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Original Research Article

Timing of maternal asthma diagnosis in relation to adverse perinatal outcomes

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ABSTRACT

Background: It is unclear if asthma diagnosed during pregnancy puts the fetus at a higher risk of poor perinatal outcomes than pre-existing asthma.

Objective: To assess if the risks of prematurity, major malformations, and small-for-gestational age (SGA) are higher in women with asthma diagnosed during versus pre-pregnancy.

Methods: We retrospectively analyzed a cohort of pregnant women aged ≥ 15 years with and without incident asthma, constructed from health administrative databases. Follow-up began 24 months before pregnancy-onset (cohort entry) and ended at delivery. Incident asthma was defined as a first diagnosis among those without asthma in the 8 years before cohort entry. Time was classified into pre-pregnancy and each trimester until delivery. We fit inverse probability weighted Poisson models to estimate marginal RRs for prematurity (delivery < 37 th week), major malformations, and SGA (birth weight < 10 th percentile) comparing women with and without asthma, assessing the asthma-timing of diagnosis interaction term via a Wald test.

Results: In a cohort of 122880 deliveries, the increased risk of prematurity, but not SGA, due to incident asthma was higher in those diagnosed during the second (RR 1.34, 95%CI 1.08-1.65; Wald $p=0.05$) and third (RR 1.93, 95%CI 1.62-2.29; Wald $p<0.01$) trimesters relative to pre-pregnancy (RR 1.06, 95%CI 0.98-1.15). A trend toward an increased risk of major malformations was observed in those diagnosed during the first trimester (RR 1.18; 95%CI 0.94-1.49, Wald $p=0.15$) than pre-pregnancy (RR 0.99; 95%CI 0.92-1.07).

Conclusions: Asthma diagnosed during, versus before, pregnancy was associated with a greater prematurity risk, suggesting an important role of preconception and prenatal screening.

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HIGHLIGHTS BOX

What is already known on this topic?

Women with pre-existing compared to without asthma during pregnancy have an increased risk of adverse perinatal outcomes, but whether pregnancy-onset asthma leads to similar increases in risk has yet to be investigated.

What does the article add to our knowledge?

Our results indicate that a new asthma diagnosis during versus before pregnancy, which can be newly developed or a latent disease exacerbated by gestation-induced physiological changes, is associated with a higher risk of preterm birth.

How does this study impact current management guidelines?

The increased risk of preterm birth as a result of an asthma diagnosis during compared to before pregnancy suggests an important role of preconception and/or prenatal asthma screening.

Keywords: Asthma diagnosis, pregnancy, preterm birth, small for gestational age, malformations, perinatal outcomes

ABBREVIATIONS

ED: Emergency department

QAPD: Quebec Asthma and Pregnancy Database

RAMQ: Régie de l'assurance du maladie du Quebec

RCT: Randomized Controlled Trial

SGA: Small for gestational age

89

90 INTRODUCTION

91 Asthma is one of the most common and potentially serious maternal chronic conditions during
92 pregnancy, with an estimated prevalence ranging from 8% to 13% in pregnant women across
93 the world.¹⁻⁴ Poorly controlled asthma during pregnancy is a well-established risk for adverse
94 perinatal outcomes, including low birth weight, preterm birth, congenital malformations, and
95 spontaneous abortions.⁵⁻⁷ Thus, investigating the mechanisms by which pregnancy leads to an
96 increased rate of asthma exacerbations, occurring in up to 45% of pregnant women with
97 asthma,⁸ can lead to interventions that improve control and prevent poor pregnancy outcomes.
98 In women with pre-existing asthma, treatment nonadherence and increased incidence of upper
99 respiratory tract infections are known underlying causes of poor control during pregnancy.^{9, 10}
100 The misconception that asthma medications, such as inhaled corticosteroids, could potentially
101 harm the fetus may cause discontinuation of treatment at pregnancy-onset, leading to further
102 loss of control.² Moreover, pregnancy may inhibit the immune response to viral infections in
103 women with pre-existing asthma, increasing susceptibility and severity of infections, which are
104 also potent exacerbation triggers.¹⁰ As a result, recent guidelines for managing asthma in
105 pregnancy have placed emphasis on providing education regarding the importance and safety
106 of asthma medications¹¹ and the Australian National Asthma Council recommends
107 preconception care including performing baseline spirometry assessments and offering
108 vaccinations.¹²
109 In addition to known exacerbation triggers in women with pre-existing asthma, physicians also
110 face the important challenge of diagnosing 'incident' asthma during pregnancy. An incident

asthma diagnosis during pregnancy can either be new-onset asthma, likely triggered by hormonal fluctuations,¹³ or a latent disease that was present prior to pregnancy, but was left undiagnosed. In women with asthma present before pregnancy but only newly diagnosed at some point during pregnancy, the fetus might suffer from uncontrolled symptoms due to the absence of adequate therapy in early gestation. Moreover, if pregnancy can trigger the development of asthma from hormonal fluctuations, the resulting 'pregnancy-onset' asthma phenotype could tend to be more severe in nature than pre-existing asthma. While we hypothesize that both mechanisms may contribute to the higher risk of uncontrolled symptoms and/or exacerbations in pregnant women with asthma, no studies have evaluated the impact of the timing of diagnosis on the fetus' development and subsequent perinatal outcomes. Therefore, the objective of this study was to assess whether women with asthma diagnosed during pregnancy are at an increased risk of adverse perinatal outcomes, as defined by preterm birth, major congenital malformations, and small-for-gestational age (SGA), relative to women with asthma diagnosed in the 24 months prior to pregnancy.

METHODS

Data Sources

The Quebec Asthma and Pregnancy Database (QAPD) was constructed by linking the Régie de l'assurance du maladie du Quebec (RAMQ) medical services and hospitalization databases to investigate the impact of maternal asthma and asthma medications on perinatal outcomes and has been described elsewhere.¹⁴⁻¹⁸ Briefly, the QAPD includes all women who gave birth in a Quebec hospital between January 1, 1990, and March 31, 2010, having at least one asthma

diagnosis recorded in the RAMQ or hospitalization databases in the 2 years prior to one or more of their deliveries, in addition to a fourfold larger random sample of other women who gave birth during the same period and had no asthma diagnosis. The date of the last menstrual period and the date of delivery for each pregnancy was retrospectively identified using validated and accurate algorithms including gestational age at birth and date of birth.¹⁹ The QAPD includes information on demographics (social assistance), details of ambulatory, emergency department (ED), and hospital visits (ICD9/10 diagnostic and service codes), and date of death (when applicable) between January 1988 and March 2010 for all pregnant women and their infants.

