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A machine-learning exploration of the exposome from preconception in early childhood atopic eczema, rhinitis and wheeze development

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ABSTRACT

Background: Most previous research on the environmental epidemiology of childhood atopic eczema, rhinitis and wheeze is limited in the scope of risk factors studied. Our study adopted a machine learning approach to explore the role of the exposome starting already in the preconception phase.

Methods: We performed a combined analysis of two multi-ethnic Asian birth cohorts, the Growing Up in Singapore Towards healthy Outcomes (GUSTO) and the Singapore PREconception Study of long Term maternal and child Outcomes (S-PRESTO) cohorts. Interviewer-administered questionnaires were used to collect

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information on demography, lifestyle and childhood atopic eczema, rhinitis and wheeze development. Data training was performed using XGBoost, genetic algorithm and logistic regression models, and the top variables with the highest importance were identified. Additive explanation values were identified and inputted into a final multiple logistic regression model. Generalised structural equation modelling with maternal and child blood micronutrients, metabolites and cytokines was performed to explain possible mechanisms.

Results: The final study population included 1151 mother-child pairs. Our findings suggest that these childhood diseases are likely programmed *in utero* by the preconception and pregnancy exposomes through inflammatory pathways. We identified preconception alcohol consumption and maternal depressive symptoms during pregnancy as key modifiable maternal environmental exposures that increased eczema and rhinitis risk. Our mechanistic model suggested that higher maternal blood neopterin and child blood dimethylglycine protected against early childhood wheeze. After birth, early infection was a key driver of atopic eczema and rhinitis development.

Conclusion: Preconception and antenatal exposomes can programme atopic eczema, rhinitis and wheeze development *in utero*. Reducing maternal alcohol consumption during preconception and supporting maternal mental health during pregnancy may prevent atopic eczema and rhinitis by promoting an optimal antenatal environment. Our findings suggest a need to include preconception environmental exposures in future research to counter the earliest precursors of disease development in children.

Abbreviations

AOR	Adjusted odds ratio
AUC	Area under the curve
CI	Confidence interval
DMG	Dimethylglycine
DOHaD	Developmental Origins of Health and Disease
EPDS	Edinburgh Postnatal Depression Scale
FSH	Follicle-stimulating hormone
GA	Genetic algorithm
GSEM	Generalised structural equation model
GUSTO	Growing Up in Singapore Towards healthy Outcomes
IGFBP	Insulin-like growth factor-binding protein
IgG2	Immunoglobulin G2
IL-10	Interleukin-10
ISAAC	International Study of Asthma and Allergies in Childhood
MCP-1	Monocyte chemoattractant protein-1
PAI-1	Plasminogen activator inhibitor-1
RSV	Respiratory syncytial virus
SHAP	SHapley Additive explanation
S-PRESTO	Singapore PREconception Study of long Term maternal and child Outcomes
STAI	State-Trait Anxiety Inventory
VIF	Variance inflation factor

1. Introduction

Childhood eczema, rhinitis and wheeze are highly heterogenous conditions that affect increasing proportions of children globally (Belgrave et al., 2014; Chad, 2001). Their rapid rise cannot be explained by genetic factors alone; our living environment and lifestyle likely play a major role (Burbank et al., 2017). This view is encapsulated by the Developmental Origins of Health and Disease (DOHaD) paradigm, which hypothesizes that environmental stimuli, especially in early life, may influence immune development and consequently risk of acquiring diseases (Waterland and Michels, 2007).

Recent research studies have attempted to examine the influence of environmental exposures in development of atopic eczema, rhinitis and wheeze cross-sectionally or with a limited repertoire of risk factors. We argue that such studies are inadequate and are unable to account for the extensive types of environmental exposures as well as their variations over time. They do not answer these important questions: 1) which environmental risk factors play the most important roles in childhood atopic eczema, rhinitis and wheeze development? and 2) when should we intervene to ensure the maximum efficacy in reducing such diseases? For instance, a meta-analysis of 162 studies found maternal smoking to be the strongest modifiable risk factor of childhood eczema in Asia and emphasised a need to tackle smoking habits (Ng and Chew, 2020). A Finnish study reported that postnatal exposure to antibiotics, as compared to prenatal exposure, conferred stronger risk of asthma after age 3 years (Metsälä et al., 2015), suggesting that reducing unnecessary postnatal usage of antibiotics would be beneficial. A study that incorporates a wide variety of environmental risk factors throughout the life course is hence needed to comprehensively understand the environmental epidemiology of early childhood inflammatory diseases.

To address these problems, an “exposome” study approach can be used. This concept was coined by molecular epidemiologist Christopher Wild in 2005 and describes the collection of environmental exposures experienced throughout life (Wild, 2005a). However, to date only two studies have adopted this method in the study of these childhood diseases. The Kingston Allergy Birth Cohort from Canada examined prenatal and postnatal exposomes and their impact on childhood respiratory symptoms in the first two years of life using Cox proportional hazards regression models (North et al., 2017). The European Human Early-Life Exposome cohort evaluated associations between prenatal and postnatal exposomes on rhinitis, food allergy, itchy rash and doctor-diagnosed eczema in children using regression-based methods (Granum et al., 2020).

Both studies considered the antenatal and postnatal exposomes, yet there is a further missing piece in the puzzle of the exposome – the preconception exposome. Environmental exposures during the preconception period are increasingly recognised in paediatric health. The Southampton Women’s Survey and Singapore PREconception Study of long Term maternal and child Outcomes (S-PRESTO) cohort reported that preconception maternal distress was linked to development of eczema at 12 months and wheeze by 18 months of life, respectively (El-Heis et al., 2017; Lau et al., 2022). The Respiratory Health in Northern Europe, Spain and Australia study also reported that maternal preconception exposure to air pollutants was associated with offspring asthma and rhinitis development (Kuiper et al., 2020).

Given the large number of environmental exposures from the preconception to postnatal period, we here utilised machine learning methods to examine the key risk factors from as early as preconception through pregnancy to the early postnatal period. We examine how the exposome influences development of early childhood atopic eczema, rhinitis and wheeze with the use of nebuliser in the first three years of life in two multi-ethnic Asian birth cohorts, the Growing Up in Singapore Towards healthy Outcomes (GUSTO) and the S-PRESTO cohorts. With this study, we aimed to identify the environmental risk factors that play the most important roles in the development of these diseases in early

life and the developmental period when these risk factors exert the greatest influence.

