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Maternal asthma symptoms during pregnancy on child behaviour and executive function: A Bayesian phenomics approach

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ABSTRACT

Objective: Maternal history of inflammatory conditions has been linked to offspring developmental and behavioural outcomes. This phenomenon may be explained by the maternal immune activation (MIA) hypothesis, which posits that dysregulation of the gestational immune environment affects foetal neurodevelopment. The timing of inflammation is critical. We aimed to understand maternal asthma symptoms during pregnancy, in contrast with paternal asthma symptoms during the same period, on child behaviour problems and executive function in a population-based cohort.

Methods: Data were obtained from 844 families from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort. Parent asthma symptoms during the prenatal period were reported. Asthma symptoms in children were reported longitudinally from two to five years old, while behavioural problems and executive functioning were obtained at seven years old. Parent and child measures were compared between mothers with and without prenatal asthma symptoms. Generalized linear and Bayesian phenomics models were used to determine the relation between parent or child asthma symptoms and child outcomes.

Results: Children of mothers with prenatal asthma symptoms had greater behavioural and executive problems than controls (Cohen's *d*: *0.43–0.75*; all $p < 0.05$). This association remained after adjustments for emerging asthma symptoms during the preschool years and fathers' asthma symptoms during the prenatal period. After adjusting for dependence between child outcomes, the Bayesian phenomics model showed that maternal prenatal asthma symptoms were associated with child internalising symptoms and higher-order executive function, while child asthma symptoms were associated with executive function skills. Paternal asthma symptoms during the prenatal period were not associated with child outcomes.

Conclusions: Associations between child outcomes and maternal but not paternal asthma symptoms during the prenatal period suggests a role for MIA. These findings need to be validated in larger samples, and further research may identify behavioural and cognitive profiles of children with exposure to MIA.

1. Introduction

The maternal immune activation (MIA) hypothesis proposes that dysregulation of the gestational immune environment affects foetal neurodevelopment (Han et al., 2021a). MIA during pregnancy can be triggered by infection or maternal factors associated with systemic chronic inflammation, such as smoking, low socioeconomic status, depression and asthma (Han et al., 2021b). MIA has been increasingly

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recognised as an environmental risk factor for neurological and psychiatric disorders of the offspring.

A number of pathophysiological processes are thought to be involved, such as inflammation and oxidative stress in maternal and foetal compartments, activation of maternal stress response systems, temporary deficiencies in nutrients and placental function disruption (Meyer, 2019). On a cellular and molecular level, brain development may be disrupted by alterations in immune molecules and cells, neuronal neurochemistry and function, and epigenetics (Bergdolt and Dunaevsky, 2019). The MIA hypothesis has enhanced our understanding of prenatal influences on neurodevelopment, but questions remain about the timing in which the effects of MIA can be detected in child development. Besides using clinical cases of children, population-based studies with typically developing children are necessary to establish the public health significance of MIA (O'Connor and Ciesla, 2022).

The prevalence of asthma during pregnancy is increasing worldwide and nearly half of women with asthma may experience an asthma exacerbation during pregnancy (Whalen et al., 2019). A history of asthma in mothers was associated with autism spectrum disorder (ASD) (Gong et al., 2019; Hisle-Gorman et al., 2018; Croen et al., 2005), attention-deficit hyperactivity disorder (ADHD) (Liu et al., 2019) and mild-moderate intellectual disability (Langridge et al., 2013) in children. However, one study reported no relation between maternal asthma and ASD or developmental disorder (DD) without autism (Lyall et al., 2014). Other earlier investigations combined mothers with asthma and mothers with one or more other inflammatory conditions in their analysis. These studies generally support these inflammatory maternal states and their associations with ADHD (Instanes et al., 2017; Cowell et al., 2019), ASD (Patel et al., 2018; Patel et al., 2020) and/or DD (Croen et al., 2019) risk or symptom severity. While the outcome of interest for most studies were specified disorders in childhood, Patel *et al.* (Patel et al., 2021) investigated MIA as a risk factor for a variety of neurodevelopmental and neuropsychiatric problems in offspring. The authors showed that maternal asthma, allergy, atopy or eczema before, during or up to 5 years after pregnancy was associated with a significant increase in behavioural and emotional problems throughout childhood and adolescence. This relation remained when only mothers with a history of asthma were analysed (Patel et al., 2021).

There are currently mixed findings on maternal immune-related conditions and child cognition. An ASD cohort study reported a link between maternal asthma history and greater externalising behaviour, but not cognitive functioning at three years old (Patel et al., 2020). In contrast, a population-based cohort study reported associations between infection in the third trimester and lower intelligence quotient at 4 and 8 years old (Kwok et al., 2022). Furthermore, elevated inflammatory biomarkers measured during pregnancy were also linked to poor child cognition. Interleukin-6 was associated with nonverbal fluid intelligence (Rasmussen et al., 2022) and indirectly related to preschool executive function ability via infant general cognitive ability (Camerota et al., 2022). In addition, high-sensitivity C-reactive protein levels and glycoprotein acetyls were associated with a greater number of neurodevelopmental delays (Girchenko et al., 2020).