Study Design and Population

We analyzed a retrospective population-based cohort of women with and without asthma aged ≥ 15 years selected from the QAPD who became pregnant and successfully delivered (referred to as the 'index' pregnancy) between January 1 1998 and March 31 2010 (the study period) like a sequence of hypothetical nested randomized controlled trials (RCTs) as previously described by Hernan and colleagues (Supplemental Figure E1).²⁰ The cohort was restricted to all first index pregnancies that ended in a delivery recorded in the QAPD during the study period. We assigned cohort entry to be 24 months prior to the estimated date of pregnancy-onset to assess the impact of the timing of an incident asthma diagnosis (prior to vs. during the index pregnancy) on perinatal outcomes. Women with a history of chronic obstructive pulmonary disease (ICD-9 491, 492, 2496; ICD-10 J41-J44), cystic fibrosis (ICD-9 277.0; ICD-10 E84), or a history of asthma (ICD-9 493, except 493.2; ICD-10 J45) in the 8 years prior to cohort entry were excluded. In addition, pregnancies lasting >45 weeks or <20 weeks (due to miscarriages or

elective abortions), or with quadruplets (due to missing perinatal outcomes) were not included as index pregnancies. Emulating an intention to treat analysis in a sequence of hypothetical RCTs,²⁰ included women were eligible to receive the exposure (asthma diagnosis) monthly from cohort entry until the delivery date, with every follow-up month considered to be a nested trial (i.e. they were eligible for up to 34 nested trials); women diagnosed with asthma at month T were considered exposed in trial T until delivery and were no longer eligible to participate in subsequent monthly nested trials. Conversely, undiagnosed women were considered unexposed and remained eligible to contribute person-time to the comparison group in each subsequent nested trial until they received a diagnosis at time T or they delivered.

Outcomes

Preterm birth, defined as a delivery date prior to the 37th week of gestation, was considered to be the primary endpoint. Secondary endpoints were major congenital malformations identified using the Two-Step Congenital Malformation Classification,²¹ defined as a malformation that is life-threatening or could cause major cosmetic defects within the first year of life, and SGA, defined as a birth weight below the 10th percentile for gestational age and sex using Canadian standards for singletons.²²

Time-varying asthma diagnosis

An incident asthma diagnosis (the 'exposure') was considered to have been received the month at which women had a first physician visit (either in the ambulatory or acute care settings) for which the primary reason for the visit was asthma (ICD-9 493.X or ICD-10 J45.X) between cohort entry and the delivery date (delivery date excluded) in the QAPD. Once women received a diagnosis of asthma, they were considered to be exposed from the month of diagnosis until the

delivery date. Time was classified into pre-pregnancy (occurring in the 24 months prior to pregnancy) or during the first (GA of 1-12 weeks), second (GA of 13-26 weeks), or third trimesters (GA of 27-45 weeks).

Time-fixed and time-varying covariates

Maternal age as well as month and year of cohort entry were treated as time-fixed covariates. Comorbidities, including chronic (anemia, anxiety, atopy, cardiac disease, depression, diabetes, hypertension, migraine, chronic sinusitis, or renal and thyroid diseases) and acute conditions (lower respiratory or urinary tract infections), health care resource utilization (number of ED visits and hospitalizations and number of ambulatory visits), miscarriages or elective abortions that occurred in the 2 years prior to the index pregnancy, and whether the mother was receiving social assistance were treated as time-varying covariates, i.e. baseline values determined using a two year lookback period from cohort entry were then updated every follow-up month. Women were considered to have the chronic disease on the month at which they received a new diagnosis during a physician visit (either in the ambulatory or acute care setting) and every month thereafter until the delivery date. In contrast, those who visited a physician for an acute infection were only considered to have the infection the month of diagnosis (see Table E1 for ICD-9/10 codes used to define comorbidities).

Statistical Analysis

We used stabilized inverse-probability of treatment (IPT-) weighting to mimic randomization of an asthma diagnosis, relative to no asthma, at each follow-up month interval (month T).²⁰ To do this, we fit month-specific logistic regression models to estimate the probability of receiving an incident asthma diagnosis conditional on all measured baseline and time-updated covariates

and subsequently computed the cumulative probability of this exposure until month T.²⁰ To stabilize the weights, we multiplied month-specific weights by the probability of receiving an asthma diagnosis conditional on all baseline measured covariates and verified that the weight distribution had a median and mean close to 1 with a reasonable range.²³ We then fit IPT-weighted modified Poisson models,²⁴ adjusted for baseline values of all covariates, to estimate marginal RRs of asthma vs no asthma with respect to each perinatal outcome and pooled estimates across all 24 months occurring pre-pregnancy and in pregnancy trimesters for interpretability. For major malformations, only asthma diagnoses occurring in the first trimester were of interest. To assess whether marginal RRs of asthma diagnosis varied in a clinically relevant manner with time, we evaluated the Wald statistic of the product terms between asthma diagnosis and an indicator variable for timing of diagnosis (prior to and each trimester of pregnancy) included in each outcome model. Robust standard errors were used to account for IPT weighting and women contributing months of follow-up within several hypothetical nested trials. We also computed E-values to assess robustness of estimated effects to unmeasured confounding for each outcome.²⁵ Data management and analyses were performed with SAS version 9.4.

RESULTS

Of the 583 071 deliveries in the QAPD, 122 880 (21.1%) were eligible for inclusion in at least one of the 34 nested trials, from 24 months prior to pregnancy until delivery (Figure 1). From these, there were 9 749 preterm births (7.9%), 17 559 SGA infants (14.3%), and 10 558 infants with a major congenital malformation (8.6%). In all, there were 10 320 (8.4%) women receiving

an incident asthma diagnosis, with 2 920 (28.3%) of diagnoses occurring during pregnancy, and a total of 3 997 170 women-trials included in the analysis (Table E2).

In general, women receiving an incident asthma diagnosis, either prior to or during pregnancy, were more likely to have previous miscarriages, comorbidities (such as anxiety, atopy, depression, lower respiratory tract conditions, sinusitis and urinary tract infections), and cohort entry prior to 2004, as well as more often on social assistance in the two years prior to cohort entry when compared to those not receiving an asthma diagnosis (Table 1). While most baseline characteristics remained similar between women with incident asthma during compared to before pregnancy, those diagnosed pre-pregnancy had more comorbidities, particularly lower respiratory tract conditions, than those diagnosed during pregnancy.

