history of asthma/wheeze, n (%)		
No asthma/wheeze, n (%)	856 (81.1)	1188 (79.5)
Self-reported asthma/wheeze without a doctor diagnosis, n (%)	46 (4.4)	69 (4.6)
Doctor-diagnosed asthma, n (%)	154 (14.6)	238 (15.9)
Missing, n	22	42

The percentages of offspring birthplace and paternal lifetime history of asthma/wheeze do not sum to 100.0% because of rounding. NZ: New Zealand; SA: South Africa; SEIFA-IRSD: socioeconomic indexes for areas – the index of relative socioeconomic disadvantage; UK: United Kingdom; USA: United States of America.

Associations between maternal passive smoke exposure before 15 years of age and offspring asthma trajectories

Weak evidence was found for an association between maternal passive smoke exposure before 15 years of age and the early-onset adult-remitting trajectory in offspring (aMOR 1.93, 95% CI 0.89–4.20; p=0.096) (table 3). There was no evidence of an association for other trajectories.

There was evidence that offspring childhood passive smoke exposure was an effect modifier (p-interaction=0.044) (table 4). Specifically, the association between maternal passive smoke exposure before 15 years of age and the early-onset adult-remitting asthma trajectory in offspring was more evident when the offspring were additionally exposed to passive smoke during their own childhood (aMOR 4.30, 95% CI 1.01–18.40) compared to that in offspring without exposure to childhood passive smoke (aMOR 1.26, 95% CI 0.43–3.69) (table 4). Furthermore, while there was some evidence of interactions between the maternal exposure with active maternal smoking (p-interaction=0.068) and offspring childhood pneumonia/pleurisy (p-interaction=0.051) (table S4), the stratified analyses based on these effect modifiers

TABLE 2 Associations between paternal passive smoke exposure before 15 years of age and asthma trajectories from ages 7 to 53 years in their offspring

Paternal passive smoke exposure before age 15 years	n/total n (%)[#]	Crude model MOR (95% CI) p-value	Adjusted model 1 aMOR (95% CI) p-value	Adjusted model 2 aMOR (95% CI) p-value
Trajectory: never asthma				
Not exposed	178/334 (53.29)		Base outcome (reference)	
Exposed	374/744 (50.27)			
Trajectory: early-onset adolescent-remitting				
Not exposed	85/334 (25.45)			
Exposed	194/744 (26.08)	1.09 (0.80–1.48) 0.60	1.11 (0.81–1.51) 0.53	1.09 (0.79–1.50) 0.61
Trajectory: early-onset adult-remitting				
Not exposed	8/334 (2.40)			
Exposed	35/744 (4.70)	2.08 (0.95–4.58) 0.068	2.11 (0.96–4.64) 0.064	2.53 (1.09–5.85) 0.031[¶]
Trajectory: early-onset persistent				
Not exposed	16/334 (4.79)			
Exposed	36/744 (4.84)	1.07 (0.58–1.98) 0.83	1.16 (0.62–2.18) 0.64	1.06 (0.56–2.02) 0.86
Trajectory: late-onset remitting				
Not exposed	16/334 (4.79)			
Exposed	23/744 (3.09)	0.68 (0.35–1.33) 0.26	0.70 (0.36–1.35) 0.29	0.71 (0.36–1.40) 0.32
Trajectory: late-onset persistent				
Not exposed	31/334 (9.28)			
Exposed	82/744 (11.02)	1.26 (0.80–1.97) 0.32	1.31 (0.83–2.06) 0.25	1.34 (0.84–2.14) 0.22

Multinominal odds ratios (MORs), adjusted MORs (aMORs) and p-values from multinomial logistic regressions. Adjusted model 1: adjustment for SEIFA-IRSD (socioeconomic indexes for areas – the index of relative socioeconomic disadvantage) scores of parents. Adjusted model 2: model 1 plus further adjustment for paternal lifetime history of asthma/wheeze and paternal age at baseline. SEIFA-IRSD: socioeconomic indexes for areas – the index of relative socioeconomic disadvantage. [#]: Numbers of each trajectory in each exposure category. [¶]: Statistically significant.

did not reveal differential significant associations between strata for the early-onset adult-remitting asthma trajectory (tables S5–S6).

The mediation analysis showed that offspring childhood passive smoke exposure mediated 0.9% (95% CI 0.4–4.9%) of the total effect between maternal passive smoke exposure before 15 years of age and the early-onset adult-remitting asthma trajectory in offspring (table S7). The other potential mediators did not demonstrate mediation.

