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A prospective study of preconception asthma and spontaneous abortion

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Abstract

Purpose: To evaluate the relationships among history of asthma, asthma severity, and spontaneous abortion (SAB).

Methods: Pregnancy Study Online (PRESTO) is a preconception cohort study of North American couples. During the preconception period, female participants reported their history of physician-diagnosed asthma, age at first diagnosis, and use of asthma medications in the previous 4 weeks. Asthma severity was classified by medication use proximal to conception, from level

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Author Contributions

JJY was responsible for formulation of the study hypotheses and study design, statistical analyses, results interpretation, manuscript writing, revision, and finalization. HMC was responsible for exposure classification, results interpretation, manuscript writing, revision, and finalization. TRW was responsible for data preparation, results interpretation, manuscript revision, and finalization. EEH, SKW, EMM, DAS, AJW, KJR were responsible for results interpretation, manuscript revision, and finalization. LAW was responsible for formulation of the study hypotheses and study design, statistical analyses, results interpretation, manuscript revision, and finalization. LAW, EEH, EMM and KJR were responsible for obtaining NIH funding for this work, study design, and primary data collection

Disclosure Statement

LAW does consultancy work for AbbVie Inc. In the last three years, Pregnancy Study Online has accepted in-kind donations from: Sandstone Diagnostics, Swiss Precision Diagnostics, LabCorps, and Kindara.com. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study. The authors report no other relationship or activity that could appear to have influenced the submitted work.

Declaration of interests

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

0 to 3 in increasing severity. Pregnancy and SAB were identified using data from follow-up questionnaires. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Among 6,325 participants who conceived, 19% experienced SAB and 17% reported a history of asthma. There was no appreciable association between asthma history and SAB incidence (HR=0.98; 95% CI: 0.84, 1.14). HRs comparing severity levels 0, 1, and 2–3 with no asthma were 0.82 (95% CI: 0.67, 1.01), 1.20 (95% CI: 0.91, 1.60), and 1.31 (95% CI: 0.97, 1.78), respectively. Among women who conceived without the use of fertility treatment, level 2–3 severity was associated with SAB (HR=1.39; 95% CI: 1.02, 1.89).

Conclusions: While history of asthma diagnosis was not materially associated with SAB, having severe asthma (based on medication use) was associated with greater SAB risk.

Keywords

Maternal asthma; asthma severity; spontaneous abortion; miscarriage

Introduction

In 2018, approximately 10% of adult women in the United States (US) were living with asthma [1]. The relationship between asthma and pregnancy is complex: pregnancy may influence asthma severity, and asthma exacerbations may inhibit fetal development via reduced oxygen flow [2]. Further, the potential effects of asthma medications are challenging to separate from effects of asthma itself. Maternal asthma diagnosis, severity, and control have been associated with preeclampsia, low birthweight, preterm birth, and small for gestational age [3–6], but less is known about their relationship with spontaneous abortion (SAB).

SAB, or pregnancy loss before 20 weeks' completed gestation, occurs in about 20% of recognized pregnancies [7]. Maternal asthma has been hypothesized as a risk factor for SAB [8], and symptom control could be a modifiable risk factor. However, studies of this association have yielded inconsistent results. A study conducted within two large US healthcare claims databases observed no association between SAB and maternal asthma diagnosis (risk ratio (RR)=1.02 for women with versus without asthma) or severity (RR=1.01 for severe versus mild asthma) [9]. In contrast, a study based on three administrative healthcare databases in Québec reported a 40% increased odds of SAB associated with asthma [8]. Although ascertainment of SABs using administrative databases has a high positive predictive value, only SABs for which clinical care is obtained are identifiable. Therefore, earlier SABs may not be captured by investigators. Studying both early and late SABs is critical for identifying modifiable risk factors of SAB and for elucidating potential modes of action [10]. This study evaluated maternal asthma and asthma severity in relation to SAB incidence within a North American preconception cohort study. Using a prospective design and regular follow-up of participants, we identified early SABs, considered gestational age at loss, and adjusted for a wide range of potential confounders.