The crude incidence of preterm births among those receiving an asthma diagnosis in the 24 months prior to pregnancy-onset was 8.5%, whereas this increased to 8.6%, 12.2%, and 13.7% for asthma diagnosed in first, second, and third trimesters, respectively. Compared to those without asthma in the 24 months prior to pregnancy-onset, women receiving an incident asthma diagnosis during this same time frame were 6% more likely to deliver prematurely (RR 1.06, 95%CI 0.98-1.15). Interestingly, asthma diagnosed in the first, second, and third trimesters was associated with an 8% (RR 1.08; 95%CI 0.85-1.38), 34% (RR 1.34; 95%CI 1.08-1.65), and 93% (RR 1.93; 95% CI 1.62-2.29) increased marginal risk of preterm birth when compared to women without asthma during each trimester, respectively (Figure 2). The Wald test for the asthma-time product term suggested a clinically relevant increase in the marginal RR for prematurity in the second (p-value of 0.051) and third trimesters (p-value<0.001) relative to pre-pregnancy.

Irrespective of the timing of diagnosis, the average marginal risk of preterm birth was elevated by 16% (RR 1.16, 95%CI 1.08-1.24) in women with incident asthma than without asthma.

The incidence of major malformations was only slightly elevated in women receiving an asthma diagnosis during the first trimester (9.5%) when compared to those with newly diagnosed asthma in the 24 months prior to pregnancy (9.0%). While there was no evidence of an association between asthma diagnosed pre-pregnancy and major congenital malformations (RR 0.99; 95% CI 0.92-1.07), there was a trend toward an increased risk (RR 1.18; 95%CI 0.94-1.49) for women diagnosed with asthma compared to those without asthma during the first trimester (Figure 3). Nevertheless, there was a lack of evidence suggesting that this increased risk significantly differed from pre-pregnancy (p-value of 0.15). Overall, women with incident asthma did not seem to have an increased risk of major malformations when compared to women without asthma (RR 1.04; 95% CI 0.97-1.11).

SGA infants occurred more frequently among women receiving an asthma diagnosis in the second (16.2%) and third trimesters (16.0%) than those receiving an asthma diagnosis pre-pregnancy (15.9%) and the first trimester (13.9%). While there was a 7% increased risk of SGA for women diagnosed with asthma pre-pregnancy than those without asthma (RR 1.07; 95%CI 1.01-1.13), estimates for the first (RR 0.92; 95%CI 0.77-1.11), second (RR 1.06; 95%CI 0.89-1.26), and third (RR 1.17; 95%CI 1.00-1.36) trimesters did not significantly differ with time (Figure 4). Regardless of timing, incident asthma was associated with an overall elevated marginal risk of SGA infants (RR 1.06; 95%CI 1.01-1.11).

The E-value sensitivity analyses for unmeasured confounding suggested that most estimates can be explained away by weak to moderate unmeasured confounding (Table E3); however, the

effect of asthma diagnosed during the third trimester on preterm birth can only be moved toward a null value if strong unmeasured confounding, conditional on measured covariates, exists (strength of association between unmeasured confounder and exposure/outcome of 2.6).

DISCUSSION

In this large retrospective cohort study of deliveries, 8.4% of women received an incident asthma diagnosis, with 28% diagnoses occurring during pregnancy. Our findings are the first to suggest that timing of an incident asthma diagnosis was particularly important for the risk of preterm birth and possibly major malformations, but not for SGA. Specifically, we showed that receiving an incident asthma diagnosis in the second and third trimesters led to a higher risk of preterm birth, in a dose-response manner, when compared to those receiving the diagnosis in the 24 months prior to pregnancy-onset. We also observed a trend toward an increased risk of major malformations among women newly diagnosed with asthma in the first trimester than those diagnosed pre-pregnancy.

While no other studies, to our knowledge, have assessed timing of incident diagnosis in relation to pregnancy-onset and the risk of adverse pregnancy outcomes, three observational studies assessed whether the strength of the association between pre-existing maternal asthma and prematurity varied with time using a fetuses-at-risk approach.²⁶⁻²⁸ All studies found that the risk of preterm birth among pregnant women with a history of asthma (diagnosis of asthma prior to pregnancy, during pregnancy or at delivery) as compared to those without asthma was highest

in the third trimester,²⁶⁻²⁸ with only one study also showing an increased risk prior to the third trimester.²⁷ In two of the large retrospective cohort studies consisting of 223512 and 284214 singleton deliveries from women with pregnancies lasting ≥ 23 weeks, Rejno et al. and Mendola et al. observed that the association between history of maternal asthma and preterm birth was only evident in women pregnant >31 and >33 weeks (OR ranging from 1.10 to 1.30), respectively.^{26, 28} While this is consistent with the highlighted relevance of diagnosis in the third trimester with respect to prematurity in our study, it differs with the increased risk we observed in the second trimester. This may be due to differences in the definition of asthma (incident vs history of asthma), the statistical approach used (grouping GA >31 weeks vs. by trimesters) and study design, since the former two studies did not adjust for time-updated covariates during pregnancy.

While not the primary objective of this study, our finding that incident asthma increases the overall risk of preterm birth and SGA, regardless of timing, has been shown consistently in several other studies,²⁶⁻³⁵ including a meta-analysis of 988252 and 923542 pregnant women reporting a 41% (RR 1.41, 95%CI 1.23-1.62) and 22% (RR 1.22, 95%CI 1.14-1.31) increased risk in women with compared to without prevalent asthma, respectively, without accounting for timing of diagnosis.⁶ In addition, our results do not support an overall increased risk of major congenital malformations in women with incident asthma compared to those without asthma, which is also consistent with a 2013 meta-analysis of 2461 singleton deliveries from 4 prospective studies evaluating the association between maternal asthma and major malformations (RR 1.31; 95%CI 0.57-3.02).⁵ Nevertheless, in a more recent retrospective cohort study of 467946 pregnant women with and without asthma, Eltonsy and colleagues observed a

higher overall odds of major malformations (OR 1.26, 95%CI 1.22-1.30).²¹ This divergence with our results may be due to the inclusion of different asthma groups. While our study included women with incident asthma, the Eltonsy et al. study included women with a history of asthma pre-pregnancy who also had disease activity in the 2 years prior to delivery.²¹ Given recent evidence that severe exacerbations in the first trimester could play an important role in the development of major malformations,¹⁴ it is plausible that the inclusion of women with prevalent compared to incident asthma are more likely to be severe and exacerbate more frequently in the first trimester, thus leading to an elevated risk estimate for major malformations.

