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Maternal asthma and early fetal growth, the MAESTRO study

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Abstract

Background: Several maternal conditions can affect fetal growth, and asthma during pregnancy is known to be associated with lower birth weight and shorter gestational age.

Objective: In a new Swedish cohort study on maternal asthma exposure and stress during pregnancy (MAESTRO), we have assessed if there is evidence of early fetal growth restriction in asthmatic women or if a growth restriction might come later during pregnancy.

Methods: We recruited women from eight antenatal clinics in Stockholm, Sweden. Questionnaires on background factors, asthma status and stress were assessed during pregnancy. The participants were asked to consent to collection of medical records including ultrasound measures during pregnancy, and linkage to national health registers. In women with and without asthma, we studied reduced or increased growth by comparing the second-trimester ultrasound with first-trimester estimation. We defined reduced growth as estimated days below the 10th percentile and increased growth as days above the 90th percentile. At birth, the weight and length of the newborn and the gestational age was compared between women with and without asthma.

Results: We enrolled 1693 participants in early pregnancy and collected data on deliveries and ultrasound scans in 1580 pregnancies, of which 18% of the mothers had asthma. No statistically significant reduced or increased growth between different measurement points were found when women with and without asthma were compared; adjusted odds ratios for reduced growth between first and second trimester 1.11 95% CI (0.63–1.95) and increased growth 1.09 95% CI (0.68–1.77).

Conclusion and clinical relevance: In conclusion, we could not find evidence supporting an influence of maternal asthma on early fetal growth in the present cohort: Although the relatively small sample size, which may enhance the risk of a type II error, it is concluded that a potential difference is likely to be very small.

KEYWORDS

asthma, epidemiology, fetal growth, obstetrics, paediatrics, pregnancy

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1 | INTRODUCTION

Asthma is one of the most common chronic diseases, affecting more than 300 million individuals worldwide,¹ with a prevalence of 8–10% among United States and Swedish women of child-bearing age.^{2,3} Maternal asthma is associated with a number of adverse pregnancy outcomes, such as preeclampsia, placental abruption, instrumental delivery and caesarean section, low birth weight and shorter gestational age,^{4–6} associations not confounded by factors shared within families.⁷

Pregnancy dating by ultrasound in the second trimester relies on the assumption that foetal growth is close to equal in all pregnancies during the first half of the pregnancy.^{8,9} This assumption is problematic since there are factors, such as genetics and maternal obesity, which may affect early fetal growth.^{10,11} This can lead to misclassification of gestational age and a risk of unnecessary preterm or post-term deliveries.^{12,13} Although there are factors that affects fetal growth in the first trimester as well as later, the variations between different pregnancies are smaller in the first compared to second trimester—may be due to factors that affects fetal growth more in the second trimester, which would suggest a more accurate estimation of gestational age by ultrasound earlier rather than later during pregnancy.¹⁴ However, routine ultrasound is offered in the second trimester to all women since it also includes organ screening, which is not feasible to the same extent in the first trimester. Kullinger et al¹⁵ showed in a large register-based study that intrauterine fetal growth measurement can be affected by many maternal factors such as body mass index (BMI), diabetes, age and tobacco use.

Although there is an association between maternal asthma during pregnancy and low birth weight, very few studies have estimated the effect of asthma during pregnancy on early fetal intrauterine growth¹⁶ and as far as we know, ultrasound measures of growth between first and second trimester in asthmatic mothers have not been previously assessed.

Our aim was to examine how maternal asthma is associated with intrauterine fetal growth between first and second trimester by the use of ultrasound scan, and if there is a difference in gestational age, child's weight, and child's length at birth in women with and without asthma. We have utilised a new pregnancy cohort, the Maternal Asthma Events, Stress and Offspring (MAESTRO), including Swedish women who were pregnant and gave birth between 2011 and 2016.