While existing literature has linked maternal history of asthma to child developmental disorders, there is a need to evaluate the effect of maternal asthma symptoms during pregnancy in conjunction with other maternal risk factors as well as paternal or child asthma symptoms (Han et al., 2021b). An association between child outcomes and maternal asthma symptoms before or after pregnancy may be due to shared genetic and environmental risk factors, whereas an association with maternal symptoms during pregnancy may suggest intrauterine immune dysregulation. Similarly, an association with maternal but not paternal asthma symptoms during the prenatal period would suggest an intrauterine process (Liu et al., 2019). However, previous reports on paternal history of inflammation are limited, inconsistent and requires further study. Specifically, paternal history of various immune conditions was not associated with child ASD/DD (Croen et al., 2019) but paternal history of asthma was associated with increased risk of child ASD (Gong et al., 2019) and ADHD (Liu et al., 2019).

To our knowledge, a Bayesian phenomics approach has yet to be used to investigate the effect of maternal immune-related conditions on offspring psychopathology and cognition. We hypothesise that behavioural problems and poor executive function in children are associated with maternal asthma symptoms during pregnancy. The first aim of this study was to compare child behaviour problems and executive functioning between mothers with and without prenatal asthma symptoms. The second aim was to determine associations between each child outcome and potential confounders, such as maternal prenatal mental health, paternal asthma symptoms during the prenatal period, and child asthma symptoms. The third aim was to investigate associations between multiple risk factors and child outcomes using a Bayesian phenomics model.

2. Methods

2.1. Participants

Data were obtained from the Growing Up in Singapore towards Healthy Outcomes (GUSTO) longitudinal birth cohort study (Soh et al., 2014). The cohort consisted of 1247 mother–child dyads from the multiethnic population in Singapore. The major ethnic groups are Chinese, Malay, and Indian. Pregnant women were recruited in their first trimester in 2009 to 2010 from two public hospitals in Singapore and the mother–child dyads were followed-up beyond 13 years after delivery. Women with preterm infants (<37 weeks' gestation), twin pregnancy or conception via in vitro fertilisation techniques were excluded from this study. All mothers gave informed consent at recruitment and after each amendment. All children who turned 7 years old in 2017 assented to the study. This study was performed according to the Declaration of Helsinki and the ethical principles in the Belmont Report. It was approved by the Domain Specific Review Board of the Singapore National Healthcare Group and the Centralised Institutional Review Board of SingHealth.

2.2. Measures

2.2.1. Asthma symptoms

Three weeks after the birth of their child, parents completed a questionnaire regarding their personal history of asthma. The presence of maternal and paternal asthma symptoms during the prenatal period were recorded as binary variables. Data on child wheezing and nebuliser use were obtained and recorded as binary variables at 2, 3, 4 and 5 years old. Children were considered to have emerging preschool asthma symptoms if they were wheezing and using a nebulizer concurrently at least once between 2 and 5 years old.

2.2.2. Child outcomes

Mothers completed the Child Behaviour Checklist for ages 6–18 (CBCL) when children were 7 years old. Items are scored on a 3-point Likert scale (0 = Not True, 1 = Somewhat or Sometimes True, 2 = Very True or Often True) and summed to produce raw scores for eight syndrome scales, namely anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour, and aggressive behaviour. Higher CBCL scores reflect greater behavioural and emotional problems in children (Achenbach and Rescorla, 2014).

The Behaviour Rating Inventory of Executive Function, Second Edition (BRIEF2) was also administered to mothers when children were 7 years old. Items are scored on a 3-point Likert scale (0 = Never, 1 = Sometimes, 2 = Often) and summed to produce raw scores for nine clinical scales, including inhibit, self-monitor, shift, emotional control, initiate, working memory, plan/organize, task-monitor, and organization of materials. Higher BRIEF2 scores reflect poorer executive functioning in children (Sherman and Brooks, 2010; Skogan et al., 2016).

2.2.3. Demographic and clinical covariates

Covariates were selected by theoretical conception and were retained for the final analyses when significantly associated with child outcomes. They included monthly household income (<S$2000 and ≥$2000), ethnicity, maternal age at delivery, number of older siblings (0, 1 or ≥ 2), maternal prenatal mental health, maternal prenatal smoking exposure, child sex, gestational age (weeks), and child body mass index (BMI) at 4 years old.

An earlier published bi-factor analysis by our group of all items of the Spielberger State-Trait Anxiety Inventory (Spielberger, 1983), the Edinburgh Postnatal Depression Scale (Cox et al., 1987) and the second edition of the Beck Depression Inventory (Beck et al., 1961) produced a general mood factor at 26–28 weeks of pregnancy. This factor may be interpreted as a general propensity to develop psychopathology symptoms or a general level of distress (Phua et al., 2017). Hence, it was used as a measure of maternal prenatal mental health in this study, with higher values indicating worse mental health.

Maternal prenatal smoking exposure was recorded as a binary variable. Mothers were considered to have prenatal smoking exposure when they reported active smoking, exposure to smoking within the same household, or had detectable plasma cotinine (>0.17 mg/dL) at 26–28 weeks' gestation (Ng et al., 2019).