Since exacerbations most commonly appear between weeks 24 and 36 of pregnancy,³⁶ it is not surprising that the risk of preterm birth was observed to be highest during the second and third trimesters in women with newly diagnosed asthma, as many likely had uncontrolled symptoms triggered by pregnancy-induced physiological changes left untreated due to undetected asthma (either latent or newly developed).³⁷ Of these physiological changes, hormone fluctuations have been hypothesized to play an important role in the development and severity of asthma, as other studies have shown that girls are more likely to develop asthma and have exacerbations following puberty than boys.³⁸⁻⁴⁰ With progesterone and estradiol increasing markedly over the course of a pregnancy (with both reaching maximum concentrations in the third trimester and progesterone rapidly subsiding just prior to delivery),³⁷ it is possible that hormones exacerbate previously undiagnosed mild asthma during the second and third trimesters of pregnancy, leading to a higher risk of adverse outcomes, such as preterm birth. Other pregnancy-related changes occurring in the second and third trimesters that may trigger or exacerbate asthma

symptoms include the elevation of the diaphragm and subsequent reduction of expiratory reserve volume, which is worst in the third trimester.³⁷ We hypothesize that labor initiates prematurely in women with an exacerbation-induced asthma diagnosis via a transient maternal stress-cortisol response and possible treatment with corticosteroids, which, together, have been shown to upregulate corticotropin-releasing hormone – a potent stimulator of prostaglandin production and myometrial activation.⁴¹ Moreover, we suspect that SGA likely develops from a *sustained* placental vascular reduction due to higher severity and chronic poor control of asthma symptoms during pregnancy.⁴² It is plausible that, by virtue of the research design, women diagnosed pre-pregnancy had a longer period of antenatal exposure to uncontrolled asthma symptoms leading to a more severe reduction in placental vascular integrity and subsequent fetal growth, than those diagnosed at some point during pregnancy. This, in turn, may have led to less evident increases in SGA risk during pregnancy.

It is worthy to note that women who received an asthma diagnosis in the 8 years prior to cohort entry were excluded from our study population. This is because the purpose of our hypothetical nested RCT study was to assess whether receiving an asthma diagnosis, serving as a proxy for administration of a perfectly sensitive hypothetical screening intervention that assumes diagnosis time can be manipulated rather than the development of asthma itself, prior to or very early during pregnancy versus later in pregnancy could possibly be associated with improved perinatal outcomes. To this end, women with pre-existing asthma would not be eligible to receive this hypothetical screening intervention and were therefore not of interest in this study.

The strengths of this study include the novelty of the research question, the large representative cohort of pregnant women and the innovative design used to assess the impact of timing of asthma diagnosis on perinatal outcomes. However, this study also has limitations. First, our cohort entry date was arbitrarily defined as 24 months prior to pregnancy-onset among women having delivered a baby during the study period, and, thus, was based on having already known that the pregnancy resulted in a delivery. Because the index pregnancies included in this study do not include women who miscarry or have an elective abortion prior to week 20 of gestation, we suspect potential selection bias, particularly if being diagnosed with asthma is associated with miscarriage. If the latter is the case, our estimates would be biased toward the null.⁴³ Second, the data within the QAPD spans from 1990-2010, making it almost 10 years old; however, we expect our findings to be even more relevant today as the prevalence of maternal asthma appears to be rising⁴⁴ and, while guidelines have emphasized the importance and urgency of managing pre-existing asthma in pregnant women, they have yet to provide any specific recommendations for screening asthma in women who have not been diagnosed or symptomatic for years once pregnancy begins. We suspect that women with asthma diagnosed prior to pregnancy may be better managed in more recent years, whereas those diagnosed during pregnancy would still remain at a higher risk of poor perinatal outcomes. Third, we defined asthma as a first physician visit with a diagnostic code for asthma and did not have access to spirometry or lung function clinical data to confirm the diagnosis. Consequently, misdiagnoses due to the presence of comorbidities that could mimic asthma symptoms, such as gastroesophageal reflux disease or pregnancy-related dyspnea that were not captured in the QAPD, may have led to nondifferential exposure misclassification and an

underestimation of the observed relative risks; this underestimation may be more prominent during compared to before pregnancy, particularly for misclassification resulting from pregnancy-related dyspnea. Fourth, we did not have information on maternal body mass index or smoking during pregnancy, which have been shown to be associated with both asthma onset and adverse perinatal outcomes.^{31, 45} However, our E-value sensitivity analysis suggested that relatively strong unmeasured confounding must exist in order to nullify the association between asthma and preterm birth in the third trimester, which seems unlikely due to the relatively low percentage of women (12%) who continue to smoke during pregnancy in Canada.⁴⁶ Last, women who deliver prematurely are removed from the population-at-risk earlier than those who deliver at term, reducing their opportunity to receive an asthma diagnosis purely from a time-at-risk perspective. This may, in turn, artificially underestimate the risk of asthma on SGA in the second and third trimesters of pregnancy.

This study has important clinical implications. The timing of asthma diagnosis appears to play an important role in the risk of preterm birth, but not SGA, and a trend toward an increased risk of major malformations. These results may suggest the presence of a pregnancy-onset asthma phenotype requiring closer monitoring or that earlier screening for undetected asthma during preconception or very early in gestation may lead to better management of symptoms, which could ultimately prevent a proportion of preterm births and major malformations, but not SGA babies, from uncontrolled symptoms. As diagnosing asthma can be a challenge due to pregnancy-induced physiological and mechanical changes, obstetrician-gynecologists may want to refer women planning to become pregnant or at their first prenatal visit, who also report a history of wheeze or breathlessness, to a pulmonologist for asthma screening. Further

prospective research investigating the underlying mechanisms of pregnancy-onset asthma are warranted to optimize asthma-related perinatal outcomes.

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FIGURE LEGENDS

Figure 1. Population flow-chart. Chronic obstructive pulmonary disease (COPD); Cystic Fibrosis (CF). *Since women with undiagnosed asthma could contribute to the comparison groups in several nested trials, the number of women-trials is calculated as the sum of the number of women without an asthma diagnosis at each person-month of follow-up (i.e. across all nested trials).

Figure 2. Relative risks of preterm birth for women with an incident asthma diagnosis compared to those without a diagnosis in the 24 months prior to pregnancy and the first, second, and third trimesters. Wald test p-values indicate whether RRs increased in a clinically relevant way with timing of diagnosis, with the 24 months prior to pregnancy serving as the reference.

Figure 3. Relative risks of major congenital malformations for women with an incident asthma diagnosis compared to those without a diagnosis in the 24 months prior to pregnancy-onset and the first trimester. Wald test p-values indicate whether there was a clinically important increase in RR if the diagnosis was received in the first trimester relative to whether diagnosis occurred pre-pregnancy.

Figure 4. Relative risks of small-for-gestational-age infants when comparing women with and without an incident diagnosis of asthma in the 24 months prior to pregnancy-onset and each trimester. Wald test p-values suggest no evidence of a clinically important difference in RR by timing of diagnosis.

