

Nonlinear effects of environment on childhood asthma susceptibility

To the Editor,

Environmental exposures such as air pollution, farm animals, and tobacco smoke have been established as risk factors for childhood asthma.¹ Single nucleotide polymorphisms (SNPs) associated with childhood asthma have also been identified in both candidate gene

and genome-wide association studies.^{2,3} However, the majority of studies consider genetic and environmental factors independently and assume the degree of risk conferred is uniform across all individuals.

As the impact of environmental risk factors may be influenced by an individual's genetic predisposition to the disease, a

TABLE 1 Association between parental smoking exposure in the first year of a child's life and the development of childhood asthma

		Risk of childhood asthma					
		Unadjusted model ^a	Unadjusted for interaction effect ^b	Adjusted for interaction effect ^c	Low PRS tertile ^b	Middle PRS tertile ^b	High PRS tertile ^b
IOWBC	N	835	797	797	266	265	266
	OR (95% CI)	1.37 (0.93, 2.01)	1.39 (0.94, 2.07)	Parental smoking: 1.27 (0.84, 1.91) Interaction: 1.43 (0.77, 2.65)	0.92 (0.40, 2.14)	1.18 (0.57, 2.44)	1.76 (0.98, 3.17)
	p-Value	.119	.10	Parental smoking: .260 Interaction: .26	.85	.66	.06
MAAS	N	765	765	765	255	255	255
	OR (95% CI)	0.95 (0.59, 1.51)	0.94 (0.58, 1.51)	Parental smoking: 2.01 (1.07–3.79) Interaction: 0.30 (0.15, 0.62)	1.64 (0.64, 4.21)	1.53 (0.71, 3.31)	0.38 (0.15, 0.97)
	p-Value	.82	.79	Parental smoking: .03 Interaction: .001	.30	.27	.04
ALSPAC	N	3,334	2,802	2,802	935	938	939
	OR (95% CI)	1.15 (0.95, 1.40)	1.27 (1.01, 1.59)	Parental smoking: 1.26 (0.98, 1.61) Interaction: 0.91 (0.64, 1.29)	1.15 (0.72, 1.83)	1.27 (0.85, 1.88)	1.36 (0.96, 1.93)
	p-Value	.16	.04	Parental smoking: .07 Interaction: .58	.56	.24	.09

Note: A *p*-value threshold of .05 was used to evaluate whether there was weak or strong evidence for an association, values < 0.05 are in bold. Individuals were assigned into low, middle, and high PRS tertiles based on the distribution of the PRS in each cohort—IOWBC: low: (−2.17, −0.35), middle: (−0.36, 0.27), high: (0.28, 2.03); MAAS: low: (−1.83, 0.19), middle: (0.20, 0.79), high: (0.80, 3.12); ALSPAC: low: (−2.98, −0.70); middle: (−0.71, −0.13); high: (−0.14, 1.86). Covariates are gender, maternal asthma, paternal asthma, and sibling asthma.

Abbreviation: OR, odds ratio.

^aModel unadjusted for covariates or PRS-by-parental smoking interaction: asthma ~ parental smoking.

^bModel unadjusted for a PRS-by-parental smoking interaction: asthma ~ parental smoking +covariates.

^cModel adjusted for covariates and a PRS-by-parental smoking interaction: asthma ~ parental smoking +PRS (continuous variable) + PRS-by-parental smoking interaction +covariates.

number of studies have investigated the presence of possible gene-environment interactions.^{4,5} However, the majority of these studies have focused on specific candidate genes. Although genome-wide interaction studies have been performed, these are also SNP-wise analyses where each genotyped SNP is independently assessed against the environmental exposure and an SNP-by-exposure interaction term.⁶

Genetic variants identified in genome-wide association studies are often common variants that only confer small effects.⁶ As such, the power to detect interactions between exposures and individual SNPs is limited. Polygenic risk scores (PRSs) have been used as a means of combining the small effects of multiple SNPs across the genome in order to derive a better estimate of an individual's overall genetic risk.⁶ It is possible that PRSs may offer increased power to identify interaction effects. For example, Aschard et al.⁷ demonstrated that whilst no interactions for pulmonary function were identified among 26 independent SNP-by-smoking interaction analyses, combining the 26 SNPs into a PRS and conducting a PRS-by-smoking interaction analysis were able to uncover an interaction effect. Yet, interactions between environmental exposures and an individual's complete genetic profile have seldom been explored,^{8,9} with no such studies currently related to childhood asthma.