2 | METHODS

2.1 | The MAESTRO study

The Maternal Asthma Events, Stress and Offspring (MAESTRO) study, launched in 2011, recruited pregnant women from eight antenatal clinics in Stockholm, Sweden, at their first visit in gestational week 10–12. All women, no matter their asthma status, were asked by their midwife to participate in the study. Women accepting participation consented to give blood samples and answered questionnaires at recruitment and once later during pregnancy, in gestational week 28–32 and 6 months after delivery. The questionnaires included questions on asthma diagnosis, asthma symptoms and control, as well as other factors such as smoking, stress (including the Perceived Stress Scale¹⁷), employment and family situation. Salivary samples, for future analyses of saliva cortisol levels, were collected at recruitment, in gestational week 28–32 and 6 months after delivery but data from these analyses are not reported in the present manuscript. A subsample of the recruited women performed a lung function test (spirometry) in week 28–32 and repeated 6 months after delivery, Figure 1. The majority (98%) of women underwent a routine fetal ultrasound around week 18–20, normally used for dating the pregnancy and assessing possible malformations. A large portion of the participants also underwent a scan for nuchal translucency in late first trimester. Medical charts, including ultrasound measurements, were collected after delivery. All women consented to have the collected data linked to the health registers held by the National Board of Health and Welfare. The Medical Birth Register includes data on >99% of all births in Sweden,^{18,19} the National Patient Register has all in-patient specialist care diagnoses since 1987 and out-patient diagnoses since 2001,²⁰ and the Prescribed Drug Register²¹ has data on all prescribed dispensed drugs since July 2005. The linkage between the MAESTRO cohort and the registers was made possible by the use of the Swedish personal identity number, unique for each resident.²²

2.2 | Exposure

Our main exposure was maternal asthma ever—either self-reported physician-diagnosed asthma in the questionnaires or medical charts

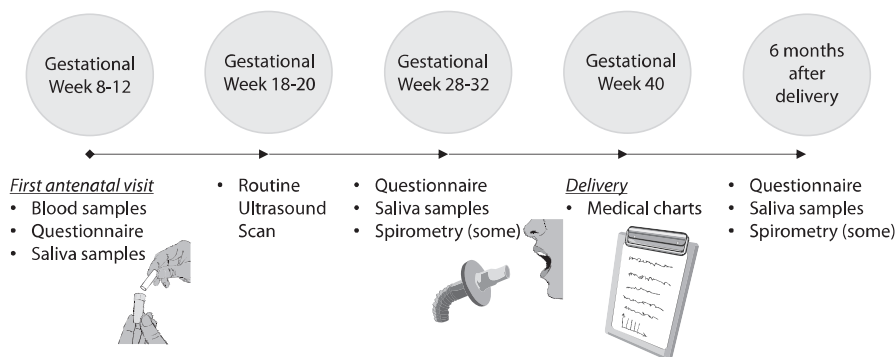


FIGURE 1 Timeline of the MAESTRO study. Questionnaire and saliva sampling conducted at home. Blood sampling and lung function testing conducted at clinic. All available medical records and ultrasound data were collected after birth

or a diagnosis of asthma (ICD-9 code 495 or ICD-10 codes J45, J46) in the National Patient Register and/or at least two dispenses of asthma medication (ATC code R03) within a year in the Prescribed Drug Register, a definition that has been validated previously.²³ In a sub-analysis asthma control was assessed according to the Asthma Control Test,²⁴ reported in late first trimester, where a score ≤ 19 indicates uncontrolled and a score ≥ 20 indicates controlled disease.

2.3 | Outcomes

The main outcome was growth discrepancy between first and second trimester estimates of gestational age, defined as the difference in number of days between the estimated gestational age at second trimester and expected gestational age at second-trimester ultrasound scan, Figure 2.

We defined gestational age in the first trimester calculated from 1. embryo transfer date ($n = 80$), 2. first-trimester ultrasound closest to week 10 ($n = 1094$), or 3. start of the last menstrual period as reported at first antenatal visit if an ultrasound was not available ($n = 476$). In the second trimester, gestational age was calculated using standardised ultrasound measurements as described above. If several measurements were available, we chose the one closest to week 20. By ultrasound, gestational age in the first trimester is calculated by means of ultrasound measurement of crown-rump-length (CRL) and bi-parietal diameter (BPD).^{25,26} In the second trimester, a combination of femur length (FL) and BPD is normally used to estimate the gestational age by ultrasound around week 20.²⁷⁻²⁹

Growth discrepancy in number of days was defined as gestational age estimated at second-trimester ultrasound minus expected gestational age at the same time, calculated from first-trimester ultrasound. This resulted in either reduced growth (the foetus was smaller than expected in second-trimester ultrasound measurement), no discrepancy (no deviation from expected pregnancy length between the two measurements) or increased growth (the

foetus was larger than expected in second-trimester ultrasound measurement).

