



Associations between maternal complications during pregnancy and childhood asthma: a retrospective cohort study

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Independent associations of gestational hypertension, gestational diabetes and gestational anaemia with risk of childhood asthma are partially explained by mediation effects <https://bit.ly/3XpuHQc>

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Abstract

Background Studies on the associations between maternal complications during pregnancy and childhood asthma are exclusively conducted in Western countries. The findings are mixed and may not be translated to other populations. We aimed to investigate the associations among the Chinese population and to determine whether the associations were mediated through pre-term birth, caesarean delivery, low birthweight and not breastfeeding in the first 6 months.

Methods We conducted a retrospective cohort study of 166 772 children in Guangzhou, China. Information on maternal gestational hypertension, gestational diabetes and gestational anaemia during pregnancy was extracted from medical records. Ever-diagnosis of asthma in children aged 6–12 years was obtained by questionnaire. Logistic regression models and mediation analyses were used to estimate the adjusted odds ratios (aORs) and 95% confidence intervals for childhood asthma.

Results Gestational hypertension, gestational diabetes and gestational anaemia during pregnancy were associated with an increased risk of ever-diagnosed childhood asthma: aOR 1.48 (95% CI 1.37–1.60), 1.71 (95% CI 1.65–1.78) and 1.34 (95% CI 1.26–1.45), respectively. A stronger association was observed for two or three gestational complications (aOR 2.02 (95% CI 1.93–2.16)) than one gestational complication (aOR 1.64 (95% CI 1.52–1.77)). The aOR for the three gestational complications was 1.35 (95% CI 1.26–1.45), 1.63 (95% CI 1.58–1.70) and 1.32 (95% CI 1.24–1.43), respectively, after controlling for the mediators, including pre-term birth, caesarean delivery, low birthweight and not breastfeeding in the first 6 months.

Conclusions Gestational hypertension, gestational diabetes and gestational anaemia were associated with childhood asthma, and the associations were partially explained by the mediation effects.

Introduction

Childhood asthma is the most common chronic disorder in children, with the prevalence varying substantially between countries, from 1.8% to 27.4% in children aged 6–7 years and from 2.6% to 30.5% in children aged 13–14 years [1]. Although mortality of childhood asthma is relatively low, asthma is among the top 20 conditions for disability-adjusted life years in children globally [2]. Therefore, it is crucially important to understand the risk factors for childhood asthma.



Early life is a sensitive period for the development of respiratory physiology, and *in utero* exposure to pregnancy complications may predispose children to the development of asthma and other chronic lung diseases later in life [3]. However, findings on the associations between maternal complications and childhood asthma are inconclusive. Although gestational hypertension [4], gestational diabetes [5, 6] and gestational anaemia [7, 8] were identified as risk factors for childhood asthma in some studies, others reported null associations [9–12]. Current knowledge of the associations is predominantly derived from Western countries [4–15], which may not be generalisable to other countries with different ethnicities, epidemiological characteristics of gestational complications, social cultures and environmental determinants [4]. Moreover, although previous studies indicated that pre-term birth mediates the associations between maternal complications and childhood asthma [4, 9, 14], it remains unknown whether other factors such as caesarean delivery, low birthweight and not breastfeeding in the first 6 months could mediate these associations. From the perspective of health management and disease prevention, to determine the association between maternal complications during pregnancy and childhood asthma is of substantial public health importance because it may inform pre-conception or antenatal prevention strategies.

In light of these considerations, we carried out a retrospective cohort study in China to investigate the associations of gestational hypertension, gestational diabetes and gestational anaemia with asthma among children aged 6–12 years, and whether the associations were mediated through pre-term birth, caesarean delivery, low birthweight and not breastfeeding in the first 6 months.

Methods

Data sources

This study was embedded within the framework of the Physical Health Monitoring Project of Primary and High School Students in Guangzhou (PHMPPHSS), launched by the Education Bureau of Guangzhou in 2017. The design, organisation and implementation of PHMPPHSS have been described previously [16]. Parents whose children planned to participate in the annual physical examination were contacted through the internet to get parental consent for their children to participate in the PHMPPHSS. A pre-developed health management software was shared with the parents after they provided informed consent. The parents were then surveyed by a structured parental questionnaire and a child's questionnaire using the software.