Discussion

This is the first study to investigate associations between parental passive smoke exposure before 15 years of age and asthma trajectories from childhood to middle age in offspring. We found that offspring were associated with higher odds of following an early-onset adult-remitting asthma trajectory, which is subsequently associated with COPD in middle age [13], when their fathers were passively exposed to smoke before 15 years of age, compared to those without the paternal exposure. Only a small proportion of this association was mediated through active paternal smoking, offspring passive smoke exposure and pneumonia/pleurisy during childhood, and subsequent active smoking by middle age. The association between maternal passive smoke exposure before 15 years of age and the early-onset adult-remitting asthma trajectory in offspring was observed for offspring who were additionally exposed to passive smoke during their own childhood.

It should be emphasised that the early-onset adult-remitting asthma trajectory does not represent a favourable health condition. It was believed that early-onset asthma during childhood was "not necessarily unfavourable" because it had a higher possibility to remit by middle age compared to asthma onset in adulthood [21]. Thus, the early-onset adult-remitting asthma trajectory may create a deceptive perception that the asthma has been cured. However, emerging evidence has suggested that asthma remission is a distinct clinical phenotype. It was associated with respiratory dysfunction by middle age compared to no

TABLE 3 Associations between maternal passive smoke exposure before 15 years of age and asthma trajectories from ages 7 to 53 years in their offspring

Maternal passive smoke exposure before age 15 years	n/total n (%)[#]	Crude model MOR (95% CI) p-value	Adjusted model 1 aMOR (95% CI) p-value	Adjusted model 2 aMOR (95% CI) p-value
Trajectory: never asthma				
Not exposed	218/417 (52.28)		Base outcome (reference)	
Exposed	581/1120 (51.88)			
Trajectory: early-onset adolescent-remitting				
Not exposed	113/417 (27.10)			
Exposed	282/1120 (25.18)	0.94 (0.72–1.22) 0.63	0.96 (0.73–1.25) 0.75	0.93 (0.71–1.23) 0.62
Trajectory: early-onset adult-remitting				
Not exposed	10/417 (2.40)			
Exposed	42/1120 (3.75)	1.58 (0.78–3.20) 0.21	1.58 (0.78–3.21) 0.20	1.93 (0.89–4.20) 0.096
Trajectory: early-onset persistent				
Not exposed	16/417 (3.84)			
Exposed	53/1120 (4.73)	1.24 (0.70–2.22) 0.46	1.23 (0.68–2.19) 0.49	1.17 (0.65–2.11) 0.60
Trajectory: late-onset remitting				
Not exposed	15/417 (3.60)			
Exposed	45/1120 (4.02)	1.13 (0.61–2.06) 0.70	1.13 (0.62–2.07) 0.69	1.14 (0.62–2.10) 0.68
Trajectory: late-onset persistent				
Not exposed	45/417 (10.79)			
Exposed	117/1120 (10.45)	0.98 (0.67–1.42) 0.90	0.99 (0.68–1.45) 0.98	1.01 (0.68–1.49) 0.97

Multinominal odds ratios (MORs), adjusted MORs (aMORs) and p-values from multinomial logistic regressions. Adjusted model 1: adjustment for SEIFA-IRSD (socioeconomic indexes for areas – the index of relative socioeconomic disadvantage) scores of parents. Adjusted model 2: model 1 plus further adjustment for maternal lifetime history of asthma/wheeze and maternal age at baseline. [#]: Numbers of each trajectory in each exposure category.

history of asthma, including airflow obstruction [22], rapid lung function decline [23] and COPD [13]. This is particularly concerning as respiratory dysfunction later in life could be difficult to recognise due to asthma symptoms in remission. Therefore, more attention should be directed towards early-onset asthma to mitigate the burden of respiratory dysfunction later in life. Identifying risk factors for this unfavourable asthma trajectory has public health implications.

Our findings align with those of others who investigated active paternal smoking before 15 years of age and maternal passive smoke exposure during their own intrauterine life. Previous studies have reported an association between active paternal smoking before 15 years of age and offspring asthma before 10 years of age [9], and ever asthma by a median age of around 24–26 years [16]. Besides active paternal smoking, maternal intrauterine passive smoke exposure was also associated with offspring asthma by 6 years of age [24, 25]. Findings from ours and previous studies emphasise an adverse intergenerational association between preconception passive smoke exposure and early-onset asthma in offspring. While these studies have only investigated the associations with offspring asthma in childhood or early adulthood, our study was the first to investigate associations with longitudinal asthma trajectories from ages 7 to 53 years.