Reduced and increased growth was defined as the time deviation (assessed as days below 10th or above 90th percentiles) from expected measurement. The reference category chosen was all measurements—discrepancies or not—between the 10th and 90th percentiles.¹⁵

Data on gestational age at birth, the child's birth weight and birth length were collected from the medical records.

2.4 | Covariates

Possible confounders, known to be associated with both the exposure and the outcomes, were maternal age, BMI, smoking at first antenatal visit, and gestational diabetes collected from the medical charts; level of education (0–9 years, 10–12 years or >12 years) collected from the questionnaires. Data on cohabitation with spouse/partner were collected from the medical charts and questionnaires. Sex of the child was recorded at birth.

2.5 | Statistical methods

The association between maternal asthma and 1. discrepancy in gestational age between first and second trimester and 2. birth outcomes were assessed with linear and logistic regression for continuous and dichotomous outcomes, respectively. Large discrepancy in days was defined by choosing 10th and 90th percentiles. The reference category chosen was all pregnancies with or without discrepancies between the 10th and 90th percentiles. Only women with a first and second-trimester dating were included in the main analyses. Low birth weight was defined as birth weight <2500 g and preterm birth defined as being born before gestational week 37 + 0.

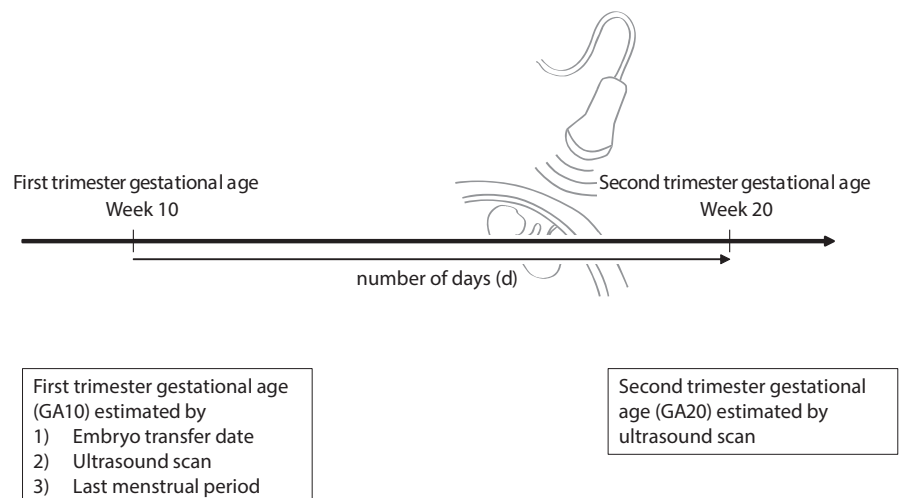


FIGURE 2 Illustration of estimation of first and second-trimester gestational age, and discrepancy between estimated and expected gestational age around gestational week 20

$$\text{Expected Gestational Age at Week 20 (expGA20)} = [\text{GA10}] + [d]$$

$$\text{Discrepancy at Week 20} = [\text{GA20}] - [\text{expGA20}]$$



FIGURE 3 Flow chart of the MAESTRO study. *Data on individual women

Crude and adjusted beta coefficients and odds ratios (ORs) with 95% confidence intervals (CI) were estimated by linear and logistic regression for continuous and dichotomous outcomes, respectively. Some women contributed to more than one pregnancy and we, therefore, used the sandwich estimator for the standard errors.

2.6 | Interaction analyses

Since intrauterine growth can be affected by fetal sex, even as early as in the second trimester³⁰ we adjusted for fetal sex. We also conducted interaction analyses between maternal asthma and fetal sex to determine if the potential association between maternal asthma and intrauterine growth differed between boys and girls. An interaction term between maternal asthma and fetal sex was introduced to test for effect measure modification on the additive scale in the linear regression models (continuous outcomes) and the multiplicative scale in logistic regression (dichotomous outcomes) and tested with the likelihood ratio test. Estimation of RERI (Relative Excess Risk due to Interaction), using the Stata package *ic*,³¹ was used to evaluate potential interaction on the additive scale also for dichotomous outcomes.

All analyses were done using Stata IC 16.0.³²

2.7 | Ethical considerations

The participants signed a written consent to participation in the study prior to enrolment. All data have been pseudonymised prior to analyses and all results are presented on group level only. The study has been approved by the Regional Ethical Review Board in Stockholm.