2. Materials and methods

2.1. GUSTO and S-PRESTO study design

The GUSTO study is a prospective population-based cohort study involving 1,247 pregnant mothers recruited during their first-trimester antenatal dating ultrasound scan (Soh et al., 2014). The S-PRESTO study is a prospective preconception cohort study which recruited 1,039 women aged 18–45 years old who planned to conceive and deliver in Singapore, with 373 infants born (Loo et al., 2020). Ethics approval for the GUSTO cohort was obtained from the Domain Specific Review Board of Singapore National Healthcare Group (D/2009/021) and the Centralised Institutional Review Board of SingHealth (2018/2767). Ethics approval for the S-PRESTO cohort was obtained from the SingHealth Centralised Institutional Review Board (reference 2014/692/D) and the study was registered at ClinicalTrials.gov (NCT 03531658). Written informed consent was provided by all participants before any study procedures were undertaken.

2.2. Definition of health outcomes

Trained interviewers gathered information on demographic characteristics, family history of allergy, socioeconomic data, and lifestyle factors. The validated modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was used to evaluate parental report of offspring health outcomes at ages 3, 6, 12 months and 1.5, 2 and 3 years in both cohorts and additionally at 9 and 15 months in the GUSTO cohort. Atopic eczema was defined as a positive response to the question "Has your child ever been diagnosed with eczema?". Wheeze with use of nebulizer/inhaler was defined by positive responses to the questions: "Has your child ever wheezed?" and "Has your child ever been prescribed with nebulizer/inhaler treatment?". Rhinitis was defined as a positive response to the question "Has your child had running nose, blocked or congested nose, snoring or noisy breathing during sleep or when awake that has lasted for 2 or more weeks duration?".

2.3. Inclusion criteria

The GUSTO and S-PRESTO cohorts were combined to obtain a larger mother-offspring cohort for analysis (Fig. 1). Participants with missing or insufficient data in the disease records in the first three years were excluded. For example, some participants were lost to follow-up, while others missed several timepoints. The atopic eczema, rhinitis and wheeze with the use of nebulisers or inhalers statuses of children were defined as positive if there were at least one reported occurrence of atopic eczema, rhinitis or wheeze with the use of nebulisers or inhalers respectively in the first three years. Healthy children were defined as those who did not report any diagnosis of atopic eczema, rhinitis and wheeze with the use of nebulisers or inhalers at all timepoints in the first three years of life and were classified into the Control Group.

2.4. Environmental factors

The environmental factors considered for analysis were based on literature review and their data collection methods and timepoints are listed in Table 1. They were classified into demography and socioeconomic status, *in utero* programming and postnatal early environment categories. For each environmental feature collected at multiple timepoints, we selected the most representative timepoints during the target periods according to clinical knowledge. Factors selected in this study were present in both the GUSTO and S-PRESTO cohorts and were similar in definitions and assessment timepoint. Therefore, the factors in the S-PRESTO cohort were mapped according to the definitions and timepoint of the features in the GUSTO cohort before combining.

2.5. GUSTO maternal and cord blood markers

Maternal and cord blood markers were collected and assayed in the GUSTO cohort (Ta et al., 2023). In brief, maternal overnight fasting (8–10 h) blood samples were collected at 26 weeks of pregnancy for assessments of plasma micronutrients, metabolites and cytokines, (Chen et al., 2015; Loy et al., 2015, 2019; Chong et al., 2015; Lai et al., 2021;

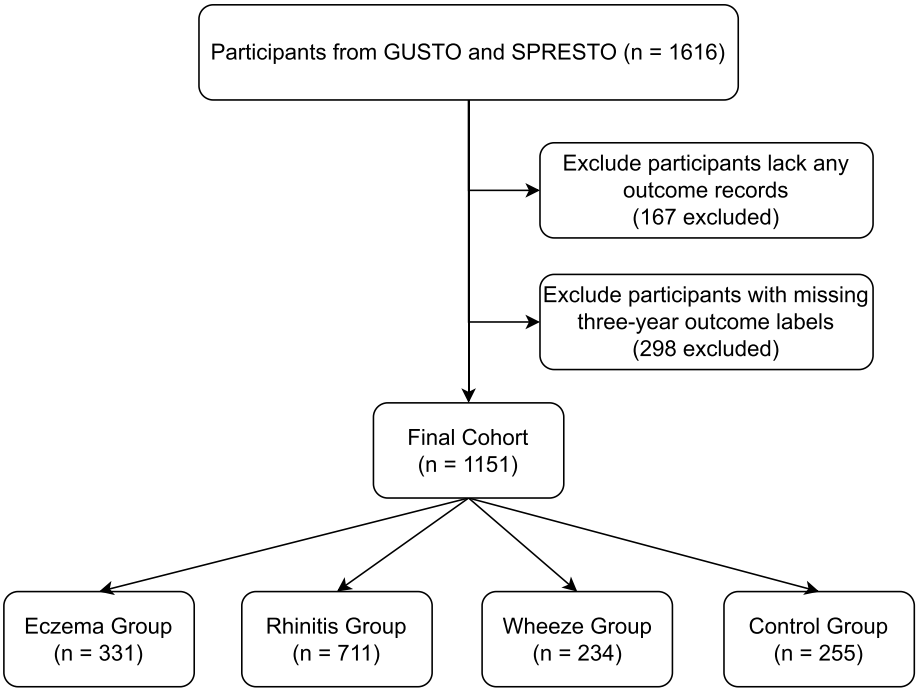

Fig. 1. Flowchart of study population selection.

Table 1
Environmental exposures considered for analysis in the GUSTO and S-PRESTO cohorts.