The association between paternal passive smoke exposure before 15 years of age and early-onset asthma in offspring may be explained by different mechanisms. Active paternal smoking has been recognised as a risk factor for offspring childhood asthma [26] and therefore may mediate the association between paternal passive smoke exposure before 15 years of age and early-onset asthma in offspring. Our finding of wide 95% confidence intervals, with high upper bound for the mediation effect of active paternal smoking (24.1%), supports this point to some extent. However, evidence for mediation by active paternal smoking, offspring childhood passive smoke exposure and their own active smoking was weak, with point estimates of mediation all below 10%. This suggests that there could be other mechanisms involved. A possible mechanism is epigenetic modifications in paternal germ cells induced by adverse environmental exposures, such as active smoking [16, 27], before completing puberty [7, 9]. It has been hypothesised, based on

TABLE 4 Associations between maternal passive smoke exposure before 15 years of age and asthma trajectories from ages 7 to 53 years in their offspring, stratified by offspring passive smoke exposure by 7 years of age

Maternal passive smoke exposure before age 15 years	Stratum 1: offspring *without* exposure to passive smoke by age 7 years (n=563)		Stratum 2: offspring *with* exposure to passive smoke by age 7 years (n=952)	
	n/total n (%)[#]	Adjusted model aMOR (95% CI) p-value	n/total n (%)[#]	Adjusted model aMOR (95% CI) p-value
Trajectory: never asthma				
Not exposed	104/191 (54.45)	Base outcome (reference)	108/217 (49.77)	Base outcome (reference)
Exposed	203/372 (54.57)		369/735 (50.20)	
Trajectory: early-onset adolescent-remitting				
Not exposed	43/191 (22.51)		69/217 (31.80)	
Exposed	97/372 (26.08)	1.21 (0.78–1.88) 0.39	183/735 (24.90)	0.77 (0.53–1.11) 0.16
Trajectory: early-onset adult-remitting				
Not exposed	7/191 (3.66)		2/217 (0.92)	
Exposed	12/372 (3.23)	1.26 (0.43–3.69) 0.68	30/735 (4.08)	4.30 (1.01–18.40) 0.049[¶]
Trajectory: early-onset persistent				
Not exposed	5/191 (2.62)		11/217 (5.07)	
Exposed	18/372 (4.84)	1.78 (0.64–4.98) 0.27	35/735 (4.76)	0.88 (0.42–1.81) 0.72
Trajectory: late-onset remitting				
Not exposed	11/191 (5.76)		4/217 (1.84)	
Exposed	17/372 (4.57)	0.79 (0.35–1.78) 0.57	27/735 (3.67)	2.12 (0.72–6.26) 0.17
Trajectory: late-onset persistent				
Not exposed	21/191 (10.99)		23/217 (10.60)	
Exposed	25/372 (6.72)	0.64 (0.33–1.23) 0.18	91/735 (12.38)	1.18 (0.70–1.99) 0.53

Interaction for the overall model: p=0.044 (likelihood ratio test). Adjusted multinominal odds ratios (aMORs) and corresponding p-values are from multinomial logistic regressions. Adjusted model: adjustment for SEIFA-IRSD (socioeconomic indexes for areas – the index of relative socioeconomic disadvantage) scores of parents, maternal lifetime history of asthma/wheeze and maternal age at baseline. [#]: Numbers of each trajectory in each exposure category. [¶]: Statistically significant.

studies of cord blood, that environmentally induced epigenetic modifications in sperm may result in abnormalities of DNA methylation in offspring at birth [28]. These abnormalities were related to subsequent childhood asthma [29].

Our findings also revealed that paternal and maternal passive smoke exposure before 15 years of age were associated offspring asthma, but with varied magnitudes of association. Specifically, a significant association was observed between paternal exposure and the early-onset adult-remitting asthma trajectory in offspring. However, the evidence for an association for maternal exposure was weaker. The observed sex difference may be partly attributed to distinct DNA methylation modifications triggered by adverse exposures in previous generations. These modifications may have varied effects on males and females. A murine study demonstrated that asthmatic lung phenotypes induced by perinatal nicotine exposure during previous generations' pregnancies were more pronounced in male offspring than in female offspring, with differential DNA methylation modification observed in the testis and ovary [30].

Although maternal passive smoke exposure before 15 years of age was not strongly associated with the early-onset adult-remitting asthma trajectory in offspring, our findings indicated that this association was evident with additional passive smoke exposure during offspring childhood. Conversely, this association was attenuated in offspring without such exposure to passive smoke during their own childhood. The impaired intrauterine environment could be an underlying mechanism to explain this interaction. Pre-conception adverse exposures in females may accumulate deleterious agents in fat tissue and gradually release them into the circulation [31]. These agents may influence maternal gestational biology and increase the risk of offspring asthma [31]. One study in rodents suggested that unhealthy maternal preconception lifestyles, such as high-fructose consumption, could disrupt the uterine environment for embryonal development [32]. Moreover, post-natal insults, such as high salt intake in offspring, have been

shown to exacerbate the high blood pressure induced by maternal high-fructose intake [33]. Hence, maternal exposure to passive smoke before 15 years of age (initial exposure) may increase offspring susceptibility to post-natal environmental insults, such as childhood passive smoke exposure (subsequent exposure). The joint effects of these exposures could synergistically contribute to early-onset asthma.