The parental questionnaire included the characteristics of the index child (age, sex, number of siblings, residential region and disease history, including asthma diagnosis), maternal age, educational status, smoking during pregnancy, family monthly income and feeding models in the first 6 months. The parental questionnaire also included pre-pregnancy body weight and height of the mother, delivery patterns, gestational weeks, pregnancy complications, and the birthweight of the index child, all of which were asked to be answered based on medical records and the birth certificate. The data were cleaned, compiled and de-identified by the Health Promotion Centre for Primary and Secondary Schools of the Education Bureau of Guangzhou.

Study population

This study is reported per the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement (www.strobe-statement.org). We conducted a retrospective cohort study among 193 471 school children aged 6–12 years who participated in the PHMPPHSS from September 2017 to June 2018 in 446 primary schools across 11 administrative districts of Guangzhou (figure 1). We excluded 7484 children whose mothers did not answer the parental questionnaire, 1647 children whose mothers had pre-existing hypertension or diabetes, 8857 children whose mothers did not answer questions related to gestational complications and 6517 children whose mothers did not answer the question about asthma diagnosis of the index child. We further excluded 1176 children who were multiple births and 1018 children with missing data on age or sex. The remaining 166 772 (86.2%) children were included in the final analysis. There was no significant difference in age, sex and residential region between children included and excluded (supplementary table S1).

Ethics

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation, and with the Helsinki Declaration of 1964, as revised in 2000. The PHMPPHSS was approved by the Institutional Review Board of the Education Bureau of Guangzhou. Informed consent was obtained from the children's parents before enrolling in this study. The present study was executed jointly by the Education Bureau of Guangzhou and Guangzhou Medical University. The review boards waived ethical approval due to the usage of de-identified data.

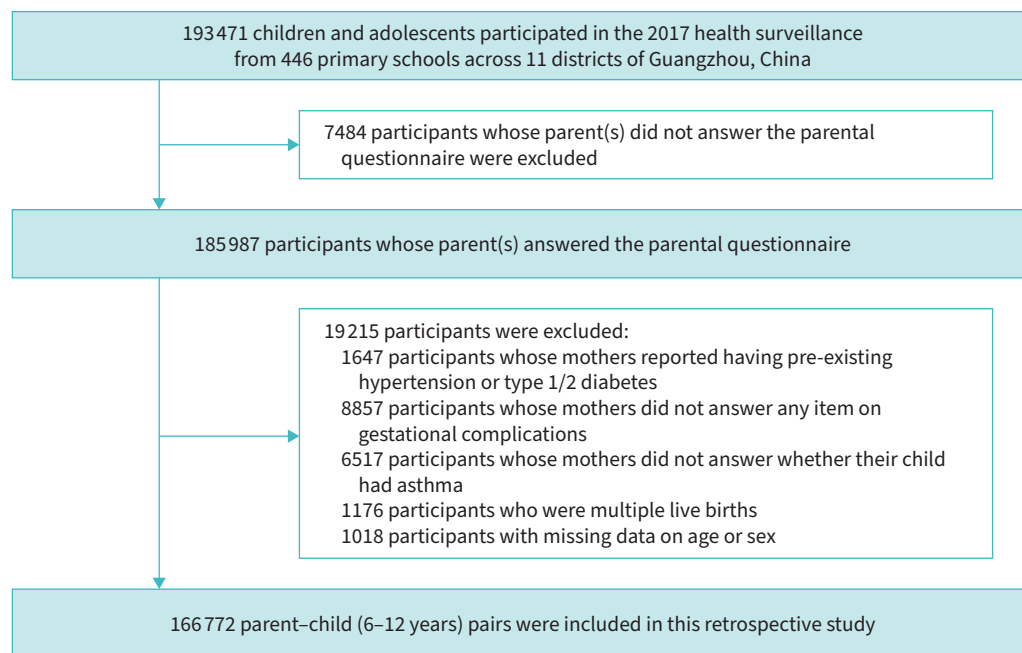


FIGURE 1 Selection of participants.