3 | RESULTS

In total, 1693 pregnancies of 1676 women were followed in the MAESTRO study, of which 1580 led to a subsequent delivery, 113 pregnancies resulted in a spontaneous or induced abortion or were lost to follow-up. We obtained data on ultrasound measurements for 1522 pregnancies; 1137 both in the first and second trimester, 20 only in the first trimester and 336 only in the second trimester. In total, we collected 1167 responses to the first questionnaire, 912 responses to the second questionnaire during pregnancy, and 733 responses to the follow-up questionnaire 6 months after delivery. Multiple gestation pregnancies ($n = 23$) were excluded for this paper since characteristics differ from single gestation pregnancies. In total 1533 pregnancies were linked to the Medical Birth Register, and 1622 women to the National Patient Register, and 1616 individuals to the Prescribed Drug Register, Figure 3.

Of all participants, 18% had asthma defined either from self-reports in the questionnaire, the medical records, the Prescribed Drug Register or the National Patient Register. Most women were 30 years or older and had a normal BMI. Among those with asthma, BMI was slightly higher, and more women were smokers compared to women without asthma, Table 1.

TABLE 1 Characteristics of the MAESTRO study population according to current asthma status^a

	Whole population	Without asthma	With asthma
	1580	1289	291
	n(%)	n(%)	n(%)
Maternal characteristics			
Age			
<20	1 (0.1)	1 (0.1)	0 (0.0)
20–24	76 (4.8)	61 (4.7)	15 (5.2)
25–29	401 (25.4)	322 (25.0)	79 (27.1)
30–34	722 (45.7)	603 (46.8)	119 (40.9)
>34	380 (24.1)	302 (23.4)	78 (26.8)
Early pregnancy BMI			
<18.5	41 (2.6)	37 (2.9)	4 (1.4)
18.5–24.9	1,067 (67.5)	883 (68.5)	184 (63.2)
25–29.9	246 (15.6)	188 (14.6)	58 (19.9)
≥30	58 (3.7)	39 (3.0)	19 (6.5)
Missing	168 (10.6)	142 (11.0)	26 (8.9)
Smoking at first antenatal visit			
No	1,489 (94.2)	1,208 (93.7)	281 (96.6)
1–9 cig/day	12 (0.8)	8 (0.6)	4 (1.4)
Missing	79 (5.0)	73 (5.7)	6 (2.1)
Cohabitation			
Living alone	93 (5.9)	86 (6.7)	7 (2.4)
Living with partner	1,487 (94.1)	1,203 (93.3)	284 (97.6)
Education			
Up to 9 years	6 (0.4)	5 (0.4)	1 (0.3)
10–12 years	143 (9.1)	104 (8.1)	39 (13.5)
More than 12 years	942 (59.6)	765 (59.3)	179 (62.2)
Missing	489 (30.9)	415 (32.2)	69 (24.0)
Gestational diabetes			
Yes	1 (0.1)	1 (0.1)	0 (0.0)
No	1,579 (99.9)	1,288 (99.9)	291 (100.0)

^aAsthma diagnose according to questionnaire, self-reported asthma at first antenatal visit, asthma diagnose in the National Patient Register, or at least two prescriptions of asthma medication ever during a year.

Large discrepancies in growth defined as below the 10th or above the 90th percentiles were found to be ≤ -7 days (reduced growth) and $\geq +3$ days (increased growth) respectively for the whole cohort. There was a mean discrepancy of -1.2 days between gestational age as estimated by ultrasound in first trimester and in second trimester in the asthma group. Among those without asthma, the corresponding mean discrepancy was -1.3 days. For reduced or increased growth, we did not observe any statistically significant associations among those with or without asthma. For a reduced growth, OR and (95% CI) was 1.09 (0.63–1.90) and for an increased growth

TABLE 2 Difference in days between calculated time and measured time between first and second-trimester date/ultrasound, stratified on asthma status

	Without asthma		With asthma		Crude OR		Adjusted OR model 1 ^a		Adjusted OR model 2 ^b	
	n(%)	n(%)	n(%)	n(%)	95% CI	95% CI	95% CI	95% CI	95% CI	p-value
Gestational age characteristics										
Gestational age difference between first and second-trimester estimation, days ^c										
Mean	1289	291	-1.3	-1.2						
Median			0	0						
Odds ratios for reduced growth 10th percentile or below (-7 days or more)					0.96 (0.62–1.47)		1.09 (0.63–1.90)		1.11 (0.63–1.95)	.723
Odds ratios for increased growth 90th percentile or above (+3 days or more)					0.90 (0.64–1.27)		1.08 (0.70–1.67)		1.09 (0.68–1.77)	.710

Note: Asthma defined as either self-reported asthma diagnosis in questionnaires during pregnancy, self-reported asthma at first antenatal visit, an asthma diagnosis in the National Patient Register and/or at least two dispensed asthma medications within a year in the Prescribed Drug Register.