2.3. Statistical analysis

Differences in paternal asthma symptoms, emerging preschool asthma symptoms, child outcomes, and covariates between mothers with and without prenatal asthma symptoms were first assessed using t-tests or chi square tests. Square root transformed CBCL and BRIEF2 raw scores were used in t-tests. Sensitivity analyses were conducted to determine differences in demographic variables between mothers with complete and incomplete data on prenatal asthma symptoms. Univariate and multivariable generalized linear models (GLM) with Gamma distribution and log link were then fitted to understand the effect of asthma symptoms on child outcomes, while adjusting for relevant covariates. Descriptive statistics and regression models were performed using Stata 17 (StataCorp, TX, USA).

The effect of maternal asthma symptoms on child psychopathology and cognition was investigated via a Bayesian phenomics approach. Phenomics is an increasingly popular technique used to analyse large datasets within the generalised linear model framework. In the phenomics approach, several responses are modelled jointly, with the aim of studying their association among themselves as well as with a usually large set of predictors. The method is based on the framework of Seemingly Unrelated Regressions (SUR) (Zellner, 1963), where different linear regressions for each response variable are related by specifying correlated error terms. By considering the dependence among the responses, this joint modelling approach provides more accurate inference. The regression coefficients are modelled using a Normal distribution with zero mean and random variances distributed as inverse-Gamma with shape and rate parameters ($a = 5$, $b = 1$). For each of these parameters, the Markov chain Monte Carlo algorithm produces a sample from the corresponding posterior distribution, which can be used to obtain posterior estimates (e.g., posterior mean and 95 % credible intervals). In this work, we perform the analyses in the Bayesian framework, which allows for the inclusion of a-priori information via the specification of prior distributions over the parameters of interest (i.e., the dependence among the response and their associations with the covariates). The model was fitted to the GUSTO data using the software R (R Core Team, 2021) interfaced with C++ (Eddelbuettel and François, 2011) and RStudio (Posit Team, 2022).

3. Results

Compared to mothers without prenatal asthma symptoms, mothers with prenatal asthma symptoms were younger and had worse prenatal mental health. A larger proportion of mothers with prenatal asthma symptoms were of Malay or Indian ethnicities, had prenatal smoke exposure, and a child with preschool asthma symptoms (Table 1). In addition, children of mothers with prenatal asthma symptoms had higher scores for the anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, rule-breaking behaviour, and aggressive behaviour scales on the CBCL and also had more deficits in shift, emotional control, initiate, working memory, plan/organise, task-monitor and organisation of materials on the BRIEF2 (Fig. 1; retransformed mean difference: 0.03–0.39). Compared to parent–child dyads with incomplete data, those with complete data had a larger proportion of Malay and Indian ethnicities, older siblings, prenatal smoke exposure and higher gestational age (Supplementary Table 1).

Univariate GLM demonstrated that maternal prenatal asthma symptoms were associated with higher scores for most child outcomes. Furthermore, child preschool asthma symptoms were associated with more problems in task-monitor and organisation of materials scales of the BRIEF2, but paternal asthma symptoms during the prenatal period were not associated with any outcome. Covariates that were associated with child outcomes included monthly household income, ethnicity, maternal prenatal mental health, maternal prenatal smoke exposure, maternal age at delivery, number of older siblings, child sex, and child BMI at 4 years old (Supplementary Tables 2 & 3). Similarly, multivariate GLMs showed that maternal prenatal asthma symptoms remained associated with most child outcomes, even when paternal asthma symptoms in the prenatal period and child preschool asthma symptoms were included in the model. Additionally, child preschool asthma symptoms and paternal asthma symptoms during the prenatal period were not associated with any outcome (Table 2).

Predictors in the Bayesian phenomics model were maternal and paternal asthma symptoms in the prenatal period, child preschool asthma symptoms, monthly household income, ethnicity, maternal prenatal mental health, maternal age at delivery, number of older siblings, child sex, and child BMI at 4 years old. Outcomes in this model were all the CBCL scales except attention problems and all the BRIEF2 scales except inhibit and self-monitor. In Fig. 2 we report pairwise correlations among all child outcomes. Correlation among outcome variables is accounted for in the phenomic framework. In the final analysis, maternal asthma symptoms in the prenatal period were associated with the somatic complaints scale of the CBCL and the organisation of materials scale of the BRIEF2. Child preschool asthma symptoms were associated with the organisation of materials and task-monitor scales of the BRIEF2. Paternal asthma symptoms during the prenatal period were not associated with any CBCL or BRIEF2 scales (Fig. 3).

4. Discussion

In this longitudinal population-based study, maternal asthma symptoms during pregnancy were associated with behavioural difficulties and executive function deficits in the offspring. GLMs showed that maternal prenatal asthma symptoms were associated with higher scores for most CBCL and BRIEF2 scales, even when other child and parent factors were controlled for. Associations that persisted in the Bayesian phenomics model suggested an association between maternal prenatal asthma symptoms, somatic symptoms, and problems with organisation of materials in the offspring. The somatic complaints scale of the CBCL does not directly measure anxiety, but higher scores may reflect physiological symptoms that are related to anxiety (Read et al., 2015). The organisation of materials scale in the BRIEF2 questionnaire may identify children with poorer functioning at home or school due to limited access to materials needed for learning or more time spent preparing rather than completing meaningful tasks (PAR.iConnect, 2015). Importantly, since paternal asthma symptoms in the prenatal period were not associated with any child outcome, these results lend

Table 1
Comparison of mothers with (n = 37) and without (n = 807) asthma symptoms in the prenatal period.