Exposure definition and ascertainment

In China, gestational hypertension, gestational diabetes and gestational anaemia are common and require routine examinations during pregnancy [17–19]. The routine examinations for these complications have covered all pregnant women in some cities and were well recorded [20]. Children were categorised as exposed if their mothers reported any of the following three complications: gestational hypertension (defined as blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic on two separate occasions at least 4 h apart after 20 weeks of pregnancy when previous blood pressure was normal) [21], gestational diabetes (defined as hyperglycaemia for the first time during pregnancy) [22] and gestational anaemia (defined as haemoglobin < 11 g·dL⁻¹ or haematocrit $< 33\%$ at any time during the pregnancy) [23]. Mothers who reported having or met the diagnostic criteria for the gestational complication(s) were asked to provide medical records through health management software. Mothers who reported having gestational complication(s) without providing medical records were interviewed by a physician through a telephone interview, recording the detailed information about gestational complication(s) reported, such as when and where the gestational complication(s) was diagnosed and what the main symptoms were. The Health Promotion Centre for Primary and Secondary Schools of the Education Bureau of Guangzhou was responsible for external quality assessment. 100 mothers who reported not having gestational complications were randomly selected in each administrative district and required to provide medical records. Interclass correlation coefficients expressing between-person variance, obtained by analysis of replicate pairs of these mothers from all administrative districts involved, were all > 0.99 .

Childhood asthma

Information on physician-diagnosed asthma (ever-asthma) in children was obtained by the parental questionnaire based on the International Study on Asthma and Allergy in Childhood questionnaire (“Has your child ever had asthma diagnosis by a doctor?”) [24]. This validated approach has been used in several nationwide epidemiological studies of asthma in China [25]. Children who reported to have ever-asthma were ascertained by a physician through on-site consultation, physical examinations or reviewing medical records and previous related auxiliary examinations. 100 children in each administrative district who reported not having asthma were randomly selected to be ascertained by the physicians through on-site consultation, physical examinations or reviewing medical records and previous related auxiliary examinations. Interclass correlation coefficients expressing between-person variance, obtained by analysis of replicate pairs of these children, were all > 0.98 .

Statistical analysis

Mean and standard deviation were calculated for age. Frequencies and proportions were used to describe the characteristics of the children and their mothers. Two-tailed, unpaired t-tests or Chi-squared tests were

used to compare the distribution of the outcome according to different characteristics of the children and their mothers.

Binomial logistic regression models were employed to estimate the crude and adjusted odds ratios (aORs) and 95% confidence intervals for childhood asthma by gestational hypertension, gestational diabetes and gestational anaemia. We selected and adjusted for potential confounding factors known to be associated with maternal complications and childhood asthma: child's sex (male or female), age (continuous variable), residential region (urban or rural), maternal age (<20, 21–35 or >35 years), maternal educational level (junior high school or below, senior high school, or college or above), maternal pre-pregnancy body mass index (BMI) (underweight ($BMI < 18.5 \text{ kg}\cdot\text{m}^{-2}$), healthy weight ($18.5 \leq BMI < 24 \text{ kg}\cdot\text{m}^{-2}$) or overweight/obese ($BMI \geq 24 \text{ kg}\cdot\text{m}^{-2}$)), maternal smoking during pregnancy (yes or no), single child (yes or no) and family monthly income (<8000, 8000–15 000 or >15 000 RMB). The gestational complications were mutually adjusted in models. We also examined the association between the number of maternal gestational complications and the offspring's asthma to determine whether multiple maternal complications during pregnancy have a synergistic effect on childhood asthma [26]. We categorised the number of gestational complications into three groups: none, one and two or three.

Because the prevalence of childhood asthma varied with age, sex and residential region, we also examined whether the association between maternal complications during pregnancy and childhood asthma varied with age (6–8, 9–10 and 11–12 years), sex (male and female) and residential region (urban and rural). Among the subgroup analyses, we adjusted for the covariates as we did in Model 2. Differences within subgroup analyses were assessed.