^aAdjusted for BMI, age, smoking, sex of child.

^bAdjusted for BMI, age, smoking, cohabitation, education, sex of child.

^cMissing 102 in non-asthma group, 12 in asthma group.

OR (95% CI) was 1.08 (0.70–1.67) in the first model where we adjusted for maternal age, BMI, sex of child and smoking. In the second model, where we additionally adjusted for maternal education and cohabitation the estimates were similar; adjusted OR for a reduced growth was 1.11 95% CI (0.63–1.95) and for an increased growth 1.09 95% CI (0.68–1.77), Table 2.

The mean birth weight of children to women with asthma was slightly smaller compared to women without asthma, however, the differences were not statistically significant, adjusted beta coefficient -29 grams 95% CI (-115–58 grams) in the first model. We saw similar results for gestational age and length of the child, Table 3.

In the interaction analyses between maternal asthma and fetal sex we found no significant interaction either on the multiplicative or the additive scale. The *p*-values ranged from 0.193 to 0.768 on the additive scale and from 0.110 to 0.749 on the multiplicative scale, Table S4.

For the sub-analysis on asthma control assessed by the Asthma Control Test, we found that women with uncontrolled asthma (score ≤19) were older than women without asthma or those with controlled asthma (score ≥20) and they had a higher BMI. Women with uncontrolled asthma also smoked to a larger extent and were less well educated, Table S1. Women with uncontrolled asthma had a mean discrepancy of -2.2 days between gestational age estimated in first and second-trimester ultrasound. For women with controlled asthma, the mean discrepancy was -0.9 days. There was no statistically significant difference between the asthma control groups for negative or positive discrepancies between first and second-trimester dating, Table S2. Likewise, there was no statistically significant difference between the asthma control groups when comparing birth weight, gestational age at birth or length of child, Table S3.

4 | DISCUSSION

In this prospective cohort study of Swedish pregnant women, growth measured as discrepancies in days from expected gestational age in second trimester, gestational age at birth, birth weight or length of child at birth did not differ between women with and without asthma. The observed differences were small and if anything, women with asthma seemed to have slightly smaller babies born compared to non-asthmatics.

Previous studies have shown that maternal asthma is associated with shorter gestational age at birth and lower birth weight.^{5,33} We have also previously observed an association between maternal asthma and adverse pregnancy outcomes such as preterm delivery and lower birth weight.⁴ We have also been able to show, by adjusting for potential unmeasured confounders shared within families, that the asthma disease per se seems to be associated with the adverse outcomes studied.⁷ In relation to our previous findings, we see fairly similar estimates, although not statistically significant, both for gestational age and birth weight where previous findings are within observed confidence intervals of this study. As we have previously shown that women with asthma are more likely to have babies born

TABLE 3 Birth characteristics in women with or without asthma

	W/o asthma	With asthma	Crude		Adjusted model 1 ^a		Adjusted model 2 ^b	
	1289	291	Beta coefficients		Beta coefficients		Beta coefficients	
	n(%)	n(%)	95% CI	p-value	95% CI	p-value	95% CI	p-value
Birth characteristics								
Birth weight, g								
Mean	3550	3539	-11 (-83 to 60)	.754	-29 (-115 to 58)	.513	-27 (-115 to 62)	.550
Median	3558	3570						
Missing, n(%)	62 (4.8)	4 (1.4)						
Birth weight ≥2500 g			Ref.		Ref.		Ref.	
Birth weight below 2500 g (OR)			1.55 (0.69–3.44)	.286	1.42 (0.59–3.45)	.434	1.44 (0.60–3.45)	.426
Gestational age ^c								
Mean weeks	40.1	39.9	-0.23 (-0.49 to 0.04)	.093	-0.29 (-0.63 to 0.05)	.090	-0.29 (-0.62 to 0.05)	.093
Median weeks	40.4	40.1						
Missing, n(%)	61 (4.7)	3 (1.0)						
Delivery from week 37 + 0			Ref.		Ref.		Ref.	
Delivery before week 37 + 0 (OR)			1.66 (0.86–3.20)	.128	1.83 (0.85–3.98)	.125	1.87 (0.84–4.15)	.123
Length of child								
Mean cm	50.5	50.4	-0.10 (-0.44 to 0.24)	.573	-0.23 (-0.65 to 0.19)	.285	-0.22 (-0.65 to 0.21)	.318
Median cm	51	51						
Missing n(%)	66 (5.1)	6 (2.1)						