Variable	Remarks	GUSTO		S-PRESTO	
		Data collection method	Timepoint	Data collection method	Timepoint
Demography and socioeconomic status					
Ethnicity	Chinese, Indian, Malay or others	Questionnaire	Pregnancy 11–12 weeks	Questionnaire	Preconception
Maternal highest education	Secondary and below, post-secondary and higher	Questionnaire	Pregnancy 11–12 weeks	Questionnaire	Preconception
Monthly household income	–	Questionnaire	Pregnancy 11–12 weeks	Questionnaire	Preconception
Infant's sex	–	Delivery records	Delivery	Delivery records	Delivery
***In utero* programming**					
Parity	–	Questionnaire	Pregnancy 11–12 weeks	Questionnaire	Preconception
Maternal history of asthma, eczema and/or rhinitis	Ever in lifetime	Questionnaire	Pregnancy 11–12 weeks	Questionnaire	Preconception, pregnancy 18–21 and 34–36 weeks
Maternal anxiety during pregnancy	–	The State-Trait Anxiety Inventory	Pregnancy 26–28 weeks	The State-Trait Anxiety Inventory	Pregnancy 24–26 weeks
Maternal depression during pregnancy	–	Beck's Depression Inventory II and Edinburgh Postnatal Depression Scale	Pregnancy 26–28 weeks	Beck's Depression Inventory II and Edinburgh Postnatal Depression Scale	Pregnancy 24–26 weeks
Gestational age	–	Delivery records	Delivery	Delivery records	Delivery
Maternal age at delivery	–	Delivery records	Delivery	Delivery records	Delivery
Birthweight	–	Delivery records	Delivery	Delivery records	Delivery
Maternal physical activity	Moderate-to-strenuous: exhausted but not breathless e.g. dancing, swimming or cycling Strenuous: breathless e.g. running or aerobics	Questionnaire	1 year before pregnancy, past six months during pregnancy 26–28 weeks	Questionnaire	Preconception, pregnancy 18–21 weeks
Smoking status	If the participant is currently smoking	Questionnaire	Pregnancy 26–28 weeks	Questionnaire	Pregnancy 18–21 weeks
Any alcohol consumption	–	Questionnaire	Before pregnancy, pregnancy 26–28 weeks	Questionnaire	Preconception, pregnancy 18–21 weeks
Passive exposure to smoke	At work or at home		Before pregnancy, pregnancy 26–28 weeks	Questionnaire	Preconception, pregnancy 18–21 weeks
Maternal plasma micronutrients and metabolites profile		Blood plasma	Pregnancy 26 weeks	Blood plasma	Pregnancy 27–28 weeks
Postnatal early environment					
Antibiotics given during labour	–	Delivery records	Delivery	Delivery records	Delivery
Mode of delivery	Vaginal or caesarean	Delivery records	Delivery	Delivery records	Delivery
Maternal anxiety during postnatal period	–	The State-Trait Anxiety Inventory	Postnatal 3 months	The State-Trait Anxiety Inventory	Postnatal 3 months
Maternal depression during postnatal period	–	Beck's Depression Inventory II and Edinburgh Postnatal Depression Scale	Postnatal 3 months	Beck's Depression Inventory II and Edinburgh Postnatal Depression Scale	Postnatal 3 months
Child infection	Bronchiolitis/bronchitis, prolonged cough, croupy cough, pneumonia, vomiting, ear infection, fever not related to vaccination, diarrhoea	Questionnaire	Postnatal 3 months	Questionnaire	Postnatal 3 months
Child's antibiotic use	–	Questionnaire	Postnatal 3 months	Questionnaire	Postnatal 3 months
Breastfeeding status	–	Questionnaire	Postnatal 6 months	Questionnaire	Postnatal 6 months
Infant sleep	–	Brief Infant Sleep Questionnaire	Postnatal 3 months and 6 months	Brief Infant Sleep Questionnaire	Postnatal 3 months and 6 months
Dog and cat ownership	–	Questionnaire	Postnatal 6 months	Questionnaire	Postnatal 3 months[a]
Proximity of residence to expressway	–	Questionnaire	Postnatal 6 months	Questionnaire	Postnatal 3 months[a]

[a] It was assumed that pet ownership and proximity to expressway remained the same at 6 months.

van Lee et al., 2016, 2018; Chia et al., 2020) while infant cord blood was collected at birth for assessments of metabolites, vitamins and cytokines (Chia et al., 2020). A list of the metabolites and cytokines measured can be found in Supplementary Text S1. Where appropriate, values were corrected for plate effects using median centering.

2.6. Statistical analysis

Descriptive statistics for continuous variables were presented as mean (standard deviation) when normality and homogeneity assumptions were satisfied, otherwise as median (interquartile range), and n (%) for categorical variables. We calculated the variance inflation factor (VIF) of each environmental exposomes in our study population. The VIF is a measure of collinearity among predictor variables within a multiple regression model, as collinearity can adversely affect the regression results. A variable with high VIF above 5 indicates a high correlation between other predictor variables. Data were pre-processed before feeding to machine-learning-based analysis models. Data were imputed by

median value if required by the model. We also normalized data by subtracting the mean and scaling to unit variance. One hot encoding technique was applied to models that were not able to analyze categorical variables directly.

Analyses were performed using XGBoost, genetic algorithm (GA) and logistic regression models (Fig. 2). Data were first trained using these three models with the objective of optimizing the area under the curve (AUC) score. We evaluated the model performances between dataset training using the GUSTO cohort only and both cohorts (Table S1) and observed superior results when the two cohorts were integrated. Four feature importance methods were applied afterwards to identify the most relevant environmental factors related to the health outcomes. XGBoost, a tree boosting machine learning technique, exhibits the capability to discern the patterns of missing values in the dataset (Chen and Guestrin, 2016). It is able to capture complex non-linear relationships and feature interactions among exposures and outcomes, while concurrently retains good capability of interpretability. From the fitted model, the feature importance score of each feature was calculated as the number of times a feature appeared in a tree. The top 15 variables with the highest importance score were recorded among all input variables. SHapley Additive exPlanation (SHAP) is a game theory based approach to offer measurement of feature importance from various machine learning techniques and assist in interpreting prediction by models (Lundberg and Lee, 2017). Shapley values were calculated from the trained XGBoost model, where a higher Shapley value represents a higher feature importance. Similarly, the top 15 variables with the highest Shapley values were identified. GA is an algorithm that was inspired by natural evolution processes. It mimics the selection, crossover, mutation and other behaviors of chromosomes (Katoch et al., 2021). GA can be applied to perform feature selection and determine relevant variables from a prediction model (Leardi et al., 1992). We built a genetic algorithm model utilizing multiple logistic regression as the base estimator to find the most relevant variables that contributed to the classifier. Lastly, a multiple logistic regression was also applied, and significant variables with p-values less than 0.05 were identified.

After evaluating the important features using the four methods, variables that were selected by at least three of these methods were chosen as input variables of a final multiple logistic regression model to evaluate the adjusted odds ratios (AORs) and 95% confidence interval (CI) of the selected variables.

All the models were implemented using R and Python. To ensure reproducibility of our work, the codes for the study can be found at https://github.com/nus-mornin-lab/gusto_allergy.