To estimate the extent to which the associations are mediated through pre-term birth, caesarean delivery, low birthweight and not breastfeeding in the first 6 months, we, therefore, conducted mediation analyses to decompose the total effects into direct and indirect effects using the “ldecomp” command in Stata [27]. We also estimated mediation proportion, *i.e.* the proportion of the total effect explained by mediators. Supplementary figure S1 shows the theoretical framework underlying our mediation analysis.

Data were missing for family monthly income (4.5%), maternal pre-pregnancy BMI (3.1%) and maternal smoking during pregnancy (4.7%). We imputed these missing covariates by using the monotone logistic regression method based on other sociodemographic covariates by creating 20 imputed datasets [28]. The significance level was set at $p=0.05$ and all tests were two-sided. Statistical analyses were conducted using Stata version 14.0 (StataCorp, College Station, TX, USA).

Results

Of 166 772 children, 44.1% were from urban areas and 54.5% were males. The age of children ranged from 6 to 12 years, with a mean \pm SD age of 8.6 ± 1.8 years. Overall, 19 722 (11.8% (95% CI 11.7–12.0%)) children had ever been diagnosed with asthma. Compared with children without asthma, children with asthma were more likely to live in urban areas, be males, born through pre-term birth, caesarean delivery, low birthweight and not breastfeeding in the first 6 months (table 1).

Association between maternal complications during pregnancy and childhood asthma

A total of 5330 (3.2%), 24 036 (14.4%) and 11 723 (7.0%) children were born to mothers who had gestational hypertension, gestational diabetes and gestational anaemia during pregnancy, respectively. The prevalence of asthma among children born to mothers with gestational hypertension was 17.8%, with gestational diabetes was 20.0% and with gestational anaemia was 15.8%. Gestational hypertension, gestational diabetes and gestational anaemia during pregnancy were associated with increased risk of childhood asthma: aOR 1.48 (95% CI 1.37–1.59), 1.71 (95% CI 1.65–1.78) and 1.34 (95% CI 1.26–1.45), respectively (Model 2 in table 2). The associations were also similar according to children's age group (figure 2), sex (figure 3) and residential region (figure 4) (all $p_{\text{trend}} > 0.05$).

Association between number of maternal complications during pregnancy and childhood asthma

Altogether, 33 355 (20.0%) and 3788 (2.3%) mothers reported having one and two or three gestational complication(s), respectively. The prevalence of asthma among children who had been exposed to one and two or three gestational complication(s) was 18.1% and 20.3%, respectively, compared with 10.0% among children born to mothers with no gestational complications (table 3). The aOR for one gestational complication was 1.64 (95% CI 1.52–1.77) and an increased aOR was observed for two or three gestational complications (2.02, 95% CI 1.93–2.16). The aOR was significantly higher for two or more gestational complications than that for one gestational complication ($p_{\text{trend}} = 0.005$).