Arshad et al.¹⁰ previously identified a number of early life risk factors, such as parental smoking in the first year of a child's life, to be associated with childhood asthma development at age 10 in the Isle of Wight Birth Cohort (IOWBC). In this study, using the environmental exposure of parental smoking in the first year of a child's life as an exemplar, a PRS-by-parental smoking interaction meta-analysis was performed to: (i) evaluate the presence of an interaction between parental smoking and polygenic risk on the development of childhood asthma and (ii) assess whether the risk of parental smoking on the development of childhood asthma is in fact uniform among individuals of different genetic risk.

Data from three UK birth cohorts were used in this study: the IOWBC, Manchester Asthma and Allergy Study (MAAS), and The Avon Longitudinal Study of Parents and Children (ALSPAC) (see Supplementary Methods for cohort details, Table S1). Childhood asthma, defined as a combination of a doctor's diagnosis ever and the presence of wheeze or the use of asthma medication in the last 12 months, was evaluated at age 10 in the IOWBC ($n = 1368$ (201 cases)) and at age 11 in MAAS ($n = 898$ (116 cases)) and ALSPAC ($n = 4704$ (728 cases)). Based on a previously published list of independent asthma SNPs summarized across existing GWASs published until 2019, weighted 105-SNP PRSs were calculated for each individual with genotype data in each cohort using PRSice (see Supplementary Methods). Logistic regression analysis was used to assess the association of parental smoking and childhood asthma in each cohort (in the first year of life in the IOWBC and ALSPAC and at the antenatal follow-up in MAAS). The analysis was then repeated with the addition of an interaction term between the parental smoking and the PRS as a continuous variable. Next, individuals in each cohort were stratified into tertiles based on the cohort PRS to group individuals with a low, middle, or high genetic predisposition for childhood asthma.

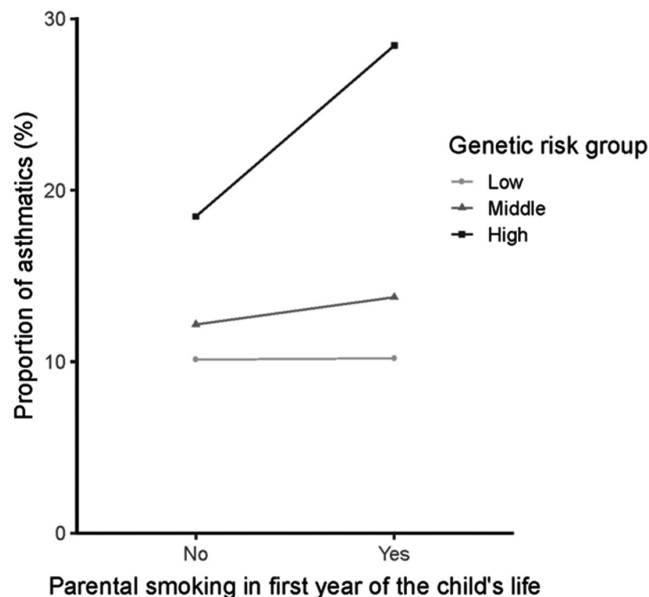


FIGURE 1 Association between parental smoking in the first year of life and childhood asthma in the IOWBC, stratified by PRS

The initial logistic regression analysis (without the interaction term) was then repeated in each genetic (PRS) subgroup. All analyses in the IOWBC (and where data were available in MAAS and ALSPAC at their respective time points, Table S1) were adjusted for gender, maternal asthma, paternal asthma, and sibling asthma. As the familial history of asthma may also account for some of the genetic effects being investigated, all analyses were also performed adjusting for gender only (see Supplementary Material). Finally, the stratified logistic regression analysis was meta-analyzed across all three cohorts using both fixed- and random-effect models using the R package “meta.”