To explore possible mechanistic links, logistic regressions were performed to evaluate associations among health outcomes and blood micronutrients, metabolites and immune markers in mother-child pairs from GUSTO. The models were adjusted for maternal age at delivery, maternal highest education, ethnicity, infant's sex, mode of delivery and family history of allergy. Thereafter, blood markers that were significantly different between each disease outcome group were included in a pathway analysis using generalised structural equation model (GSEM) in STATA 17.0. (Stata, Corporation Texas, USA). Significant environmental factors identified earlier in machine learning analyses were also included in the GSEM. All plausible pathways were considered and the

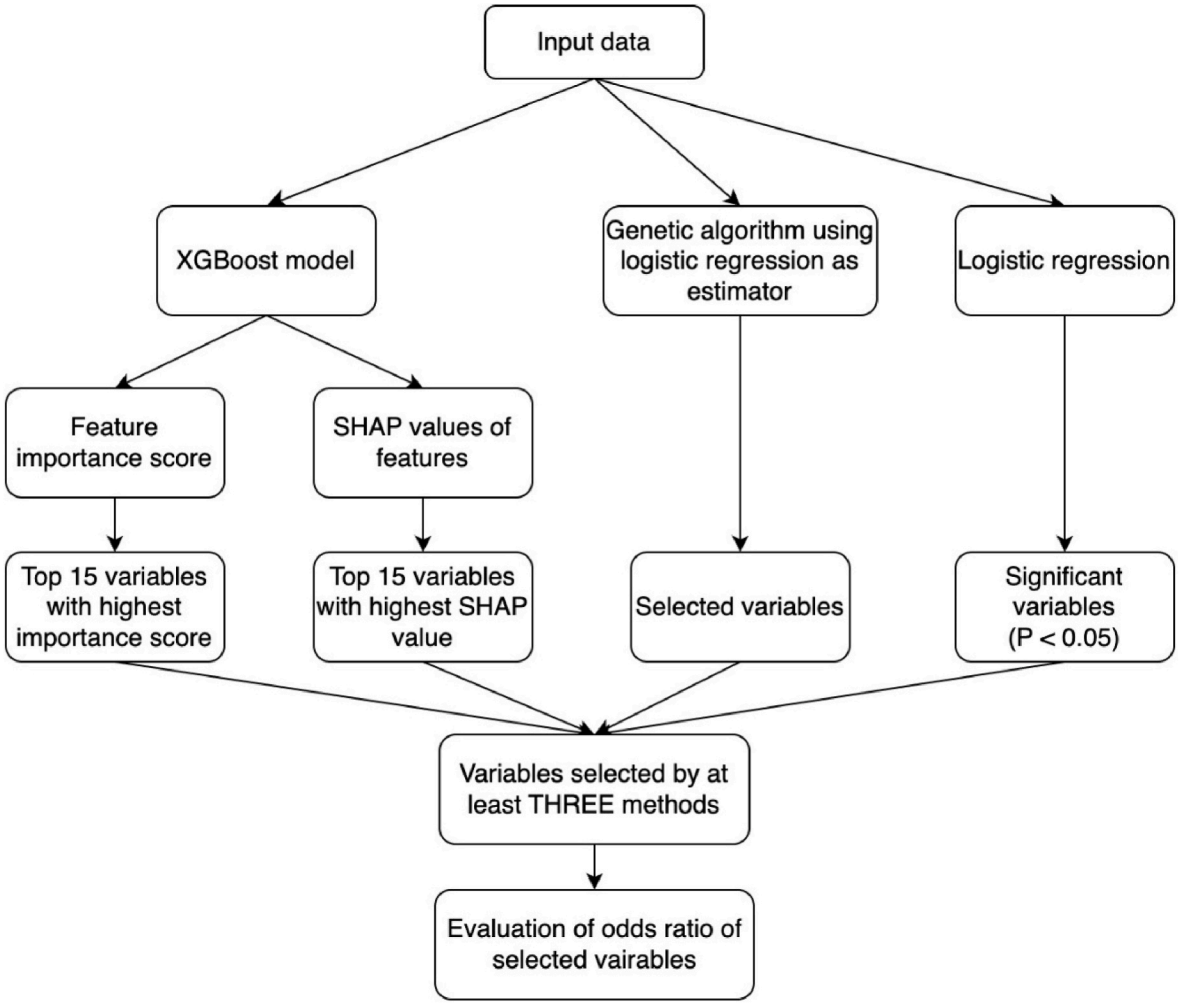

Fig. 2. Flowchart of statistical analysis and variables selection using machine learning methods XGBoost, genetic algorithm and logistic regression.

final GSEM model included only the significant pathways ($p < 0.05$). These analyses were not carried out in S-PRESTO due to unavailability of data.

3. Results

Out of 1616 participants with data on health outcomes, 1151 participants were included into the final study population, out of which 331 had atopic eczema, 711 had rhinitis, 234 had wheeze and 255 did not report any disease (Fig. 1). Most participants were Chinese (62.2%), had post-secondary or higher education (77.7%), had a monthly household income exceeding SGD$6000 (40.9%) and delivered vaginally (69.6%) (Table 2). 51.1% of the children were boys. When compared to included participants, the proportion of excluded mothers of Chinese ethnicity was smaller (56.3% vs 62.2%), while that of Indian ethnicity was higher (20.6% vs 13.7%) (Table S2). A lower proportion of excluded mothers had post-secondary or higher education (69.5% vs 77.7%) and household income exceeding SGD$6000 per month (33.4% vs 40.9%). Mean maternal age at delivery and gestational age were lower in excluded participants (30.2 vs 31.6 years and 38.9 vs 39.0 weeks, respectively). There were no significant differences in mode of delivery and infant's sex. Maternal postnatal anxiety symptoms, as assessed using State-Trait Anxiety Inventory (STAI) trait scores during postnatal three months, had a high VIF value of 5.01 (Fig. 3), and a high correlation of 0.87 to STAI state scores during postnatal three months. Therefore, the maternal STAI trait score during postnatal three months variable was dropped from the analysis. Consequently, the range of VIF observed in the environmental exposomes included in this study was 1.05–4.07, signifying little evidence for collinearity between the environmental exposomes in the model.

3.1. Atopic eczema

The results of the four individual machine learning models are in the Supplementary Material (Tables S3–5). In the final regression model, five risk factors were significantly associated with atopic eczema development in the first three years of life (Table 3). Maternal alcohol consumption before pregnancy [AOR (95% CI) 2.16 (1.51–3.09)], higher maternal Edinburgh Postnatal Depression Scale (EPDS) score during pregnancy [AOR 1.07 (1.01–1.14)], child's infection by age three months [AOR 2.21 (1.32–3.79)] and breastfeeding at six months [AOR 2.23 (1.57–3.19)] were associated with higher risk of atopic eczema development. Higher neopterin level in maternal plasma during pregnancy [AOR 0.93 (0.89–0.97)] was associated with a lower risk of atopic eczema development.

3.2. Rhinitis

Five risk factors were significantly associated with rhinitis development in the first three years of life in the final regression model (Table 4). Maternal alcohol consumption before pregnancy [AOR 1.48 (1.09–2.03)], higher level of plasma cystathionine during pregnancy [AOR 1.30 (1.02–1.68)], child's infection by three months [AOR 1.63 (1.05–2.62)] and breastfeeding at six months [AOR 1.79 (1.32–2.43)] were associated with higher risk of rhinitis development. Higher maternal age at delivery [AOR 0.96 (0.93–0.99)] was associated with lower risk of rhinitis development.