Table 1. Baseline characteristics of women with and without asthma across all nested trials

Baseline Characteristics	Prior to Pregnancy		During Pregnancy	
	Incident Asthma N=7 400*	No Asthma N=2 866 559 [†]	Incident Asthma N=2 920*	No Asthma N= 1 120 291 [†]
Demographics				
Maternal age, mean (SD)	25.73 (5.7)	26.50 (5.4)	27.88 (5.8)	27.93 (5.3)
Social assistance in the 2 years prior to cohort entry, N (%)	1 211 (16.4)	323 542 (11.3)	544 (18.6)	123 217 (11.0)
Medical care received in the 2 years prior to cohort entry				
No. of ambulatory visits, Median (IQR)	6 (7)	4 (7)	5 (8)	4 (6)
No. of acute care visits, Median (IQR)	0 (1)	0 (1)	0 (1)	0 (1)
Previous miscarriage or abortion, N (%)	410 (5.5)	128 863 (4.5)	149 (5.1)	49 540 (4.4)
Comorbidities in the 2 years prior to cohort entry, N (%)				
Anemia	106 (1.4)	36 042 (1.3)	47 (1.6)	13 949 (1.3)
Anxiety	832 (11.2)	213 181 (7.4)	295 (10.1)	81 378 (7.3)
Atopy [‡]	1 019 (13.8)	281 713 (9.8)	339 (11.6)	108 397 (9.7)
Cardiac disease	90 (1.2)	26 793 (0.9)	31 (1.1)	10 306 (0.9)
Depression	450 (6.1)	106 142 (3.7)	155 (5.3)	40 264 (3.6)
Diabetes	51 (0.7)	13 734 (0.5)	18 (0.6)	5 153 (0.5)
Hypertension	104 (1.4)	25 704 (0.9)	35 (1.2)	9 649 (0.9)
Lower respiratory tract conditions	3 121 (42.2)	777 739 (27.1)	981 (33.6)	297 211 (26.5)

Migraine	320 (4.3)	86 187 (3.0)	105 (3.6)	33 148 (3.0)
Renal disease	145 (2.0)	37 140 (1.3)	49 (1.7)	14 183 (1.3)
Sinusitis	741 (10.0)	162 453 (5.7)	229 (7.8)	61 606 (5.5)
Thyroid disease	239 (3.2)	63 548 (2.2)	77 (2.6)	24 367 (2.2)
Urinary tract infections	976 (13.2)	300 433 (10.5)	332 (11.4)	116 133 (10.4)
Year of Cohort Entry, N (%)				
1996	174 (2.4)	66 862 (2.3)		
1997	512 (6.9)	192 705 (6.7)	0	170 (0.0)
1998	779 (10.5)	243 365 (8.5)	177 (6.1)	61 709 (5.5)
1999	666 (9.0)	237 354 (8.3)	289 (9.9)	96 253 (8.6)
2000	679 (9.2)	235 516 (8.2)	249 (8.5)	92 365 (8.2)
2001	647 (8.7)	236 776 (8.3)	266 (9.1)	92 245 (8.2)
2002	610 (8.2)	241 000 (8.4)	229 (7.8)	90 806 (8.1)
2003	645 (8.7)	245 145 (8.6)	280 (9.6)	94 077 (8.4)
2004	592 (8.0)	256 011 (8.9)	259 (8.9)	94 612 (8.5)
2005	576 (7.8)	262 458 (9.2)	231 (7.9)	98 205 (8.8)
2006	616 (8.3)	264 778 (9.2)	261 (8.9)	103 103 (9.2)
2007	537 (7.3)	247 497 (8.6)	228 (7.8)	103 266 (9.2)
2008	336 (4.5)	125 033 (4.4)	242 (8.3)	105 754 (9.4)
2009	31 (0.4)	12 059 (0.4)	193 (6.6)	84 076 (7.5)
2010			16 (0.6)	3650 (0.3)

554 *Number of women with incident asthma

555 †Number of women summed across all nested trials, which includes women without asthma contributing to several

556 trials.

557 ∫ Atopy includes eczema, dermatitis, food allergy, rhinitis, and/or chronic conjunctivitis.