TABLE 1 Characteristics of children and their mothers

	Ever-asthma		Total (n=166 772)
	No (n=147 050)	Yes (n=19 722)	
Children's characteristics			
Residential area			
Urban	63 013 (42.9)	11 419 (57.9)	74 432 (44.6)
Rural	84 037 (47.1)	8303 (42.1)	92 340 (55.4)
Sex			
Male	78 133 (53.1)	12 699 (64.4)	90 832 (54.5)
Female	68 917 (46.9)	7023 (35.6)	75 940 (45.5)
Age (years)	8.6±1.8	8.7±1.8	8.6±1.8
Single child	63 998 (43.5)	9108 (46.2)	73 106 (43.8)
Pre-term birth	9996 (6.8)	1904 (9.7)	11 900 (7.1)
Caesarean delivery	51 990 (35.4)	9565 (48.5)	61 555 (36.9)
Low birthweight	5317 (3.6)	776 (3.9)	6093 (3.7)
Not breastfeeding	92 316 (62.8)	13 118 (66.5)	105 434 (63.2)
Maternal characteristics			
Age (years)	27.8±4.9	27.8±4.9	27.8±4.9
Educational level			
Junior high school or below	9861 (6.7)	589 (3.0)	10 450 (6.3)
Senior high school	72 219 (49.1)	8176 (41.5)	80 395 (48.2)
College or above	64 970 (44.2)	10 957 (55.6)	75 927 (45.5)
Smoking during pregnancy	1009 (0.7)	182 (1.0)	1191 (0.7)
Family monthly income (RMB) [#]			
<8000	64 132 (45.7)	8525 (44.8)	72 657 (45.6)
8000–15 000	28 266 (20.2)	3811 (20.0)	32 077 (20.1)
>15 000	47 799 (34.1)	6695 (35.2)	54 494 (34.2)
Pre-pregnancy BMI (kg·m ⁻²) [#]			
Underweight (BMI<18.5)	7738 (5.4)	1095 (5.8)	8833 (5.5)
Healthy weight (18.5≤BMI<24)	118 006 (82.7)	15 621 (82.2)	133 627 (82.7)
Overweight/obese (≥24)	16 894 (11.8)	2283 (12.0)	19 177 (11.9)
Data are presented as n (%) or mean±sd. [#] : missing data existed.			

Mediation analysis

Caesarean delivery, pre-term birth, low birthweight and not breastfeeding in the first 6 months were significantly associated with childhood asthma and were risk factors for childhood asthma (table 1). We therefore evaluated the potential indirect effect of gestational hypertension, gestational diabetes and gestational anaemia on childhood asthma mediated through these mediators. The results from the mediation analyses indicated a significant direct effect of gestational hypertension (aOR 1.35 (95% CI 1.26–1.45)),

TABLE 2 Associations between maternal gestational complications and childhood asthma

Gestational complication	Ever-asthma	Unadjusted		Adjusted [#]	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Gestational hypertension					
No (n=161 442)	18 773 (11.6)	1.00 (reference)		1.00 (reference)	
Yes (n=5330)	949 (17.8)	1.65 (1.53–1.77)	<0.001	1.48 (1.37–1.59)	<0.001
Gestational diabetes					
No (n=142 736)	14 904 (10.4)	1.00 (reference)		1.00 (reference)	
Yes (n=24 036)	4818 (20.0)	2.15 (2.07–2.29)	<0.001	1.71 (1.65–1.78)	<0.001
Gestational anaemia					
No (n=155 049)	17 873 (11.5)	1.00 (reference)		1.00 (reference)	
Yes (n=11 723)	1849 (15.8)	1.44 (1.36–1.51)	<0.001	1.34 (1.26–1.45)	<0.001
Data are presented as n (%), unless otherwise stated. [#] : adjusted for children's age, sex, single child, residential region, family monthly income, maternal age, maternal educational level, maternal body mass index before pregnancy and maternal smoking during pregnancy, and mutually gestational complications.					

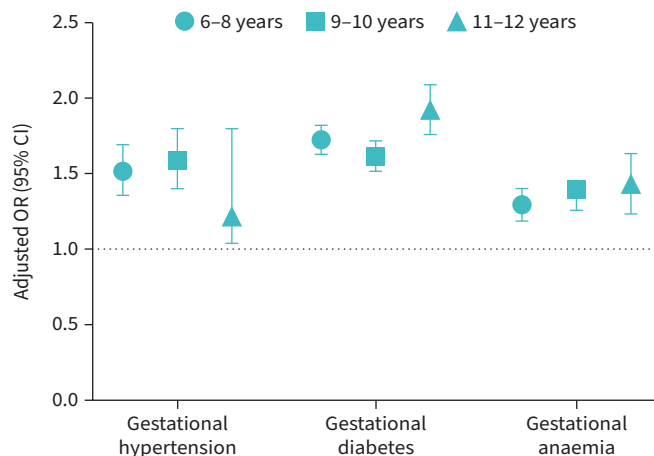


FIGURE 2 Associations of maternal gestational complications with childhood asthma according to children's age group.