3.3. Wheeze

Wheeze development in the first three years of life was significantly associated with six risk factors in the final regression model (Table 5). Higher maternal education [AOR 1.85 (1.17–2.97)], maternal history of allergy [AOR 1.47 (1.00–2.15)] and plasma creatine during pregnancy [AOR 1.02 (1.01–1.04)] were associated with higher risk of wheeze development. Higher level of neopterin during pregnancy [AOR 0.94 (0.90–0.98)], higher gestational age [AOR 0.82 (0.71–0.94)] and higher maternal age at delivery [AOR 0.94 (0.91–0.98)] were associated with lower risk of wheeze development.

3.4. GUSTO maternal and cord blood markers

A total of 980 mother-child pairs from the GUSTO cohort were included in this sub-analysis.

3.4.1. Atopic eczema

Higher levels of insulin like growth factor binding protein (IGFBP-4) [AOR 0.98 (0.96–1.00)] and interleukin 10 (IL-10) [AOR 0.70 (0.50–0.98)] were both associated with reduced risk of child's atopic eczema. However, in the supervised GSEM, no significant associations were found linking maternal alcohol consumption and EPDS score before pregnancy, neopterin, maternal IGFBP-4, infant cord blood IL-10 and child's atopic eczema.

3.4.2. Rhinitis

While there was some evidence of an association between child's rhinitis and maternal insulin-like growth factor I, IGFBP-1, IGFBP-3 and cord blood levels of monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1) and immunoglobulin G2, the 95% CI crossed the null value (Table S6). There were no potential associations among the significant environmental, maternal and infant blood markers in pathway analysis.

3.4.3. Wheeze

Higher maternal cytokine MCP-1 levels and infant cord blood dimethylglycine (DMG) levels were associated with a reduced risk of wheeze [AOR 0.997 (0.995–1.00); AOR 0.68 (0.50–0.92) respectively], while higher maternal follicle-stimulating hormone (FSH) was associated with increased risk of wheeze [AOR 1.36 (1.01–1.83)]. Two potential mechanistic pathways were observed through GSEM (Fig. S1). Maternal neopterin and creatine were positively and negatively associated with child's DMG respectively, and child's DMG was negatively associated with wheeze. We observed a second pathway involving neopterin, MCP-1 and FSH; however, the addition of associations among maternal creatine, cord blood DMG and wheeze into the GSEM diminished the association between FSH and wheeze.

4. Discussion

The exposome is an emerging research concept that aims to study the roles of a wide range of possible environmental exposures experienced throughout the life course in disease development (Wild, 2005b). This approach is informative in understanding the interactions between environmental exposures and identifying the likely critical developmental period for effective disease interventions. In this study, we aimed to answer two main questions: 1) which environmental risk factors play the most important roles in childhood atopic eczema, rhinitis and wheeze development in the first three years of life? and 2) when do these environmental exposures exert the highest risk? To the best of our knowledge, this is the first such study conducted in Asian children and the first to incorporate the preconception exposome.

The antenatal environment is the bridge linking maternal and child's exposomes. It forms the child's first environmental exposures and is shaped by maternal characteristics and environmental exposures that influence her health and immune profile (Wright et al., 2016). From our results, we postulate that childhood inflammatory diseases are mainly programmed *in utero*. We identified key modifiable factors that can increase the inflammatory potential of the antenatal environment to trigger childhood atopic eczema and rhinitis – maternal alcohol consumption during preconception and maternal depressive symptoms during pregnancy. We postulate that preconception alcohol consumption may trigger immune dysregulation of the earliest fetal environment.

Table 2
Characteristics of the study population (n = 1151).

	Mean (SD), median (IQR) or n (%)	Missing data (%)	Missing data in Eczema Group (%)	Missing data in Rhinitis Group (%)	Missing data in Wheeze Group (%)
Ethnicity		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chinese	716 (62.2)				
Malay	269 (23.4)				
Indian	158 (13.7)				
Others	8 (0.7)				
Parity	1.0 [0.0,1.0]	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal highest education		10 (0.9)	2 (0.6)	9 (1.3)	4 (1.7)
Secondary or below	255 (22.3)				
Post-secondary or higher education	886 (77.7)				
Monthly household income		104 (9.0)	27 (8.2)	65 (9.1)	20 (8.5)
$0-$999	16 (1.5)				
$1000-$1999	100 (9.6)				
$2000-$3999	262 (25.0)				
$4000-$5999	241 (23.0)				
More than $6000	428 (40.9)				
Duration of strenuous PA before pregnancy		16 (1.4)	3 (0.9)	10 (1.4)	1 (0.4)
Never	773 (68.1)				
0–74 min/wk	207 (18.2)				
75+ min/wk	155 (13.7)				
Duration of moderate-to-strenuous PA before pregnancy		14 (1.2)	3 (0.9)	9 (1.3)	1 (0.4)
Never	388 (34.1)				
0–149 min/wk	468 (41.2)				
150–299 min/wk	148 (13.0)				
300+ min/wk	133 (11.7)				
Duration of strenuous PA during pregnancy		208 (18.1)	76 (23.0)	141 (19.8)	43 (18.4)
Never	916 (97.1)				
0–74 min/wk	17 (1.8)				
75+ min/wk	10 (1.1)				
Duration of moderate-to-strenuous PA during pregnancy		206 (17.9)	76 (23.0)	141 (19.8)	43 (18.4)
Never	654 (69.2)				
0–149 min/wk	206 (21.8)				
150–299 min/wk	35 (3.7)				
300+ min/wk	50 (5.3)				
Smoking status during pregnancy	20 (1.8)	20 (1.7)	6 (1.8)	11 (1.5)	2 (0.9)
Passive smoke exposure before pregnancy	413 (37.5)	50 (4.3)	10 (3.0)	28 (3.9)	11 (4.7)
Passive smoke exposure during pregnancy	364 (33.1)	52 (4.5)	16 (4.8)	27 (3.8)	13 (5.6)
Alcohol consumption before pregnancy	485 (42.5)	11 (1.0)	3 (0.9)	8 (1.1)	1 (0.4)
Alcohol consumption during pregnancy	31 (2.8)	37 (3.2)	7 (2.1)	25 (3.5)	6 (2.6)
Maternal history of allergy	488 (43.6)	31 (2.7)	7 (2.1)	23 (3.2)	9 (3.8)
Gestational age	39.0 [38.1,39.7]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antibiotics given during labour	383 (34.4)	38 (3.3)	17 (5.1)	23 (3.2)	9 (3.8)
Mode of delivery		15 (1.3)	9 (2.7)	7 (1.0)	3 (1.3)
Vaginal	791 (69.6)				
Caesarean	345 (30.4)				
Maternal age at delivery	31.6 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infant's sex		1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Female	562 (48.9)				
Male	588 (51.1)				
Birthweight	3.1 [2.9,3.4]	8 (0.7)	4 (1.2)	3 (0.4)	2 (0.9)
Maternal STAI state during pregnancy week 26–28	33.0 [26.0,41.0]	96 (8.3)	26 (7.9)	64 (9.0)	13 (5.6)
Maternal STAI trait during pregnancy week 26–28	36.0 [30.0,43.0]	98 (8.5)	27 (8.2)	66 (9.3)	17 (7.3)
Maternal STAI state during postnatal 3 months	33.0 [26.0,41.0]	318 (27.6)	100 (30.2)	209 (29.4)	65 (27.8)
Maternal STAI trait during postnatal 3 months	36.0 [29.0,43.0]	334 (29.0)	106 (32.0)	222 (31.2)	72 (30.8)
Maternal EPDS total score during pregnancy week 26–28	7.0 [4.0,10.0]	80 (7.0)	25 (7.6)	59 (8.3)	13 (5.6)
Maternal EPDS total score during postnatal 3 months	6.0 [3.0,9.0]	323 (28.1)	103 (31.1)	210 (29.5)	65 (27.8)
Child infection by 3 months	190 (17.4)	57 (5.0)	20 (6.0)	43 (6.0)	16 (6.8)
Child's antibiotic use by 3 months	85 (7.7)	51 (4.4)	18 (5.4)	39 (5.5)	14 (6.0)
Breastfeeding status at 6 months	564 (51.6)	57 (5.0)	13 (3.9)	48 (6.8)	12 (5.1)
BISQ night time sleep hours at 6 months	9.0 [7.7,10.0]	366 (31.8)	101 (30.5)	241 (33.9)	66 (28.2)
BISQ total sleep hours at 6 months	12.0 [10.4,14.0]	372 (32.3)	101 (30.5)	244 (34.3)	68 (29.1)
BISQ night time sleep hours at 12 months	9.0 [8.0,10.0]	509 (44.2)	140 (42.3)	326 (45.9)	107 (45.7)
BISQ total sleep hours at 12 months	12.0 [11.0,13.0]	510 (44.3)	140 (42.3)	327 (46.0)	107 (45.7)
Cat ownership in early life	35 (3.8)	230 (20.0)	51 (15.4)	140 (19.7)	46 (19.7)
Dog ownership in early life	61 (6.6)	226 (19.6)	49 (14.8)	139 (19.5)	39 (16.7)
Proximity of residence to expressway in early life	128 (14.7)	279 (24.2)	70 (21.1)	175 (24.6)	53 (22.6)