The associations observed in this study for both paternal and maternal passive smoke exposure before 15 years of age were exclusively for the early-onset adult-remitting asthma trajectory rather than the early-onset persistent asthma trajectory into mid-adult life in offspring. The reasons remain unclear. Epigenetics could be a potential explanation. Environmental exposure-induced epigenetic modifications are partly reversible [34–36], including those induced by smoking [37]. Thus, these associations may attenuate in offspring during adulthood. Alternatively, remitting asthma may represent a distinct phenotype that is more responsive to early-life exposures. Multigenerational exposures may increase susceptibility to early-onset asthma that later remits. In contrast, persistent asthma may be more strongly influenced by gene–environment interactions across the offspring's life course. Additionally, limitations in statistical power or survivor bias might have attenuated the associations with persistent asthma. Further research into the underlying mechanisms is warranted.

The major strength of this study was that it was based on the TAHS, which has gathered comprehensive asthma data from offspring (probands of the TAHS cohort) childhood to middle age, enabling a detailed analysis for their asthma trajectories. Leveraging longitudinal asthma data, we provided novel evidence that paternal and maternal passive smoke exposure before 15 years of age had varied magnitudes of associations with the early-onset adult-remitting asthma trajectory in offspring. Our analysis was also the first to identify an interaction between two exposures of passive smoke exposure across generations in mother–offspring pairs, one preceding maternal completing puberty and the other during offspring childhood. Moreover, rich data on respiratory illnesses and passive smoke exposure during offspring childhood and their parental lifetime smoking history enabled the analysis for potential mediating pathways.

However, this study has limitations. Passive smoke exposure before 15 years of age was retrospectively reported by the parents based on their own parents' smoking (offspring's grandparents), without validation from grandparents. This might have introduced recall bias. Nevertheless, evidence has shown that adult offspring and their parents provided consistent reports about parental smoking during offspring childhood [38], suggesting that recall bias might be less likely to have substantially affected the findings. Second, offspring childhood passive smoke exposure, assessed at 7 years of age, might have included both intrauterine and post-natal exposure. Some parents might have smoked during pregnancy and continued afterwards, while others might have commenced smoking only after the offspring were born. However, we were unable distinguish such windows of exposure. Further research is warranted to differentiate the impact of post-natal or intrauterine exposures. Similarly, parental passive smoke exposure before 15 years of age might also include intrauterine and post-natal exposure, or both. The absence of grandparents in the cohort meant their smoking during pregnancy could not be ascertained, making it difficult to differentiate between intrauterine and post-natal exposure and to quantify the intensity (*e.g.* pack-years) of exposure. Third, in the 1970s, smoking prevalence was higher among men than women in Australia [39]. Fathers with a smoking history might have died earlier or be less healthy and were therefore under-represented in the follow-up. As a result, a healthier subset of fathers and their offspring might have been included, which could explain the lower smoking prevalence observed in father–offspring pairs compared to mother–offspring pairs. This potential bias might have attenuated the observed associations. Fourth, offspring asthma was reported by parents or self-reported, which might have introduced misclassification. However, asthma definitions in TAHS questionnaires have been validated by respiratory physician diagnoses, reducing the risk of misclassification [40]. Firth, small sample sizes in stratified analyses might have limited the power to detect some associations. Lastly, TAHS does not collect data on parental or offspring epigenetics during childhood, limiting our ability to further explore underlying mechanisms.

In conclusion, paternal passive smoke exposure before 15 years of age was associated with higher odds of offspring developing the early-onset adult-remitting asthma trajectory, which is associated with COPD in middle age. This association was only modestly mediated through active paternal smoking, offspring childhood passive smoke exposure and subsequent active smoking. A similar association with maternal exposure was only found when offspring were also exposed to passive smoke during childhood. These findings suggest that avoiding smoking around children may be associated with a reduced asthma risk in future generations, even among parents who were exposed to passive smoke during childhood/puberty. Nonetheless, more research is needed to replicate our findings before causation can be established.

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Data availability: Individual participant data can be provided upon request to anyone with a suitable proposal. The proposal will be reviewed by the steering committee of the TAHS. Requests can be directed to S.C. Dharmage, the principal investigator of the TAHS and the corresponding author of this article. Individual deidentified data for all TAHS participants may be provided.

Provenance: Submitted article, peer reviewed.

Ethics statement: This study was based on the TAHS, which was approved by Human Ethics Review Committees at The Universities of Melbourne (040375), Tasmania (040375.1 and H0012710), New South Wales (08094), The Alfred Hospital (1118/04), and Royal Brisbane and Women's Hospital Health Service District (2006/037). Written informed consent was obtained from all participants.

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