	Cohort		Maternal asthma symptoms in the prenatal period		No maternal asthma symptoms in the prenatal period		*p*-value
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	
Parent factors							
Household income of ≥ 2000 SGD	1126 (84.4 %)		28 (82.4 %)		648 (85.6 %)		0.599
Ethnicity							**0.030**
Chinese	824 (56.3 %)		12 (32.4 %)		438 (54.3 %)		
Malay	370 (25.3 %)		14 (37.8 %)		220 (27.3 %)		
Indian	269 (18.4 %)		11 (29.7 %)		148 (18.4 %)		
Maternal age at delivery	1197	31.2 ± 5.2	37	29.4 ± 5.7	807	31.2 ± 5.1	**0.038**
Number of older siblings							0.929
0	543 (45.3 %)		15 (40.5 %)		347 (43 %)		
1	414 (34.6 %)		14 (37.8 %)		281 (34.8 %)		
≥2	241 (20.1 %)		8 (21.6 %)		179 (22.2 %)		
Maternal prenatal smoke exposure	182 (14.7 %)		13 (35.1 %)		128 (15.9 %)		**0.002**
Maternal prenatal mental health	1066	0 ± 0.3	37	0.1 ± 0.3	779	0 ± 0.3	**0.037**
Paternal asthma symptoms in the prenatal period	30 (3.6 %)		2 (5.4 %)		28 (3.5 %)		0.535
Child factors							
Sex							0.366
Male	630 (52.7 %)		17 (45.9 %)		432 (53.5 %)		
Female	566 (47.3 %)		20 (54.1 %)		375 (46.5 %)		
Gestational age (weeks)	1197	38.6 ± 1.8	37	38.8 ± 1.2	807	38.8 ± 1.3	0.971
BMI at 4 years old	857	15.6 ± 1.8	30	16.2 ± 2.5	634	15.5 ± 1.7	0.052
Preschool asthma symptoms	124 (18 %)		12 (44.4 %)		87 (16 %)		**<0.001**

p-values < 0.05 are in bold.