(*continued on next page*)

Table 2 (*continued*)

	Mean (SD), median (IQR) or n (%)	Missing data (%)	Missing data in Eczema Group (%)	Missing data in Rhinitis Group (%)	Missing data in Wheeze Group (%)
Neopterin during pregnancy week 26–28 (nmol/L)	17.2 [15.1,20.5]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Riboflavin during pregnancy week 26–28 (nmol/L)	14.6 [9.4,24.9]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Trigonelline during pregnancy week 26–28 (μmol/L)	0.1 [0.1,0.3]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Pyridoxal during pregnancy week 26–28 (nmol/L)	19.6 [10.5,34.1]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Pyridoxal phosphate during pregnancy week 26–28 (nmol/L)	77.7 [33.9,143.0]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Vitamin D3 during pregnancy week 26–28 (nmol/L)	81.7 (26.8)	404 (35.1)	146 (44.1)	258 (36.3)	72 (30.8)
Arginine during pregnancy week 26–28 (μmol/L)	31.6 [26.3,38.3]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
ADMA during pregnancy week 26–28 (μmol/L)	0.4 [0.4,0.4]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Creatine during pregnancy week 26–28 (μmol/L)	43.2 [35.5,51.1]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Cystathionine during pregnancy week 26–28 (0.1 μmol/L)	1.4 [1.1,1.9]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
3-methylhistidine during pregnancy week 26–28 (μmol/L)	1.6 [0.6,3.4]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Histidine during pregnancy week 26–28 (μmol/L)	67.3 [61.2,74.6]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Methionine during pregnancy week 26–28 (μmol/L)	18.7 [14.4,21.8]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Hydroxyanthranilic acid during pregnancy week 26–28 (nmol/L)	70.0 [60.3,82.0]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Kynurenic acid during pregnancy week 26–28 (nmol/L)	16.9 [13.7,21.7]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Kynurenine during pregnancy week 26–28 (μmol/L)	1.0 [0.9,1.1]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Tryptophan during pregnancy week 26–28 (μmol/L)	47.0 (7.9)	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Betaine during pregnancy week 26–28 (μmol/L)	12.9 [11.3,14.7]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Choline during pregnancy week 26–28 (μmol/L)	9.0 [7.9,10.2]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Dimethylglycine during pregnancy week 26–28 (μmol/L)	1.8 [1.5,2.2]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)
Trimethylamine N oxide during pregnancy week 26–28 (μmol/L)	1.4 [0.9,2.3]	375 (32.6)	137 (41.4)	244 (34.3)	67 (28.6)

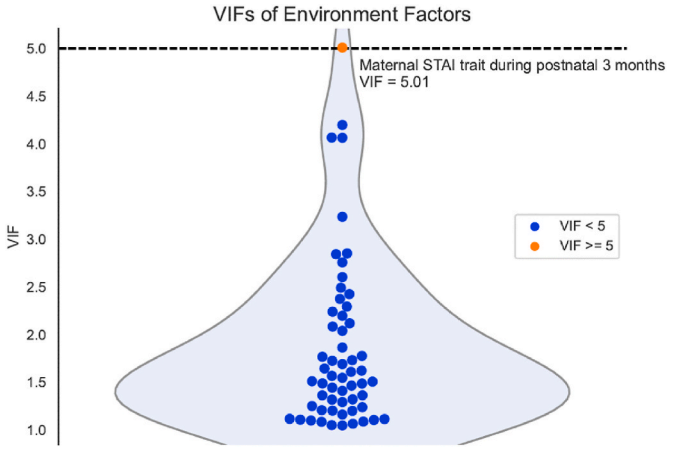

Fig. 3. VIF distribution of environmental factors included in our study. Each dot represents an individual environmental factor with its corresponding VIF value, spacing was adjusted to prevent overlap. The width of the violin plot indicates the data density. With the exception of one environment factor (maternal STAI trait during postnatal 3 months) exhibiting a VIF value greater than five, VIFs of all other factors are less than five which indicated low collinearity.

Table 3
Association between eczema development in the first three years of life and environmental risk factors in the final regression model.

