Pre-pubertal smoke exposure of fathers and increased risk of offspring asthma: a possible transgenerational effect

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To the Editor:

Asthma is a major non-communicable disease in children [1]. Pre- and post-natal exposure to tobacco smoke are major risk factors for childhood asthma [1, 2]. While there is evidence that mothers' intrauterine exposure to second-hand smoke is associated with asthma in the offspring [3, 4], there is also increasing concern that fathers who start smoking before completing puberty may elevate the risk of asthma in their offspring [4, 5]. The suggestion is that this may be as a result of epigenetic changes to sperm precursor (stem) cells during gonadal maturation [4, 5]. However, this is rather speculative, and as yet little is actually known about whether fathers' passive smoke exposure throughout childhood to puberty is indeed associated with increased asthma risk in their offspring.

We investigated this potential association using data from 1689 father-offspring pairs in the Tasmanian Longitudinal Health Study (TAHS). Offspring in this study were the probands in TAHS [6], where their childhood asthma and hay fever status had been reported by their parents at age 7 years, in 1968. Offspring asthma was defined as more than one attack of asthma/wheezy breathing by this age of 7 years, and was classified as allergic asthma if they had both asthma and hay fever during the same period. Fathers of the probands reported their personal lifetime active smoking history and also pre-pubertal passive smoke exposure (between 0 and 15 years) from their own parents (*i.e.* offspring paternal grandparents) in the 2010 follow-up survey. The study was approved by human ethics review committees at the Universities of Melbourne (approval number: 040375), Tasmania (040375.1) and New South Wales (08094), Alfred Hospital (1118/04), and Royal Brisbane and Women's Hospital Health Service District (2006/037).

We used logistic regression for offspring asthma at age 7 years (asthma *versus* no asthma), and multinomial logistic regression for offspring asthma phenotypes (non-allergic asthma *versus* no asthma; allergic asthma *versus* no asthma). Analyses were adjusted for fathers' educational levels, and prior asthma history. These potential confounders were identified by directed acyclic graph models. The analyses were additionally adjusted and stratified for fathers' lifetime active smoking history. In addition, we investigated potential interaction between fathers' pre-pubertal passive smoke exposure and lifetime active smoking, using a likelihood ratio test. We also combined fathers' pre-pubertal passive smoke exposure (yes/no) and fathers' lifetime active smoking history (yes/no), and categorised them into four groups (as: no/no (reference), yes/no, no/yes, yes/yes) and fitted this new variable in the analyses.

Fathers' passive smoke exposure before 15 years of age was associated with increased odds of offspring non-allergic asthma by 7 years of age (adjusted multinomial odds ratio (aMOR) 1.59, 95% CI 1.09–2.32) (adjusted model 1) (table 1). After further stratifying by fathers' lifetime active smoking history, the association between fathers' passive smoke exposure and offspring non-allergic asthma was stronger in ever-smoked fathers (n=985; aMOR 1.72, 95% CI 1.02–2.92) than in fully non-smoking fathers (n=601; aMOR 1.39, 95% CI 0.78–2.46). Further interaction analyses suggested a significant association of combined fathers' exposure to passive smoke before completing puberty and active smoking with offspring non-allergic childhood asthma (aMOR 1.68, 95% CI 1.02–2.79). There were increased odds of offspring non-allergic childhood asthma for fathers' exposure to pre-pubertal passive smoke only (aMOR 1.38, 95% CI 0.78–2.43), but not fathers' lifetime active smoking only (aMOR 0.99, 95% CI 0.51–1.94). Notably, the observed associations with offspring overall asthma (adjusted OR 1.23, 95% CI 0.92–1.65) or allergic asthma (aMOR 0.84, 95% CI 0.54–1.30) were not statistically significant at the 5% threshold.

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The risk of non-allergic childhood asthma in offspring may increase if their fathers were exposed to pre-pubertal passive smoke https://bit.ly/3bMHZnP

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TABLE 1 Association between fathers' passive smoke exposure before the age of 15 years and offspring non-allergic asthma by the age of 7 years

	Full sample (n=1586)				Non-smoking fathers (n=601)			Ever-smoked fathers (n=985)		
	Cases/total	Crude model MOR (95% CI)	Adjusted model 1 MOR (95% CI)	Adjusted model 2 MOR (95% CI)	Cases/total	Crude model MOR (95% CI)	Adjusted model 1 MOR (95% CI)	Cases/total	Crude model MOR (95% CI)	Adjusted model 1 MOR (95% CI)
Fathers' passive smoke exposure before the age of 15 years from their own parent(s)										
Not exposed (ref.)	38/455	1	1	1	20/240	1	1	18/215	1	1
Exposed	144/1131	1.60 (1.10–2.33)*	1.59 (1.09–2.32)*	1.54 (1.05–2.26)*	40/361	1.37 (0.78–2.41)	1.39 (0.78–2.46)	104/770	1.71 (1.01–2.89)*	1.72 (1.02–2.92)*

MOR: multinominal odds ratio. Adjusted model 1: adjustment for fathers' educational levels and fathers' prior asthma history. Adjusted model 2: model 1 plus further adjustment for fathers' lifetime active smoking history. *: $p<0.05$.