In the IOWBC, MAAS, and ALSPAC, data for asthma, parental smoking in the first years of life, and PRS were available for 835, 765, and 3,334 individuals, respectively (Table 1 and S2). In ALSPAC, there were some evidence for a 27% increased risk of developing childhood asthma when parents smoked in the first year of life, OR (95% CI): 1.27 (1.01, 1.59) but not in the IOWBC or MAAS ($p = .10$ and $p = .79$, respectively) (Table 1).

The interaction analysis showed no evidence for an interaction effect between the PRS and parental smoking in the development of childhood asthma; however, the stratified analysis did reveal a trend effect. In the IOWBC and ALSPAC, parental smoking was shown to confer a larger effect (with a higher degree of statistical evidence) among individuals with higher PRSs (Table 1, Figure 1). Strong evidence for this trend effect was demonstrated in the fixed-effect meta-analysis model ($p = .02$) (Figure 2). Similar meta-analysis results are presented when adjusting only for gender as a covariate (Table S3, Figure S1).

Particularly as childhood asthma is a highly heterogeneous disease, this study illustrates the importance of not evaluating environmental risk factors in isolation, as these too may be heterogeneous themselves. For example, this study demonstrates the risk conferred by parental smoking is not uniform but can vary depending on an individual's genetic susceptibility.

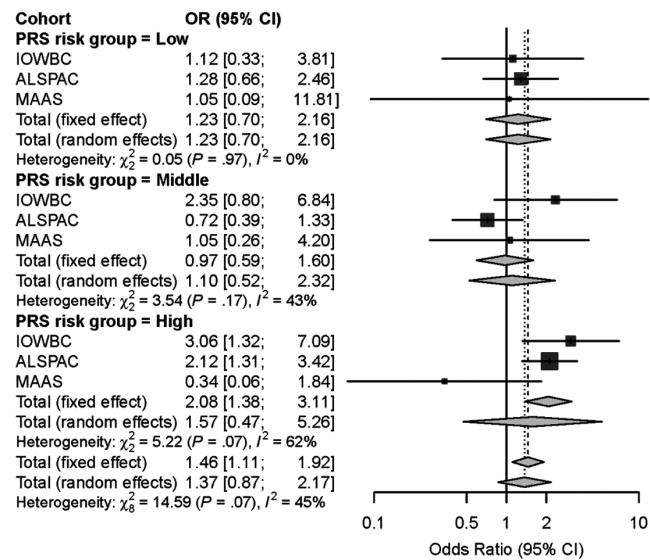


FIGURE 2 Forest plot showing the association of parental smoking in the first year of a child's life on the development of childhood asthma. The forest plot was constructed using summary statistics derived from the logistic regression analysis conducted across each PRS tertile in each cohort. The risk (odds ratio (OR) of parental smoking on the development of childhood asthma for each cohort (grey squares) with 95% confidence intervals (95% CI, from the solid black horizontal lines) is shown for each cohort, stratified by the PRS tertiles. The size of the grey squares corresponds to the cohort sample size. Subgroups with an odds ratio to the right (left) of the reference line (OR = 1, solid black vertical line) indicate an increased (decreased) risk of asthma among children exposed to parental smoking in the first year of life. Average effect sizes pooled across all three cohorts are presented for each PRS tertile and across all PRS tertiles, for both the fixed- and random-effect meta-analyses (diamonds). Dashed and dotted black vertical lines show the pooled effects across all PRS tertiles for the fixed- and random-effect models, respectively. In this analysis, covariates adjusted for included gender, maternal asthma, paternal asthma, and sibling asthma

However, it is important to acknowledge that this study was unable to offer conclusive evidence for a genetics-by-environment interaction (or direction of an interaction effect) based on the use-case of parental smoking in the first year of life. This may merely be a product of the inherent complexity of PRS-environment effects being explored or the need to account for additional complex influences such as collider bias.¹¹