Risk Factor	AOR (95% CI)	*p*
Maternal consumption of alcohol before pregnancy	2.16 (1.51–3.09)	**<0.001**
Maternal EPDS score during pregnancy week 26–28	1.07 (1.01–1.14)	**0.018**
Maternal STAI trait score during pregnancy week 26–28	0.97 (0.95–1.00)	0.069
Neopterin during pregnancy week 26–28	0.93 (0.89–0.97)	**0.001**
Choline during pregnancy week 26–28	1.04 (0.92–1.17)	0.54
Gestational age	0.88 (0.77–1.00)	0.06
Child's infection by 3 months	2.21 (1.32–3.79)	**0.003**
Breastfeeding status at 6 months	2.23 (1.57–3.19)	**<0.001**

AOR: adjusted odds ratio; CI: confidence interval; EPDS: Edinburgh Postnatal Depression Scale; STAI: State-Trait Anxiety Inventory.
Significant *p* in bold.

Robust research evidence demonstrated that alcohol accentuates Th2 responses and immunoglobulin E production (González-Quintela et al., 2002; Latif et al., 2002). This suggests that fetuses of mothers who consumed alcohol before conception are likely to be conceived in an inflammatory environment with a highly pronounced bias towards Th2 responses. The heightened Th2 skew may leave a prolonged imprint into infancy and increase the child's susceptibility to atopic eczema and both allergic and viral rhinitis subtypes (McFadden et al., 2015; Klemens et al., 2005). Another possible mechanism involves alcohol-induced epigenetic changes in the oocytes that may compromise embryo and

Table 4
Association between rhinitis development in the first three years of life and environmental risk factors in the final regression model.

Risk Factor	AOR (95% CI)	*p*
Maternal history of allergy	1.33 (0.98–1.81)	0.066
Maternal consumption of alcohol before pregnancy	1.48 (1.09–2.03)	**0.013**
Cystathionine during pregnancy week 26–28	1.30 (1.02–1.68)	**0.041**
Methionine during pregnancy week 26–28	0.98 (0.94–1.01)	0.217
Duration of moderate-to-strenuous PA during pregnancy		
Never (ref)		
0–149 min/wk	0.89 (0.60–1.32)	0.552
150–299 min/wk	0.89 (0.40–2.12)	0.780
300+ min/wk	0.90 (0.45–1.93)	0.777
Maternal age at delivery	0.96 (0.93–0.99)	**0.014**
Child's infection by 3 months	1.63 (1.05–2.62)	**0.034**
Maternal STAI state during postnatal 3 months	1.01 (1.00–1.03)	0.124
Breastfeeding status at 6 months	1.79 (1.32–2.43)	**<0.001**

AOR: adjusted odds ratio; CI: confidence interval; PA: physical activity; STAI: State-Trait Anxiety Inventory.
Significant *p* in bold.

Table 5
Association between wheeze development in the first three years of life and environmental risk factors in the final regression model.

Risk Factor	AOR (95% CI)	*p*
Maternal post-secondary or higher education	1.85 (1.17–2.97)	**0.009**
Maternal history of allergy	1.47 (1.00–2.15)	**0.049**
Creatine during pregnancy week 26–28	1.02 (1.01–1.04)	**0.011**
Kynurenic acid during pregnancy week 26–28	1.02 (0.99–1.06)	0.170
Neopterin during pregnancy week 26–28	0.94 (0.90–0.98)	**0.007**
Gestational age	0.82 (0.71–0.94)	**0.006**
Maternal age at delivery	0.94 (0.91–0.98)	**0.003**

AOR: adjusted odds ratio; CI: confidence interval.
Significant *p* in bold.

fetal development (Carpenter et al., 2021; VandeVoort et al., 2015). Preconception alcohol consumption may be more damaging as intake tends to be higher before pregnancy recognition (Alvik et al., 2006). A Finnish study of 14,822 women reported a huge contrast between preconception and pregnancy alcohol consumption (86% vs 4.5%) (Voutilainen et al., 2022). In our cohort, 42.5% of mothers reported alcohol consumption before conception, as compared to 2.8% during pregnancy. It is thus insufficient to abstain from alcohol only from pregnancy since preconception intake can induce lasting effects on antenatal development. The burden of maternal depression during pregnancy is high, with estimates ranging between 15% and 65% (Dadi et al., 2020). Many studies have demonstrated how poor maternal mental health during pregnancy can trigger a cascade of inflammatory responses, including increased Th2 cytokines secretion elevated placental transfer of glucocorticoids, fetal hypothalamic-pituitary-adrenal axis dysregulation, fetal oxidative stress and stimulation of placental production of cortisol-releasing hormone (Karlsson et al., 2017; Suh et al., 2017).

To support our hypothesis of *in utero* programming, we examined possible mechanisms by modelling maternal and cord metabolites and immune markers in relation to health outcomes. We observed that higher neopterin in maternal blood exhibited a protective effect against wheeze. Neopterin is a biomarker elevated in Th1 immune activation, which counteracts Th2 inflammation (Widner et al., 2000; Hamerlinck, 1999). It is produced *in vivo* through stimulation of M1 macrophages and monocytes by the Th1 cytokine interferon gamma (Widner et al., 2000; Hamerlinck, 1999). Neopterin was positively associated with MCP-1 in our model, a chemokine also produced by M1 macrophages (Yang et al., 2020). Although MCP-1 is commonly regarded as a Th2 marker, it is also capable of enhancing Th1 responses (Singh et al., 2021). This notion is supported by evidence of a protective effect by MCP-1 against both atopic and non-atopic wheeze in children (Keszei et al., 2006; McDougall et al., 2015). In addition, research shows ethnic variations in the effects of MCP-1 on asthma outcomes, where higher risks were present in Caucasians and not in the Chinese or African populations (Yao et al., 2004; Chen et al., 2019). We found higher MCP-1 to be associated with lower FSH, but the association between FSH and wheeze was diminished by the addition of maternal creatine and cord blood DMG into the model. The mechanistic processes linking this section of the model is unclear possibly due to the limited panel of metabolites and cytokines studied. In summary, we postulate that maternal blood neopterin and MCP-1 during pregnancy may represent a Th1 intrauterine environment that protects against childhood wheeze. Maternal neopterin and creatine were both associated with child's serum DMG levels, albeit in opposing directions. Creatine, an amino acid present in diets and supplements, has been strongly associated with airway inflammation in murine models (Garcia et al., 2019; Vieira et al., 2007; Ferreira et al., 2010). DMG is an intermediate immunomodulatory amino acid in the choline pathway that synthesises glycine and promotes enhanced humoral and cell-mediated immune responses (Hogeveen et al., 2013; Brosnan et al., 2011; Graber et al., 1981). Lower serum DMG level had been reported in children with mite-sensitized asthma (Chiu et al., 2020), implying that maternal metabolites can prime fetal immune responses to protect against wheeze development.