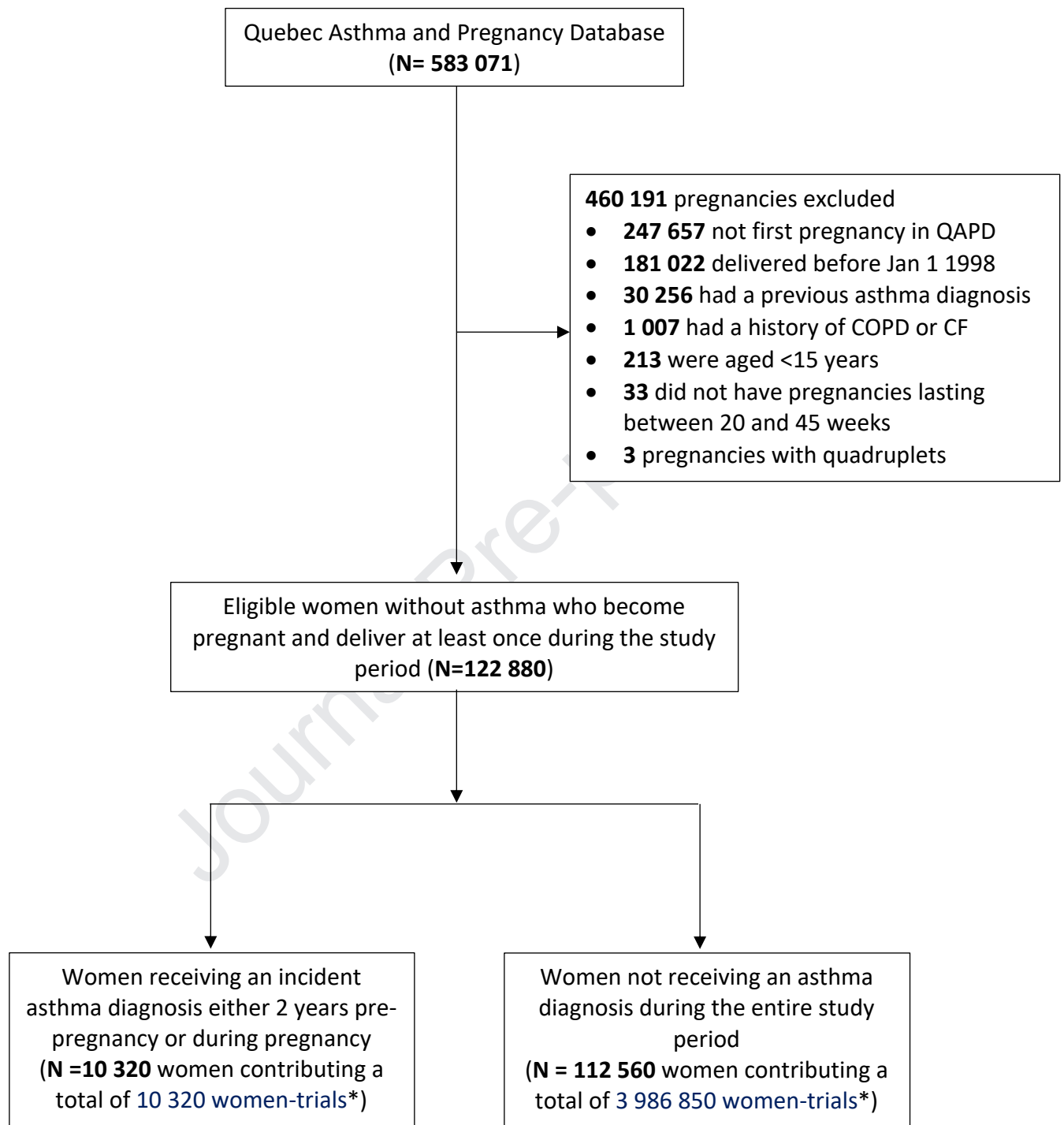
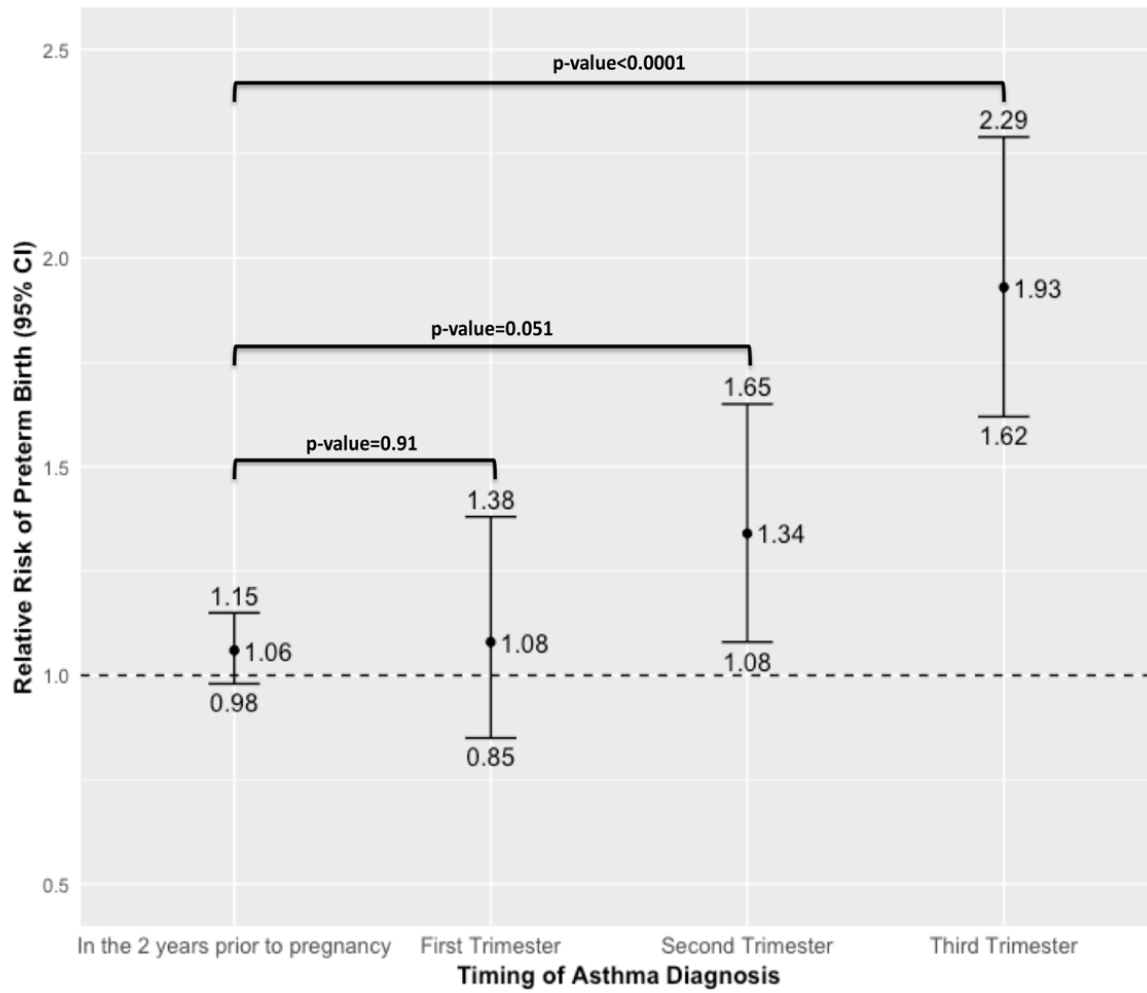
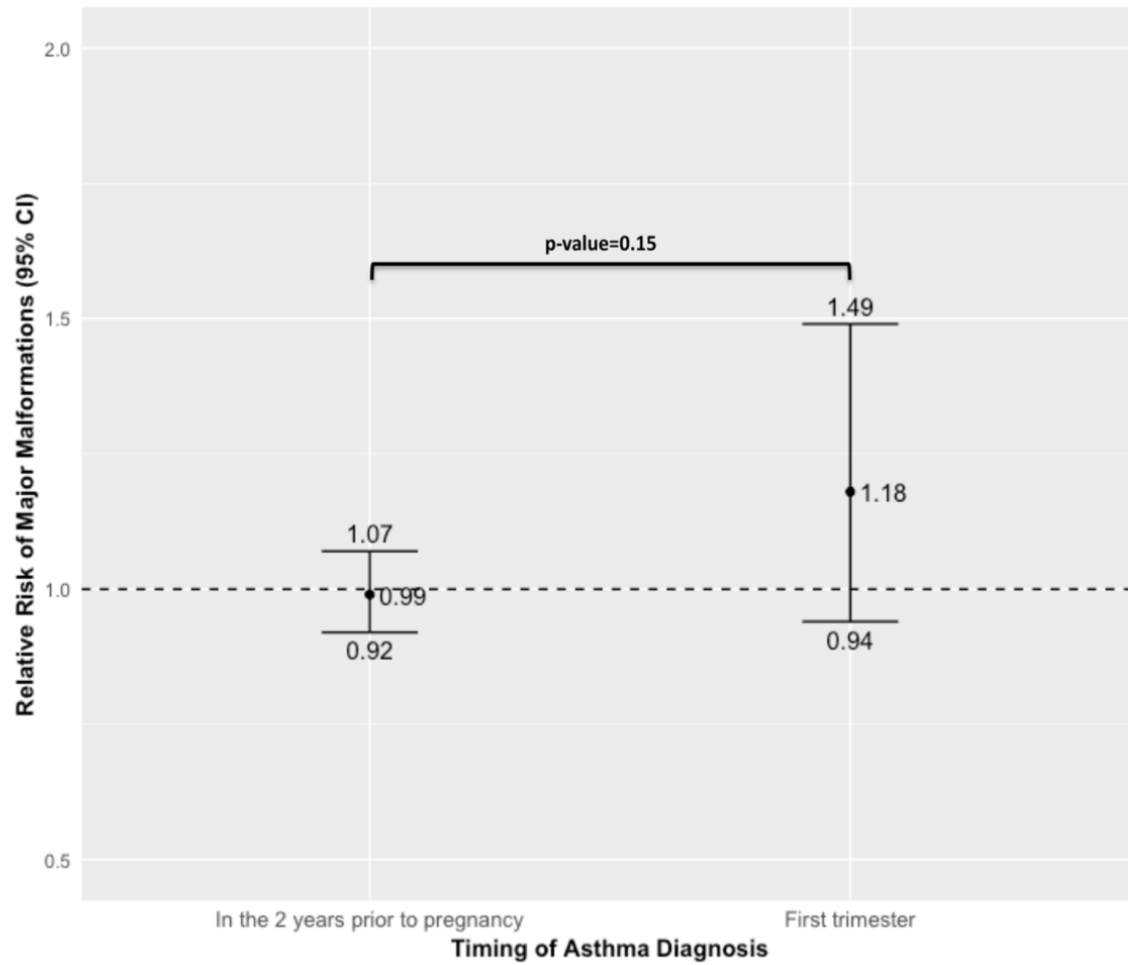