The conflicting findings in MAAS in comparison to ALSPAC and IOWBC may stem from antenatal parental smoking rather than parental smoking within the first year of the child's life (as in the IOWBC and ALSPAC) being evaluated in MAAS. However, this may also be explained by inherent cohort differences; MAAS conducted selective recruitment from specific regions of South Manchester and Cheshire (see Supplementary Methods) whilst the IOWBC and ALSPAC are unselected cohorts representative of the general population. Although there was a 91% agreement between parental smoking status at recruitment and age three in MAAS (time points at which parental smoking data were available) and it is likely that parental smoking status reported at recruitment

was therefore representative of parental smoking in the first year of a child's life, it is highly possible that parental smoking behavior may have been different in the year immediately following the child's birth.

Ultimately, further investigation is needed to untangle the association of established environmental risk factors for asthma and improve the accuracy of their main effects. However, this study highlights the importance of future studies considering heritable (genetic) risk and any potential interaction effects that may influence the magnitude of risk estimates. Such studies would be particularly important for the formulation of public health policies and guidelines. Similarly, if associations with risk factors are only observed among certain subgroups of individuals, developing personalized prediction models using only predictors relevant within those specific patient subgroups could improve upon the limited performance of current asthma prediction models.

CONTENT

This publication is the work of the authors and Dilini M. Kothalawala & John W. Holloway will serve as guarantors for the contents of this paper.

KEYWORDS

ALSPAC, childhood asthma, meta-analysis, parental smoking, polygenic risk score, PRS-by-environment interactions

FUNDING INFORMATION

This work was supported by the NIHR Southampton Biomedical Research Centre and a University of Southampton Presidential Research Studentship. The 10-year follow-up of the IOWBC was supported by the National Asthma Campaign, UK (Grant No 364). MAAS was supported by the Asthma UK Grants No 301 (1995-1998), No 362 (1998-2001), No 01/012 (2001-2004), No 04/014 (2004-2007), BMA James Trust (2005), and the JP Moulton Charitable Foundation (2004-current), the North West Lung Centre Charity (1997-current), and the Medical Research Council (MRC) G0601361 (2007-2012), MR/K002449/1 (2013-2014), and MR/L012693/1 (2014-2018). UNICORN (Unified Cohorts Research Network): Disaggregating asthma MR/S025340/1. The UK Medical Research Council and Wellcome (Grant ref: 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. GWAS data were generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. RG is in part funded through Wellcome Trust Strategic Award 108818/15/Z.

AUTHOR CONTRIBUTIONS

Dilini M. Kothalawala: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (lead); Project administration (lead); Software (equal); Validation (equal); Visualization (lead); Writing – original draft (lead); Writing – review & editing (lead). **Veronique B.N. Weiss:** Formal analysis (equal); Investigation (equal); Software (equal); Validation (equal); Writing – original draft (supporting); Writing – review & editing (supporting). **Latha Kadalayil:** Methodology (supporting); Writing – review & editing (supporting).

Raquel Granell: Validation (equal); Writing – review & editing (supporting). **John Curtin:** Validation (supporting); Writing – review & editing (supporting). **Clare Suzanne Murray:** Resources (equal); Writing – review & editing (supporting). **Angela Simpson:** Funding acquisition (equal); Resources (equal); Writing – review & editing (supporting). **Adnan Custovic:** Funding acquisition (equal); Resources (equal); Writing – review & editing (supporting). **William J. Tapper:** Methodology (supporting); Supervision (equal); Writing – review & editing (supporting). **Faisal I. Rezwan:** Supervision (equal); Writing – review & editing (supporting). **Hasan Arshad:** Funding acquisition (equal); Methodology (supporting); Resources (equal); Supervision (equal); Writing – review & editing (supporting). **John W. Holloway:** Conceptualization (lead); Funding acquisition (equal); Methodology (lead); Project administration (supporting); Resources (equal); Supervision (equal); Writing – review & editing (supporting).

Editor: Ömer Kalayci

Correspondence

John W. Holloway, Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK.