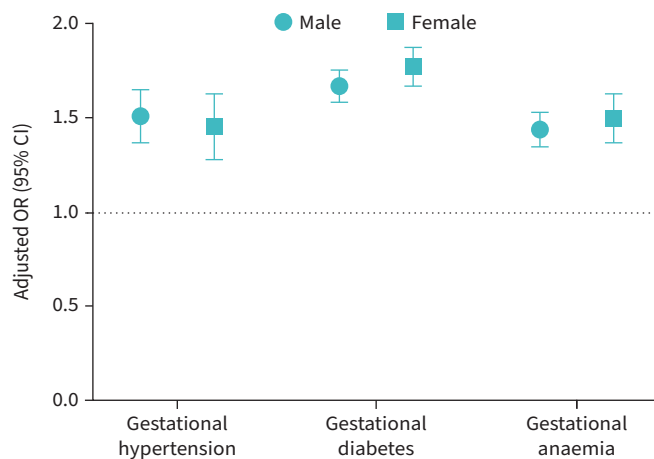


FIGURE 3 Associations of maternal gestational complications with childhood asthma according to children's sex.

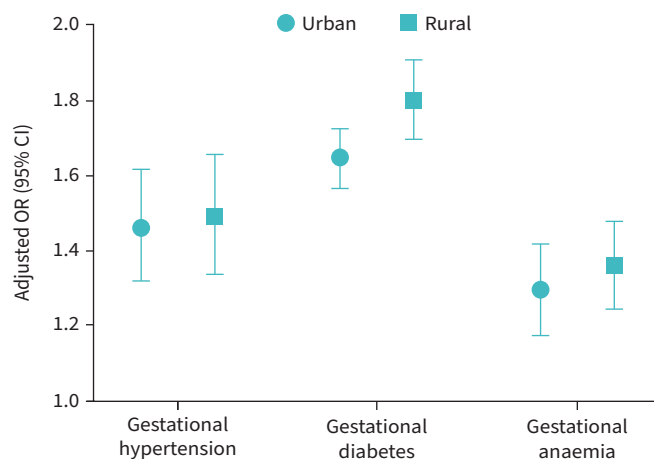


FIGURE 4 Associations of maternal gestational complications with childhood asthma according to children's residential region.

TABLE 3 Association between number of maternal gestational complications[#] and childhood asthma

Gestational complications	Ever-asthma	Unadjusted		Adjusted [¶]	
		OR (95% CI)	p-value	OR (95% CI)	p-value
0 (n=129 629)	12 907 (10.0)	1.00 (reference)		1.00 (reference)	
1 (n=33 355)	6046 (18.1)	2.00 (1.94–2.07)	<0.001	1.64 (1.52–1.77)	<0.001
2 or 3 (n=3788)	769 (20.3)	2.30 (2.12–2.50)	<0.001	2.02 (1.93–2.16)	<0.001

Data for ever-asthma are presented as n (%). [#]: maternal gestational complications include gestational hypertension, gestational diabetes and gestational anaemia; [¶]: adjusted for children's age, sex, single child, residential region, family monthly income, maternal age, maternal educational level, maternal body mass index before pregnancy and maternal smoking during pregnancy.

gestational diabetes (aOR 1.63 (95% CI 1.58–1.70)) and gestational anaemia (aOR 1.32 (95% CI 1.24–1.43)) on childhood asthma. The combined indirect effects of caesarean delivery, pre-term birth, low birthweight and not breastfeeding in the first 6 months on associations between gestational complications and childhood asthma were also significant: aOR 1.09 (95% CI 1.08–1.10) for gestational hypertension, aOR 1.05 (95% CI 1.04–1.06) for gestational diabetes and aOR 1.01 (95% CI 1.00–1.01) for gestational anaemia. The mediating proportion of these mediators on the association between the maternal complications and childhood asthma was 2.7%, 9.3% and 4.8%, respectively. The separated indirect effects of these mediators were not all significant (table 4); however, the effects of caesarean delivery and pre-term birth on associations with gestational complications and childhood asthma were all significant (all $p < 0.05$).