Figure 1. Population flow-chart. Chronic obstructive pulmonary disease (COPD); Cystic Fibrosis (CF).
*Since women with undiagnosed asthma could contribute to the comparison groups in several nested trials, the number of women-trials is calculated as the sum of the number of women without an asthma diagnosis at each person-month of follow-up (i.e. across all nested trials).





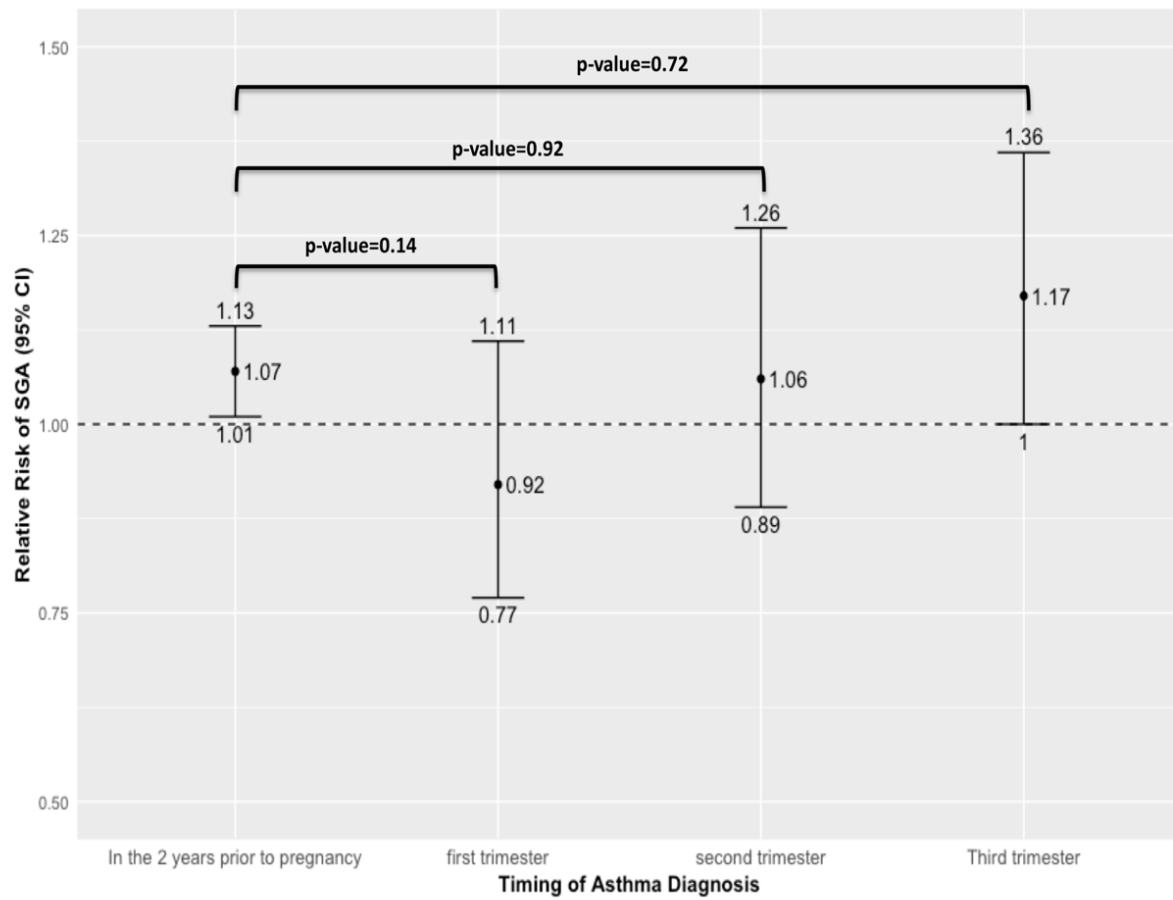


Table E1. Diagnostic codes used to define covariates

Characteristics	ICD-9 Codes	ICD-10 Codes
Anemia	648.2, 280.9, 281, 282, 283, 284, 285	O9900, D50, D51, D52, D53, D54, D55, D56, D57, D58, D59, D60, D61, D62, D63, D64
Anxiety	300.0, 300.2, 300.9	F40, F41
Atopy Eczema or Dermatitis Food allergy Rhinitis Conjunctivitis	691.8, 692.9 693.1, 995.6, 995.7 472.0, 477 372.1	L20 T78.0, T78.1, L23.6, L27.2 J30.1, J30.2, J30.3, J30.4, J31.0 H10.4
Cardiac disease	391-398, 402, 404, 410-414, 415.0, 416, 420-429	I05-I13, I20-I25, I26.0, I27.8, I27.9, I30-I51 I97.0, I97.1
Depression	296.2, 296.3, 300.4, 311	F32, F33, F34.0, F34.1, F34.9 F38.1, F38.8
Diabetes	250, 648.0, 648.8	E10, E11, E13, E14, O24.5, O24.6, O24.7, O24.8, P70.0
Hypertension	401, 402, 403, 404, 405, 642.0, 642.1, 642.2, 642.3, 642.4, 642.5, 642.7, 642.6, 642.9	I10-I13, I15, O10, O11, O13-O16
Respiratory tract conditions	38.0, 38.2, 360-466, 480-486, 487.0	J00-J06, J12-J18, J20-J22
Migraine	346	G43
Renal disease	580-593	N00-N08, N10-N23, N25.8, N25.9, N26, N28
Chronic sinusitis	473	J32
Thyroid disease	240-246	E01-E07
Urinary tract infections	112.2, 590, 595.0, 595.9, 599.0	B37.4, N10, N30, N39.0
Miscarriages/ elective abortions	630-639, 761.8, 779.6	O00-O05, O07, O08