Email: j.w.holloway@soton.ac.uk

ORCID

Dilini M. Kothalawala  <https://orcid.org/0000-0002-5804-0457>

Veronique B. N. Weiss  <https://orcid.org/0000-0003-4116-950X>

Latha Kadalayil  <https://orcid.org/0000-0002-3757-5487>

Raquel Granell  <https://orcid.org/0000-0002-4890-4012>

John A. Curtin  <https://orcid.org/0000-0001-6299-9110>

Clare S. Murray  <https://orcid.org/0000-0002-8961-8055>

Angela Simpson  <https://orcid.org/0000-0003-2733-6666>

Adnan Custovic  <https://orcid.org/0000-0001-5218-7071>

William J. Tapper  <https://orcid.org/0000-0002-5896-1889>

Faisal I. Rezwan  <https://orcid.org/0000-0001-9921-222X>

Syed Hasan Arshad  <https://orcid.org/0000-0001-5988-235X>

John W. Holloway  <https://orcid.org/0000-0001-9998-0464>

REFERENCES

1. Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. *CMAJ*. 2009;181(9):E181-E190.
2. Meyers DA, Bleecker ER, Holloway JW, Holgate ST. Asthma genetics and personalised medicine. *Lancet Respir Med*. 2014;2:405-415.
3. Morales E, Duffy D. Genetics and gene-environment interactions in childhood and adult onset asthma. *Front Pediatr*. 2019;7:499.
4. London SJ, Romieu I. Gene by environment interaction in asthma. *Annu Rev Public Health*. 2009;30:55-80.
5. Ege MJ, Strachan DP, Cookson WOCM, et al. Gene-environment interaction for childhood asthma and exposure to farming in Central Europe. *J Allergy Clin Immunol*. 2011;127:138-44.e4.
6. Hernandez-Pacheco N, Pino-Yanes M, Flores C. Genomic predictors of asthma phenotypes and treatment response. *Front Pediatr*. 2019;7:6.
7. Aschard H, Tobin MD, Hancock DB, et al. Evidence for large-scale gene-by-smoking interaction effects on pulmonary function. *Int J Epidemiol*. 2017;46(3):894-904.
8. Sikdar S, Wyss AB, Lee MK, et al. Interaction between genetic risk scores for reduced pulmonary function and smoking, asthma and endotoxin. *Thorax*. 2021;76(12):1219-1226.
9. Qi Q, Chu AY, Kang JH, et al. Sugar-sweetened beverages and genetic risk of obesity. *N Engl J Med*. 2012;367:1387-1396.
10. Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. *Chest*. 2005;127:502-508.
11. Akimova ET, Breen R, Brazel DM, Mills MC. Gene-environment dependencies lead to collider bias in models with polygenic scores. *Sci Rep*. 2021;11:9457.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Dilini M. Kothalawala^{1,2} 

Veronique B. N. Weiss¹ 

Latha Kadalayil^{1,3} 

Raquel Granell⁴ 

John A. Curtin^{5,6} 

Clare S. Murray⁵ 

Angela Simpson⁵ 

Adnan Custovic⁷ 

William J. Tapper¹ 

Faisal I. Rezwan^{1,8} 

Syed Hasan Arshad^{1,3,9} 

John W. Holloway^{1,2} 

STELAR/UNICORN investigators

¹Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK

²NIHR Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, UK

³Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

⁴MRC Integrative Epidemiology Unit, Bristol Medical School, University of Bristol, Bristol, UK

⁵Division of Infection, Immunity, and Respiratory Medicine, Manchester Academic Health Science Centre, School of Biological Sciences, Manchester University Hospital NHS Foundation Trust, University of Manchester, Manchester, UK

⁶NIHR Manchester Biomedical Research Unit, Manchester, UK

⁷Imperial College of Science, Technology, and Medicine, National Heart and Lung Institute, London, UK

⁸Department of Computer Science, Aberystwyth University, Aberystwyth, UK

⁹The David Hide Asthma and Allergy Research Centre, St. Mary's Hospital, Newport, Isle of Wight, UK