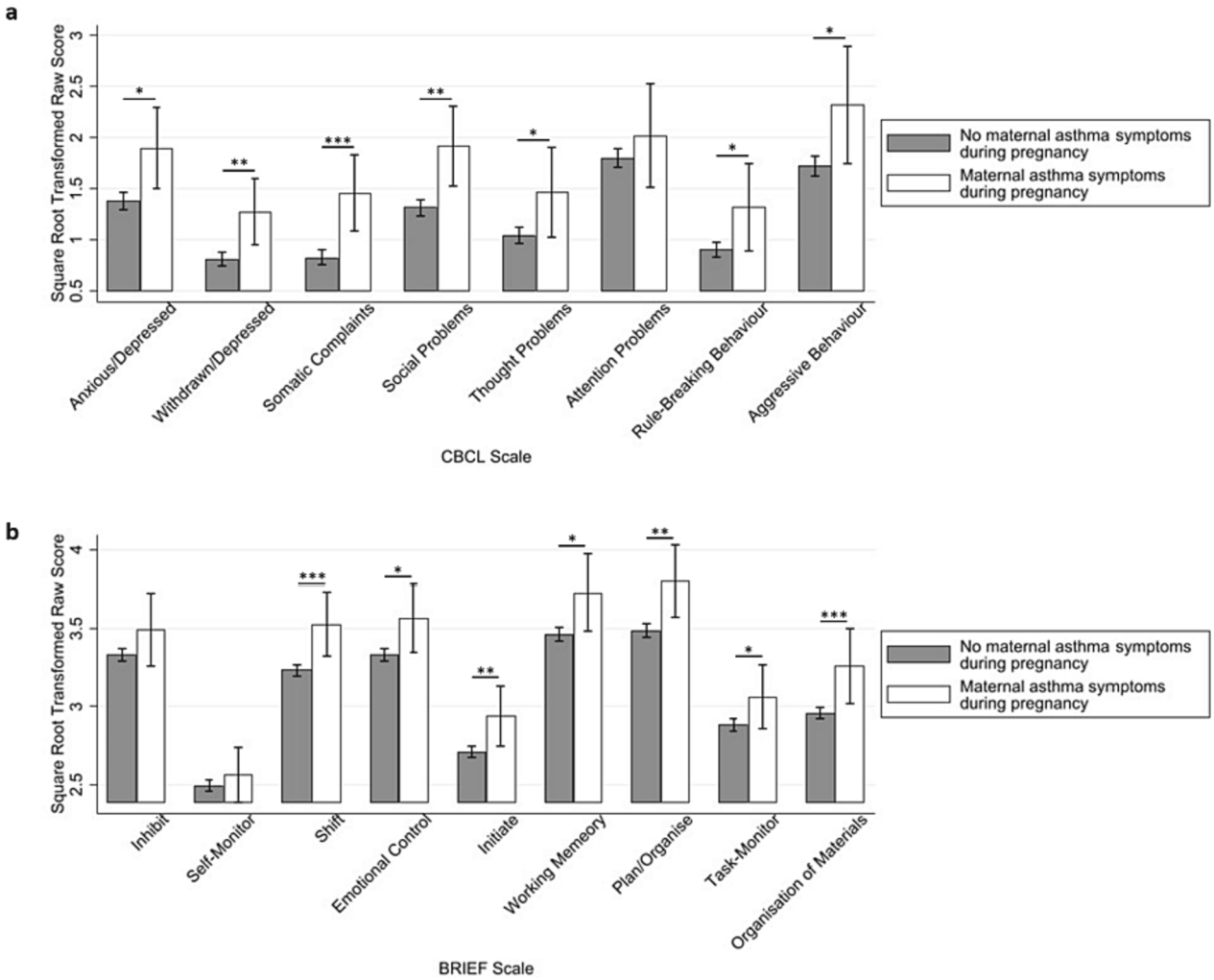

Fig. 1. Comparison of square root transformed **(a)** CBCL and **(b)** BRIEF2 raw scores at 7 years old between children of mothers with (CBCL, n = 24; BRIEF2, n = 22) and without (CBCL, n = 476; BRIEF2, n = 456) asthma symptoms during pregnancy using t-tests (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

Table 2
Relation between CBCL or BRIEF2 raw scores at 7 years old and parent or child asthma symptoms using multivariate GLMs.

Dependent variable	Model 1[a]			Model 2[b]		
	Maternal asthma symptoms in the prenatal period	Paternal asthma symptoms in the prenatal period	Child preschool asthma symptoms	Maternal asthma symptoms in the prenatal period	Paternal asthma symptoms in the prenatal period	Child preschool asthma symptoms
Anxious/ depressed	0.492 (0.051–0.933)*	−0.150 (-0.865, 0.566)	0.077 (-0.181, 0.335)	0.440 (-0.015, 0.896)	−0.048 (-0.814, 0.718)	0.031 (-0.240, 0.301)
Withdrawn/ depressed	0.604 (0.049, 1.158)*	0.010 (-0.900, 0.920)	−0.016 (-0.343, 0.311)	0.556 (-0.034, 1.145)	0.147 (-0.851, 1.146)	0.019 (-0.333, 0.371)
Somatic complaints	0.719 (0.131, 1.307)*	−0.830 (-1.795, 0.136)	0.145 (-0.201, 0.491)	0.669 (0.052, 1.286)*	−0.572 (-1.638, 0.494)	0.166 (-0.213, 0.545)
Social problems	0.601 (0.164, 1.037)**	−0.369 (-1.076, 0.338)	0.056 (-0.198, 0.310)	0.486 (0.041, 0.931)*	−0.019 (-0.768, 0.729)	0.004 (-0.260, 0.269)
Thought problems	0.602 (0.092, 1.113)*	−0.516 (-1.341, 0.309)	−0.062 (-0.360, 0.235)	0.539 (0.004, 1.073)*	−0.682 (-1.575, 0.210)	−0.143 (-0.460, 0.173)
Attention problems	0.189 (-0.165, 0.543)	−0.508 (-1.083, 0.067)	0.094 (-0.113, 0.302)	0.119 (-0.271, 0.510)	−0.501 (-1.161, 0.160)	0.066 (-0.163, 0.296)
Rule-breaking behaviour	0.583 (0.083, 1.083)*	−0.181 (-0.985, 0.624)	−0.007 (-0.299, 0.285)	0.532 (0, 1.064)	0.081 (-0.800, 0.962)	−0.032 (-0.351, 0.287)
Aggressive behaviour	0.453 (0.024, 0.883)*	−0.218 (-0.912, 0.477)	0.096 (-0.156, 0.347)	0.436 (-0.018, 0.891)	−0.177 (-0.934, 0.581)	0.059 (-0.212, 0.329)
Inhibit	0.097 (-0.025, 0.220)	−0.033 (-0.227, 0.161)	0.050 (-0.020, 0.121)	0.098 (-0.019, 0.215)	−0.007 (-0.203, 0.190)	0.041 (-0.027, 0.109)
Self-monitor	0.062 (-0.069, 0.193)	0.074 (-0.133, 0.281)	0.045 (-0.031, 0.120)	0.064 (-0.065, 0.194)	0.073 (-0.144, 0.290)	0.034 (-0.041, 0.109)
Shift	0.179 (0.071, 0.286)**	−0.036 (-0.206, 0.134)	0.041 (-0.021, 0.103)	0.146 (0.039, 0.253)**	0.031 (-0.145, 0.206)	0.036 (-0.026, 0.098)
Emotional control	0.136 (0.016, 0.256)*	−0.0.35 (-0.226, 0.156)	0.057 (-0.012, 0.127)	0.106 (-0.013, 0.225)	−0.045 (-0.244, 0.155)	0.063 (-0.006, 0.131)
Initiate	0.138 (0.016, 0.261)*	−0.084 (-0.279, 0.110)	0.048 (-0.022, 0.119)	0.121 (0.001, 0.241)*	−0.003 (-0.205, 0.199)	0.046 (-0.024, 0.115)
Working memory	0.124 (-0.001, 0.248)	−0.081 (-0.279, 0.116)	0.070 (-0.002, 0.142)	0.117 (-0.005, 0.239)	−0.047 (-0.251, 0.158)	0.060 (-0.011, 0.130)
Plan/organise	0.151 (0.030, 0.273)*	−0.076 (-0.268, 0.117)	0.041 (-0.029, 0.112)	0.157 (0.038, 0.276)*	−0.034 (-0.233, 0.166)	0.039 (-0.030, 0.108)
Task-monitor	0.104 (-0.023, 0.230)	−0.086 (-0.287, 0.114)	0.068 (-0.004, 0.141)	0.120 (-0.001, 0.241)	−0.050 (-0.253, 0.153)	0.057 (-0.013, 0.127)
Organisation of materials	0.190 (0.067, 0.312)**	−0.092 (-0.285, 0.102)	0.065 (-0.006, 0.135)	0.208 (0.090, 0.326)**	−0.034 (-0.232, 0.164)	0.059 (-0.009, 0.127)