Discussion

This is the first study to examine the association between gestational complications and childhood asthma in a large Chinese population, which also investigated the effects of gestational complications on childhood asthma mediated through caesarean delivery, pre-term birth, low birthweight and not breastfeeding in the first 6 months. In this study, we found that gestational hypertension, gestational diabetes and gestational anaemia were positively associated with childhood asthma. The association was consistent for subgroups of children stratified by residential region, age and sex. A stronger association was observed for two or three gestational complications than one gestational complication. Part of the associations was through mediating factors.

Comparison with previous studies

Several studies have examined the associations between gestational hypertension disorders (gestational hypertension or pre-eclampsia) and childhood asthma [4, 9, 13–15], but only two studies focused on gestational hypertension, with conflicting results [4, 9]. HENDERSON and QUENBY [4] used the Millennium cohort data to examine the association between hypertensive disease and asthma by age 5 years and found that gestational hypertension was positively associated with childhood asthma after adjustment (aOR 1.32

TABLE 4 Logistic regression model of direct and indirect effects through mediators of gestational complications on childhood asthma

Effects asthma versus no asthma	Gestational hypertension [#]	Gestational diabetes [#]	Gestational anaemia [#]
Total effect	1.47 (1.38–1.58)	1.71 (1.66–1.79)	1.34 (1.25–1.46)
Direct effect	1.35 (1.26–1.45)	1.63 (1.58–1.70)	1.32 (1.24–1.43)
Indirect effect, combined	1.09 (1.08–1.10)	1.05 (1.04–1.06)	1.01 (1.00–1.01)
Mediating ratio, combined	22.7	9.3	4.8
Indirect effect, through:			
Pre-term birth	1.04 (1.03–1.05)	1.01 (1.00–1.01)	1.01 (1.00–1.01)
Caesarean delivery	1.07 (1.06–1.08)	1.04 (1.03–1.05)	1.01 (1.01–1.02)
Low birthweight	1.00 (1.00–1.01)*	1.00 (0.99–1.01)*	1.00 (0.99–1.00)*
Non-breastfeeding	1.01 (1.00–1.01)	1.00 (0.99–1.01)*	1.00 (0.99–1.01)*

Data are presented as OR (95% CI) for effect or % for ratio. [#]: adjusted for children's age, sex, single child, residential region, family monthly income, maternal age, maternal educational level, maternal body mass index before pregnancy and maternal smoking during pregnancy, and mutually gestational complications. *: $p > 0.05$.

(95% CI 1.09–1.59)). SHAHEEN *et al.* [9] used the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort data and found that gestational hypertension was unlikely to be a risk factor for childhood respiratory disorders, including asthma and wheezing.

Studies that examined the association between gestational diabetes and childhood asthma also demonstrated inconsistent results [5, 6, 10]. MARTINEZ *et al.* [5] found that the risk of childhood asthma was increased for gestational diabetes requiring medication (hazard ratio (HR) 1.12 (95% CI 1.01–1.25)), but not for gestational diabetes not requiring medication (HR 1.01 (95% CI 0.93–1.10)). LIU *et al.* [6] found that gestational diabetes was associated with a small increased risk of early-onset transient wheezing (prevalence ratio (PR) 1.08 (95% CI 1.00–1.17)) and early-onset persistent wheezing (PR 1.15 (95% CI 1.05–1.26)). However, a pooled analysis of 14 European birth cohorts found a null association between diabetes and wheezing up to 24 months [10].

Four studies examined the association between gestational anaemia and childhood asthma [7, 8, 11, 12]. NAFSTAD *et al.* [7] found that gestational anaemia was associated with an increased risk of childhood asthma (OR 1.67 (95% CI 1.24–2.36)). TRICHE *et al.* [8] found that gestational anaemia was associated with recurrent infant wheezing in the first year (OR 2.17 (95% CI 1.18–4.00)) and wheezing before 3 years (OR 2.42 (95% CI 3.18–4.23)). However, a third study based on the Generation R Study [11] and a fourth study based on the ALSPAC cohort [12] suggested that gestational anaemia was not associated with childhood asthma.