Table E2. Number of women with asthma and perinatal events in each cohort nested month “trial” relative to pregnancy onset

Month Relative	No. of Preterm Births/	No. of SGA Events/	No. of Malformations/	No. of Preterm Births/	No. of SGA Events/	No. of Malformations/
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to Pregnancy	No. without Asthma*	No. without Asthma [†]	No. without Asthma	No. with Asthma	No. with Asthma	No. with Asthma
-24	9749/122880	17559/120161	10558/122880	12/200	37/196	19/200
-23	9737/122680	17522/119965	10539/122680	17/207	35/205	16/207
-22	9720/122473	17487/119760	10523/122473	31/249	42/244	25/249
-21	9689/122224	17445/119516	10498/122224	18/211	24/203	16/211
-20	9671/122013	17421/119313	10482/122013	21/204	33/199	13/204
-19	9650/121809	17388/119114	10469/121809	15/214	29/207	23/214
-18	9635/121595	17359/118907	10446/121595	17/215	29/210	18/215
-17	9618/121380	17330/118697	10428/121380	20/215	34/213	23/215
-16	9598/121165	17296/118484	10405/121165	29/247	35/237	17/247
-15	9569/120918	17261/118247	10388/120918	34/336	56/328	31/336
-14	9535/120585	17205/117919	10357/120585	29/360	53/355	37/360
-13	9506/120222	17152/117564	10320/120222	27/369	58/360	27/369
-12	9479/119853	17094/117204	10293/119853	32/380	63/372	47/380
-11	9447/119473	17031/116832	10246/119473	35/354	49/348	31/354
-10	9412/119119	16982/116484	10215/119119	24/361	48/356	33/361
-9	9388/118758	16934/116128	10182/118758	37/379	59/369	27/379
-8	9351/118379	16875/115759	10155/118379	30/372	67/369	31/372
-7	9321/118007	16808/115390	10124/118007	25/362	63/357	42/362
-6	9296/117645	16745/115033	10082/117645	29/387	59/385	43/387
-5	9267/117258	16686/114648	10039/117258	30/348	61/346	26/348
-4	9237/116910	16625/114302	10013/116910	30/361	61/358	31/361
-3	9207/116549	16564/113944	9982/116549	27/352	49/345	27/352
-2	9180/116197	16515/113599	9955/116197	33/327	50/325	19/327
-1	9147/115870	16465/113274	9936/115870	29/390	62/387	43/390
1	9118/115480	16403/112887	9893/115480	24/301	45/296	28/301
2	9094/115179	16358/112591	9865/115179	23/272	31/270	28/272
3	9071/114907	16327/112321	9837/114907	21/216	32/211	19/216
4	9050/114691	16295/112110	9818/114691	24/239	45/232	19/239
5	9026/114452	16250/111878	9799/114452	31/276	40/271	29/276
6	8966/114147	16210/111598	9766/114147	38/250	36/245	23/250
7	8584/113553	16136/111099	9683/113553	33/287	54/286	31/287
8	8087/112802	15996/110426	9494/112802	48/308	44/295	35/308
9	6380/110835	15726/108785	9102/110835	39/283	49/273	29/283
10	0/97165	13930/96086	7657/97165	0/488	68/486	46/488

*The number of women without asthma at the beginning of each month

[†]The number of women included in the SGA analyses differed from the other perinatal outcomes due to missing birth weight data

Table E3. Sensitivity of Results to Unmeasured Confounding

Outcome	Timing	RR (95% CI)	E-value (LCI)	Interpretation
Prematurity	Pre-pregnancy	1.06 (0.98-1.15)	1.31 (1.00)	Average estimate can be explained away with weak unmeasured confounding ($RR_{EU}=1.31$ & $RR_{UY}=1.31$)
	First trimester	1.08 (0.85-1.38)	1.37 (1.00)	Average estimate can be explained away with weak unmeasured confounding ($RR_{EU}=1.37$ & $RR_{UY}=1.37$)
	Second trimester	1.34 (1.08-1.65)	2.01 (1.37)	Average estimate can be explained away with moderate unmeasured confounding ($RR_{EU}=2$ & $RR_{UY}=2$)
	Third trimester	1.93 (1.62-2.29)	3.26 (2.62)	Average estimate can be explained away with strong unmeasured confounding ($RR_{EU}=3.3$ & $RR_{UY}=3.3$)
Major Congenital Malformations	Pre-pregnancy	0.99 (0.92-1.07)		
	First trimester	1.18 (0.94-1.49)	1.64 (1.00)	Average estimate can be explained away with moderate unmeasured confounding ($RR_{EU}=1.64$ & $RR_{UY}=1.64$)
Small-for-Gestational Age	Pre-pregnancy	1.07 (1.01-1.13)	1.34 (1.11)	Average estimate can be explained away with weak unmeasured confounding ($RR_{EU}=1.34$ & $RR_{UY}=1.34$)
	First trimester	0.92 (0.77-1.11)		
	Second trimester	1.06 (0.89-1.26)	1.31 (1.00)	Average estimate can be explained away with weak unmeasured confounding ($RR_{EU}=1.31$ & $RR_{UY}=1.31$)
	Third trimester	1.17 (1.00-1.36)	1.62 (1.00)	Average estimate can be explained away with weak unmeasured confounding ($RR_{EU}=1.62$ & $RR_{UY}=1.62$)

Lower Confidence Interval (LCI); RR_{EU} represents the strength of association between the exposure E and the unmeasured confounder U; RR_{UY} represents the strength of association between the unmeasured confounder U and the outcome Y.

ONLINE REPOSITORY TEXT

Figure Legends

Figure E1. Study design illustrating the hypothetical nested RCTs within the QAPD cohort. Chronic Obstructive Pulmonary Disease (COPD); Cystic Fibrosis (CF); Inverse Probability of Treatment Weighting (IPTW).