Data are presented as β (95 % CI). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

[a] Independent variables were maternal, paternal and child asthma symptoms only.

[b] In addition to maternal, paternal and child asthma symptoms, other demographic or clinical variables that were associated with CBCL/BRIEF2 raw scores in the univariate GLMs were included as independent variables (Anxious/depressed, withdrawn/depressed, social problems, thought problems or shift with household income and maternal prenatal mental health; Somatic complaints or rule-breaking behaviour with household income, ethnicity and maternal prenatal mental health; Attention problems with household income, maternal age at delivery, maternal prenatal smoke exposure, maternal prenatal mental health and child sex; Aggressive behaviour with household income, maternal prenatal mental health and child BMI at 4 years old; Inhibit, self-monitor, plan/organise or organisation of materials with ethnicity, maternal prenatal mental health and child sex; Emotional control with maternal prenatal mental health; Initiate with ethnicity, number of older siblings and maternal prenatal mental health; Working memory with ethnicity, maternal age at delivery, maternal prenatal mental health and child sex; Task-monitor with ethnicity, number of older siblings, maternal prenatal mental health and child sex).

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Anxious/depressed																
2. Withdrawn/depressed	**0.562**															
3. Somatic complaints	**0.396**	**0.324**														
4. Social problems	**0.634**	**0.542**	**0.412**													
5. Thought problems	**0.544**	**0.462**	**0.458**	**0.553**												
6. Attention problems	**0.462**	**0.415**	**0.331**	**0.563**	**0.550**											
7. Rule-breaking behaviour	**0.517**	**0.419**	**0.357**	**0.583**	**0.630**	**0.535**										
8. Aggressive behaviour	**0.637**	**0.483**	**0.444**	**0.688**	**0.604**	**0.624**	**0.674**									
9. Inhibit	**0.353**	**0.230**	**0.283**	**0.425**	**0.466**	**0.609**	**0.490**	**0.560**								
10. Self-monitor	**0.338**	**0.250**	**0.244**	**0.388**	**0.444**	**0.571**	**0.400**	**0.473**	**0.749**							
11. Shift	**0.458**	**0.406**	**0.320**	**0.467**	**0.472**	**0.533**	**0.421**	**0.498**	**0.706**	**0.644**						
12. Emotional control	**0.504**	**0.328**	**0.312**	**0.477**	**0.468**	**0.507**	**0.439**	**0.598**	**0.730**	**0.645**	**0.735**					
13. Initiate	**0.312**	**0.244**	**0.251**	**0.391**	**0.435**	**0.573**	**0.408**	**0.462**	**0.728**	**0.734**	**0.689**	**0.640**				
14. Working memory	**0.306**	**0.238**	**0.246**	**0.392**	**0.401**	**0.683**	**0.384**	**0.438**	**0.736**	**0.739**	**0.664**	**0.610**	**0.789**			
15. Plan/organise	**0.320**	**0.215**	**0.252**	**0.386**	**0.417**	**0.625**	**0.408**	**0.458**	**0.757**	**0.761**	**0.713**	**0.681**	**0.842**	**0.821**		
16. Task-monitor	**0.238**	**0.196**	**0.204**	**0.351**	**0.359**	**0.585**	**0.366**	**0.413**	**0.678**	**0.715**	**0.551**	**0.551**	**0.742**	**0.772**	**0.766**	
17. Organisation of materials	**0.240**	**0.192**	**0.251**	**0.357**	**0.387**	**0.582**	**0.416**	**0.405**	**0.689**	**0.612**	**0.569**	**0.518**	**0.712**	**0.754**	**0.727**	**0.708**

Scale 0.84 0.19

Fig. 2. Heat map of associations between square root transformed CBCL and BRIEF2 raw scores at 7 years old. Bold values indicate statistically significant Pearson's *r* values. All correlations were statistically significant after correcting for multiple comparisons.