Our findings suggest that when fathers are passively exposed to their parent(s)' tobacco smoke before the age of 15 years, their offspring have increased risk of non-allergic childhood asthma, but not allergic asthma. These findings provide new insights and stronger evidence for the possible transgenerational effects caused by paternal passive smoke exposure on their offspring's health. In comparison to our study that investigates the impact of fathers' pre-pubertal passive smoke exposure, one study reported an association between fathers' active smoking before the age of 15 years and their offspring's risk of non-allergic childhood asthma [5]. This would support our findings, given the similar timing of exposure, albeit likely differing quantity and constituents of smoke exposure. However, our findings are novel as they provide the first evidence on a possible transgenerational transmission of an adverse impact of pre-pubertal passive smoke exposure in fathers.

Epigenetics is a potential mechanistic link between paternal pre-pubertal smoking and offspring elevated asthma risk [4, 5], *via* changes in sperm stem cell including DNA methylation [5] and altered miRNA profiles [4]. Further, offspring prenatal passive smoke exposure may modify their responses to nicotine metabolites and other smoking related substances [7–9], and adversely affect lung functional development and their immunity in later life [4, 7, 10]. For example, one rat study demonstrated potentially heritable nicotine-induced DNA methylation [11], and increased CG methylation levels of immune genes in human offspring by 6 years of age were attributed to prenatal paternal smoking and related to childhood asthma [10]. Therefore, the detrimental effect of fathers' early life exposure to any type of tobacco smoke may be epigenetically transmitted to the next generation. Any differences in this between passive smoke exposure and active smoking requires further investigations.

Our findings also suggest that abstinence from active smoking by the father could potentially attenuate offspring non-allergic asthma risk imposed by the fathers' pre-pubertal passive smoke exposure, and this needs to be followed up. This finding could be supported by the hypothesis that although epigenetic programming is in part heritable, there is a developmental reprogramming process, in which DNA methylation and histone modifications may be reset or erased at every generation to different degrees [7]. In other words, there might be an adaptive response or maintenance mechanism that prevents further damage [5]. There is evidence that initial smoking-related DNA methylation changes can partially recover following smoking cessation [12]. One murine model showed that the perinatal nicotine-induced asthmatic lung phenotype tended to be less prominent in successive generations that were no longer exposed, but was exacerbated after re-exposure during the second pregnancy [11]. These findings, together with ours, suggest that fathers' active smoking may exacerbate the impact of their passive smoke exposure before the age of 15 years on offspring asthma risk.

Asthma is a heterogeneous disease [13]. In the modern era of precision medicine, understanding risk factors for different asthma phenotypes is important, potentially for treatment responsiveness [14]. Our data showed that paternal smoke exposure before the age of 15 years is a major risk factor for non-allergic asthma, shedding light on the potential epigenetic and pathophysiological mechanisms of disease. Furthermore, non-allergic asthma may be less responsive to inhaled corticosteroids and so more difficult to treat [15]. Therefore, public health interventions to reduce early-life smoke exposure could help prevent difficult-to-treat asthma in offspring. Moreover, our findings may be valuable to direct researchers to conduct further investigations to identify specific mechanisms and propose a new paradigm of non-allergic asthma treatments from epigenetic level in the future, such as treatments to reduce epigenetic effects of smoke exposure. Lastly, our results revealed some limited evidence for an increased risk of overall asthma (point estimate increased by 23% but confidence intervals included the null value of 1). Power was possibly the issue. The association for allergic asthma has a wide confidence interval, thus our result was inconclusive to determine whether passive smoke exposure of fathers influenced risk of allergic asthma in their offspring. More studies with larger sample sizes are required.

TAHS is a population-based birth cohort study which has collected longitudinal data among probands and their relatives in multiple generations [6], which is a major strength. Nevertheless, we acknowledge that fathers' reports of their smoke exposure was potentially subject to misclassification. However, fathers' passive smoke exposure and smoking history were ascertained in 2010, which was far away from their report of offspring asthma in 1968; report of their smoke exposure was less likely to be influenced by offspring asthma status. Hence, any such misclassification was more likely to be non-differential, which would only bias the associations towards the null. We were unable to validate fathers' report of their smoke exposure, which is a limitation of this study.

In conclusion, this study suggests that the risk of non-allergic childhood asthma in offspring may increase if their fathers had been exposed to pre-pubertal passive smoke. Avoidance of smoking, in addition to the multitude of known health benefits, can also reduce asthma risk in offspring.

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