We also identified maternal and birth risk factors of early childhood inflammatory diseases, namely maternal history of allergy, low maternal age at delivery and shorter duration of gestation. Maternal history of allergy is a well-established risk factor linked to inheritance of high-risk allergy genes and inflammatory immune profile (Ravn et al., 2020). The current evidence on the role of maternal age at delivery on offspring rhinitis and wheeze development is conflicting (Amera et al., 2020; Nafstad et al., 2000; Lu et al., 2020; Wang et al., 2016). A younger maternal age may be linked to higher infant immunoglobulin E levels as reported in a study of one-week-old infants from the Netherlands (van Gool et al., 2004). We postulate that infants with a shorter duration of gestation may have underdeveloped airway epithelium and immune systems (Looi et al., 2019). Coupled with earlier exposure to pro-inflammatory environmental stimuli, this may trigger airway inflammation and wheeze development (Looi et al., 2019; Goedicke-Fritz et al., 2017). In support of our findings, the UK Millennium Cohort Study and Kyushu Okinawa Child Health Study reported that children born preterm had higher odds of wheeze development as compared to those born at full term (Leps et al., 2018; Takata et al., 2019). A shorter gestational duration may also indicate impaired maternal-child immunoregulation resulting from a decline in suppressive functions of regulatory T cells (Tregs) during pregnancy (Aghaeepour et al., 2017; Schober et al., 2012). The progression of pregnancy is accompanied by increasing activation of the interleukin-2–dependent STAT5ab signalling pathway, which is essential for Tregs production (Aghaeepour et al., 2017). Besides maintaining immune tolerance to the semi-allogenic fetus, evidence suggests that Tregs may play a role in controlling airway inflammation (Noval Rivas and Chatila, 2016). These characteristics can be used to identify a high-risk group of children that should be monitored and treated early for inflammatory diseases.

While early childhood atopic eczema, wheeze and rhinitis development were highly influenced by environmental exposures during preconception and pregnancy, the postnatal period provides another window for disease intervention. We demonstrated that early infection, likely viral in origin, was a common risk factor for atopic eczema and rhinitis development. Research has pointed towards the viral-mediated pathway of early childhood atopic eczema and rhinitis development (Medeleanu et al., 2022; Sultész et al., 2010; Doulaptsi et al., 2019). However, a limitation of the study is the lack of viral cultures to ascertain infections. We also observed that breastfeeding beyond six months was associated with elevated risks of atopic eczema and rhinitis development. At present, the evidence on the role of prolonged breastfeeding in these diseases is highly inconsistent and weak, with some studies concurring with our findings (Kim, 2017; Lodge et al., 2015). Our use of machine learning facilitated the investigation of a wide range of

environmental risk factors, with adjustment for confounding variables. This strengthens the reliability of our findings and provides the foundation for future mechanistic studies.

In this study of the exposome in early childhood atopic eczema, rhinitis and wheeze development, we leveraged on our extensive and regular data collection of environmental exposures from as early as the preconception period in both cohorts. We were able to analyze a wide range of environmental exposures simultaneously using advanced machine learning techniques. By combining two comparable cohorts, we were able to ascertain the role of the exposome with a more robust study population size. The use of interviewer-administered questionnaires reduced response bias and errors. The limitations include the use of parental reports to assess early childhood atopic eczema, rhinitis and wheeze outcomes but recall bias was minimised through regular follow-up with structured standardised questionnaires. In addition, although the validated ISAAC questionnaire is commonly used in studies of these paediatric diseases, we were unable to differentiate the allergic and non-allergic variants of rhinitis and wheeze. We were unable to include environmental exposures that were not present, defined similarly or evaluated at the same timepoints in both cohorts, such as environmental toxins and microbiome. In addition, the panel of maternal and cord blood cytokines examined was limited in scope and longitudinal coverage and may preclude further observations of mechanistic links between environmental exposures and disease outcomes.

5. Conclusion

This is the first study to examine the influence of the exposome from as early as the preconception period on early childhood atopic eczema, rhinitis and wheeze development in two Asian cohorts. Through comprehensive machine learning methods, we highlight preconception and antenatal exposomes that might programme the development of inflammatory diseases *in utero*. Reducing maternal alcohol consumption during preconception and supporting maternal mental health during pregnancy may prevent atopic eczema and rhinitis development by promoting an optimal antenatal environment. Our findings suggest a need to include preconception environmental exposures in future research to counter the earliest precursors of disease development in children.

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Data sharing statement

Data used in this study is available on request from the corresponding author due to ethical and privacy limitations. The codes for the study can be found at https://github.com/nus-mornin-lab/gusto_allergy.

CRediT authorship contribution statement

Yizhi Dong: Conceptualization, Data curation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing, Formal analysis. **Hui Xing Lau:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Noor Hidayatul Aini Suaini:** Conceptualization, Writing – review & editing, Formal Analysis. **Michelle Zhi Ling Kee:** Conceptualization, Writing – review & editing. **Delicia Shu Qin Ooi:** Conceptualization, Writing – review & editing. **Lynette Pei-chi Shek:** Conceptualization, Writing – review & editing. **Bee Wah Lee:** Conceptualization, Writing – review & editing. **Keith M. Godfrey:** Conceptualization, Writing – review & editing. **Elizabeth Huiwen Tham:** Conceptualization, Writing – review & editing. **Marcus Eng Hock Ong:** Conceptualization, Funding acquisition, Writing – review & editing. **Nan Liu:** Conceptualization, Writing – review & editing. **Limsoon Wong:** Conceptualization, Funding acquisition, Writing – review & editing. **Kok Hian Tan:** Conceptualization, Writing – review & editing. **Jerry Kok Yen Chan:** Conceptualization, Writing – review & editing. **Fabian Kok Peng Yap:** Conceptualization, Writing – review & editing. **Yap Seng Chong:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Johan Gunnar Eriksson:** Conceptualization, Funding acquisition, Writing – review & editing. **Mengling Feng:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing – review & editing. **Evelyn Xiu Ling Loo:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yap Seng Chong reports a relationship with Abbott Nutrition that includes: funding grants and speaking and lecture fees. Keith M Godfrey reports a relationship with Abbott Nutrition that includes: funding grants and speaking and lecture fees. Yap Seng Chong reports a relationship with Nestle that includes: funding grants and speaking and lecture fees. Keith M Godfrey reports a relationship with Nestle that includes: funding grants and speaking and lecture fees. Yap Seng Chong reports a relationship with Danone that includes: funding grants and speaking and lecture fees. Keith M Godfrey reports a relationship with Danone that includes: funding grants and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.118523.

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