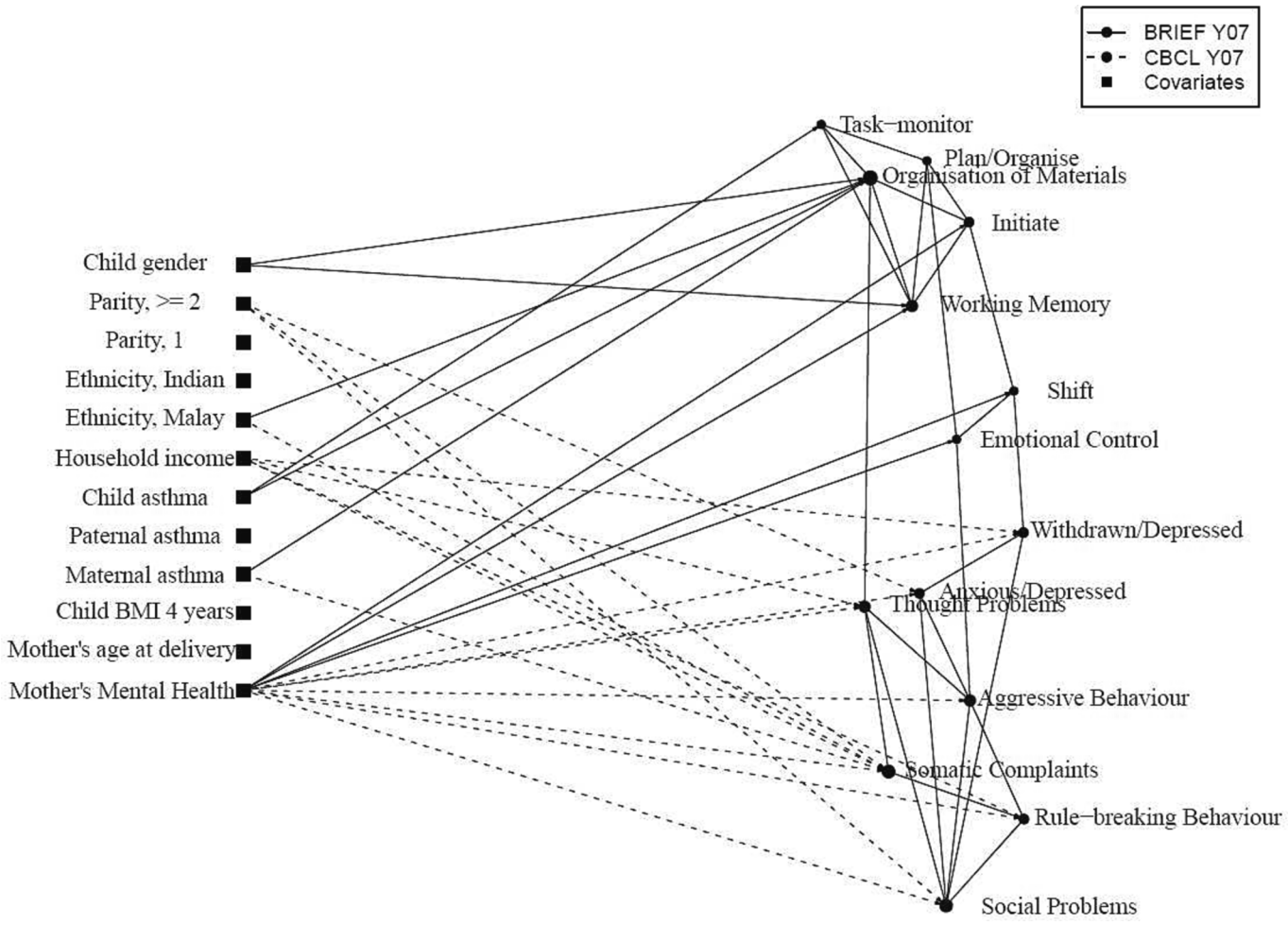

Fig. 3. Bayesian phenomics model linking maternal prenatal asthma symptoms or child preschool asthma symptoms to CBCL or BRIEF2 scales raw scores at 7 years old. Solid or dashed lines indicate significant associations between a covariate and an outcome variable or between two response variables. The covariates labelled parity, child asthma, paternal asthma, maternal asthma and mother's mental health in this figure refers to number of older siblings, emerging preschool asthma symptoms, paternal asthma symptoms in the prenatal period, maternal asthma symptoms in the prenatal period and maternal prenatal mental health, respectively.

further support for the MIA hypothesis.

Although this study did not examine a direct mechanism to specific child outcomes, a study by Mac Giollabhui *et al.* suggests that the timing of maternal inflammation during pregnancy is associated with certain child phenotypes at age 9-11. Specifically, elevated IL-8 in the first trimester was associated with higher externalizing symptoms, while elevated IL-1ra in the second trimester was associated with higher internalizing symptoms (Mac Giollabhui et al., 2019). Furthermore, animal models suggest that MIA results in a variety of neurochemical abnormalities in the offspring. Microglial priming has been proposed as a putative pathway that may lead to a wide spectrum of neuronal dysfunctions (Knuesel et al., 2014). Other studies suggest that gestational asthma induces innate and T helper 2 (T_H2) driven immune responses, which may alter offspring neuronal development and behaviour (Tamayo et al., 2024). Further study of the underlying biological pathways may elucidate the mechanisms for these specific associations. Hence, maternal and cord inflammatory cytokine measures that are available in this cohort will be analysed.