Asthma defined as either self-reported asthma diagnosis in questionnaires during pregnancy, self-reported asthma at first antenatal visit, an asthma diagnosis in the National Patient Register and/or at least two dispensed asthma medications within a year in the Prescribed Drug Register. Dichotomous outcomes are shown as odds ratios.

^aAdjusted for BMI, maternal age, and smoking, sex of child.

^bAdjusted for BMI, maternal age, smoking, education, cohabitation, sex of child.

^cGestational age according to medical records at birth.

small for gestational age, we have in this study tried to determine if this previously observed growth retardation occurs in early half of the pregnancy or later. The results show no statistically significant discrepancy in measurement between first and second trimester but it cannot be excluded that a possible discrepancy occurs later in pregnancy. Kullinger et al¹⁵ showed that several factors, such as maternal age, BMI, smoking and cohabitation affect fetal growth. After adjustment for those factors, we were still no statistically significant differences between the asthma and non-asthma groups. We adjusted for sex in our analyses as well as tested for interactions between maternal asthma and fetal sex since it has been previously shown that fetal growth retardation during pregnancy in asthmatic women differs between female and male fetuses.³⁴ A possible mechanism for this discrepancy might be sex-specific placental expression as previously suggested by Clifton et al.^{16,35} The demand on the placenta increases in later pregnancy and this might explain

why we could not detect any differences in the second trimester in this study.

A limitation in our study might be that we have a selection of participants that exhibit different characteristics compared to the general population. All women that came for their first visit to the antenatal clinic were asked to participate. If the MAESTRO cohort would reflect the general population, we should for instance have had about half the prevalence of asthma. This finding is not very surprising since people with a certain disease are probably more interested in participating in a study concerning their own ailment.³⁶ Also, people more interested not only in their disease but also in their health, in general, might be more interested in participating which could mean that we have ended up with a biased cohort of asthmatic women healthier than other asthmatic women,³⁷ which also could explain why we had fewer individuals with uncontrolled asthma than expected. However, having lower

prevalence of uncontrolled asthma compared to other studies could also be because we only used the Asthma Control Test as our definition. The Asthma Control Test assesses asthma control during the last 4 weeks, whereas many other studies define asthma control as exacerbations and/or excessive use of asthma medication during a year.^{38,39} We have attempted to adjust for some of the known confounders that could give spurious associations, however, there may very well be some residual confounding that we were not able to adjust for.

The fact that the differences in women with uncontrolled asthma and controlled asthma compared to women without asthma were small and not statistically significant needs some attention. It has been shown that asthma exacerbations and hypoxia is associated with fetal risks.⁴⁰ But the global trend is less hospital admissions for asthma^{41,42} which could indicate that, although some pregnant women in Sweden do have uncontrolled asthma, the treatment available is much more efficient than before, leading to less pregnancy complications.

There are some strengths of this study that are worth mentioning. All data have been collected prospectively, which minimises the risk of recall bias. We have also been able to collect data from different sources, that is, medical charts, and questionnaires, which allows us to get more complete information compared to only using one data source. The MAESTRO cohort also includes a rich set of biosamples—both blood and saliva—as well as data from spirometry, which makes the cohort ideal for further studies and linkage to other cohorts.

5 | CONCLUSION

The MAESTRO study allows us to further investigate the mechanisms between maternal asthma, stress and pregnancy outcomes. We only saw small, statistically non-significant risk increase of early fetal growth retardation in women with asthma compared to those without. Although there might be an increased risk for impaired growth, the effect size is most likely small. Future studies using the MAESTRO cohort in combination with national registers and analysis of collected biomarkers in blood and saliva will allow us to further test the impact of maternal asthma or stress on pregnancy outcomes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

The study was initiated by GR and CA and designed by GR, CL and CA. GR performed the statistical analyses and wrote the initial draft with the aid of CL and CA. SS and KL contributed with invaluable support for data analyses, interpretation of findings and critical revision of the article. All authors reviewed and approved the final version of the article submitted for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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