The discrepancies in the associations of gestational complications with childhood asthma among previous studies may be related to the differences in the prevalence of these gestational complications, definitions of childhood asthma, adjustment strategies and sample sizes, with small studies failing to find an association. Our findings that gestational hypertension, gestational diabetes and gestational anaemia during pregnancy were independently associated with childhood asthma are consistent with most of the previous studies conducted in Western countries [4–8], although the epidemiological characteristics of childhood asthma and maternal complications during pregnancy in China are different from those in Western countries [1, 4].

Explanations of maternal complications associated with childhood asthma

Potential biological mechanisms linking maternal pregnancy complications and childhood asthma remain unknown. The intrauterine environment provides the substrate for lung and immune system development, and support for optimal fetal growth requires adequate maternal nutritional status [12]. Gestational hypertension, gestational diabetes and gestation anaemia may predispose the fetus to stress, chronic inflammation, hypoxia, malnutrition status and fetal hyperinsulinaemia, which in turn may lead to immune suppression and interfere with lung growth and maturation, alveolar sac formation, proliferation and expansion, and impaired surfactant production, which then predispose the offspring to newborn respiratory conditions and chronic lung disease such as asthma [5, 29, 30]. Our study and a previous study suggested that the association between maternal complications during pregnancy and childhood asthma may partially be due to intermediate factors, such as pre-term birth, caesarean delivery and low birthweight [13, 14]. Therefore, mechanisms linking these intermediate factors and childhood asthma could also be explanations for maternal complications associated with childhood asthma. Of note, our study found only part of the associations was due to mediators, which is different from a large mediation proportion reported in a previous study [14].

Strengths and limitations

This is the first study to evaluate the independent associations between three common gestational complications and asthma in children in a large Chinese population. Mediation analyses allowed us to estimate to what extent these intermediate variables explain the impacts of maternal gestational complications on childhood asthma.

Some limitations should be acknowledged. First, data were collected by self-reported questionnaires. Mothers may recall their gestational complications incorrectly and mothers with pre-existing diabetes may be first diagnosed during pregnancy, both of which would lead to misclassification. However, the prevalences of the three gestational complications and childhood asthma are comparable with the prevalences reported previously [18, 19, 25, 31]. Moreover, our quality assessment shows high interclass correlations. Together, these suggest that the information bias is minimal. Second, we did not have data on asthma phenotypes so we cannot determine whether the associations differ by asthma phenotypes. Third, we do not have data on the severity of complications, which hampers us from analysing the associations between the severity of complications and childhood asthma. Fourth, although we have adjusted for many important confounders, residual confounding owing to unmeasured factors such as family history of

asthma, air pollution or allergies could not be ruled out. Fifth, our results may not be generalisable to other populations with different characteristics.

Implications

Our findings have important clinical and public health implications. Childhood asthma is a heavy disease burden in China, which drives the need for prevention and treatment [32]. However, clinicians and health professionals pay less attention to monitoring and intervention for gestational hypertension, gestational diabetes and gestational anaemia because of the lack of conclusive evidence on associations between these maternal complications and childhood asthma. Our findings from 166 772 mother–child pairs conformed statistically significant associations of gestational hypertension, gestational diabetes and gestational anaemia with childhood asthma. This suggests that screening for these gestational complications and taking interventions might be necessary for reducing the risk of asthma in the offspring. Furthermore, preventing pre-term birth, caesarean delivery, low birthweight and not breastfeeding in the first 6 months may attenuate the impact of these gestational complications on risk of childhood asthma.

Conclusions

In this cohort study, we found that gestational hypertension, gestational diabetes and gestational anaemia were independently associated with childhood asthma, and a stronger association was observed for two or three gestational complications. The impacts of maternal gestational complications on childhood asthma could be partially through mediating factors.

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Data availability: Data generated and/or analysed during the current study can be shared publicly by contacting the corresponding author (J. Tang: gzy_tangjie@gzhmu.edu.cn). All data on the PHMPPHSS are available from the Health Promotion Centre for Primary and Secondary Schools, Education Bureau of Guangzhou (N. Deng: 763302334@qq.com) on reasonable request for researchers.

Conflict of interest: None declared.

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