Expectant mothers with prenatal asthma symptoms had poorer prenatal mental health in this study. Findings on the associations between asthma and mental health in adults are mixed (Oh et al., 2019), and research in obstetric populations is limited. Thus far, the majority of studies indicate that women with a history of asthma tend to report psychopathology issues during pregnancy (Whalen et al., 2020) and they may have a slight risk of mental health illness in the perinatal period (Aker et al., 2022). Mental illnesses, such as depression, are thought to be inflammatory in nature and may trigger MIA (Han et al., 2021b). Expectedly, maternal prenatal mental health was initially associated with higher scores for several CBCL and BRIEF2 scales in this study. Yet maternal prenatal mental health was not associated with the organisation of materials scale in the Bayesian phenomics model. This may suggest that asthma and psychopathology during pregnancy may affect foetal neurodevelopment through different pathways. A larger sample of women with asthma who also report mental health illnesses during pregnancy is needed to test this hypothesis.

Asthma symptoms in children enrolled in this study were not associated with outcomes when parent and other child factors were included in GLMs. However, the Bayesian phenomics model showed an association with the organisation of materials and task-monitor scales. The task-monitor scale in the BRIEF2 questionnaire assesses work-checking habits. Children with task-oriented monitoring difficulties may rush through their work, make careless mistakes and fail to check their work (PAR.iConnect, 2015). Our findings were in line with one earlier study that reported lower scores for an executive function task battery in children with asthma (Sonney and Insel, 2019). In this study, preschool asthma symptoms were also not associated with CBCL scales. Children with higher internalising problems may also be less likely to experience improvement or remission in asthma symptoms (Feitosa et al., 2016; Verkleij et al., 2013). Yet one study reported higher somatic complaints but lower anxious/depressed symptoms in a sample of children on

asthma maintenance treatment compared to healthy controls (Quak et al., 2012). Therefore, low severity or proper management of asthma, including daily use of inhaled corticosteroids, may explain why most child outcomes were not associated with a history of preschool asthma symptoms in this study.

Although the initial correlation analysis showed strong positive relation between all CBCL and BRIEF2 scales, the phenomics analysis indicated fewer associations between outcomes. Nevertheless, the phenomics model suggests that behavioural problems were closely related to executive functions. Specifically, associations were observed between withdrawn/depressed and shift, thought problems and organisation of materials, as well as aggressive behaviour and emotional control. While this study did not determine the directionality of these associations, extant literature generally supports that poor executive function predicts later behavioural problems (Yang et al., 2022). Hence, future human studies that test the MIA hypothesis should consider including measures of child executive function when examining developmental disorders or behavioural problems.

This study has several limitations. Firstly, the sample size was small relative to other cohort studies. Hence, several environmental factors and other inflammatory conditions that have been linked to childhood behaviour problems or poor executive function were not included in the analysis. Future studies may include predictors such as home context (Tamana et al., 2019), parenting (Prime et al., 2023) and infection or systemic chronic inflammation in the prenatal period (Han et al., 2021b). Secondly, the child outcomes in this study were reported by mothers, which may lack objectivity. Further investigation should include scores from cognitive tasks or teacher-reported questionnaire scores. Thirdly, the parent-reported child wheezing symptoms may have varied by aetiology and may be viral infections instead of emerging asthma. Studies with careful delineation of symptom chronicity and severity are warranted. Fourthly, maternal covariates such as mental health and smoke exposure were measured once during pregnancy. Lastly, maternal asthma medication use during pregnancy was not studied. Liang *et al.* found that ADHD in offspring was not associated with in utero exposure to β-2-adrenergic receptor agonist when mothers had a history of asthma before pregnancy (Liang et al., 2017). In this study, most mothers with prenatal asthma symptoms also had a history of asthma before pregnancy (n = 34). Hence, the effect of maternal asthma medication use in the prenatal period may have had a minimal effect on child outcomes. Despite these limitations, this study included multiple covariates that may not be available in other asthma studies, such as maternal prenatal mental health, number of older siblings, and child BMI. It is also the first study to apply Bayesian phenomics to investigate the role of maternal inflammatory condition on child developmental outcomes.

5. Conclusions

This study suggests that maternal asthma symptoms during pregnancy are linked to increased somatic symptoms and poor organisational skills in children. While these findings need to be confirmed in larger samples, this study highlights the importance of managing asthma symptoms, thereby reducing inflammation, in pregnant women. More studies are warranted to examine the exposure of MIA on the behavioural, emotional and cognitive profile of offspring. This will enable a clearer understanding of whether targeted screening or interventions are needed for children with increased risks related to MIA.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be provided by the corresponding author upon reasonable 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.bbi.2024.02.028.

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