Material and Methods

Pregnancy Study Online (PRESTO) is an ongoing prospective cohort study of pregnancy planners (2013–2020) [11,12]. Eligible female participants were aged 21–45 years, residing in the US or Canada, not using fertility treatment, and attempting to conceive. Questionnaires were administered at baseline and every 8 weeks for up to 12 months or until pregnancy, cessation of pregnancy attempt, loss to follow-up, or study withdrawal. Participants who conceived were invited to complete an early pregnancy questionnaire at a median of 9 weeks (interquartile range (IQR): 6–11 weeks) after the date of last menstrual period, and a late pregnancy questionnaire at a median of 32 weeks after the last menstrual period (IQR: 32–34 weeks). This analysis was conducted among participants who reported pregnancy during follow-up (N=6,325). The Boston University Medical Campus Institutional Review Board approved the study protocol. All participants provided online informed consent.

Assessment of Asthma

At baseline, participants reported whether they had ever been diagnosed with asthma and, if so, the year of first diagnosis. On baseline and follow-up questionnaires, participants who had ever received an asthma diagnosis reported whether they had used asthma medication in the last four weeks, and the names of their asthma medication in up to two open-text boxes. Participants could also list medications taken for other indications, and some individuals reported asthma medications in this section.

We classified asthma severity based on medication use according to the Global Initiative for Asthma guidelines, which detail five steps of asthma severity based on controller medications [13]. Preconception asthma severity was classified using data collected from the follow-up questionnaire that was completed most recently before pregnancy. The median time from completion to conception (last menstrual period+14 days) was 28 days (interquartile range (IQR): 11–49). Severity was categorized as level 0 (asthma diagnosis without medication use); level 1 (only short-acting β-agonists); level 2 (inhaled corticosteroids or leukotriene receptor antagonists); or level 3 (inhaled corticosteroids in combination with long-acting β-agonists).

Assessment of Spontaneous Abortion

On follow-up questionnaires, participants reported the date of their last menstrual period, whether they were currently pregnant, and whether they had had a “miscarriage (including chemical pregnancy)” since completing the last questionnaire. Participants who were currently pregnant were directed to the early pregnancy questionnaire. Here, participants reported whether they had a SAB since their last follow-up, the due date of their current pregnancy, and the date of their first positive pregnancy test. SABs occurring after the early pregnancy questionnaire were identified on the late pregnancy questionnaire. Participants who reported a SAB were asked how many weeks the pregnancy lasted and on what date the pregnancy ended. We attempted to collect information on participants who were lost to follow-up by contacting them via email or phone, by linking them to birth registries in selected states (CA, FL, MA, MI, OH, PA, TX, NY), and by searching for baby registries and birth announcements online.

Among participants for whom self-reported gestational age in completed weeks at SAB was missing, we estimated gestational age at loss as follows: (pregnancy end date – (pregnancy due date – 280 days))/7 [14]. Among women who reported neither gestational age at SAB nor a pregnancy due date, we estimated gestational age at loss as: (pregnancy end date – last menstrual period date)/7.

Covariates

At baseline, participants reported their age, height, weight, race, ethnicity, smoking history, education, household income, and region of residence; number of primary care physician visits in the past year; type of health insurance; parity; and history of physician-diagnosed endometriosis, uterine leiomyomata, polycystic ovarian syndrome, depression, anxiety, and hay fever. Information was also collected on physical activity; consumption of alcohol, caffeine, and sugar sweetened beverages; and use of multivitamins and folate supplements. On follow-up questionnaires, we updated information on select covariates including age; body mass index (BMI); physical activity; intake of caffeine, alcohol, and sugar sweetened beverages; and use of multivitamins and folate supplements.

Statistical analysis

SAB was compared between women with and without a history of asthma, and between women with each level of asthma severity versus those with no history of asthma. We combined severity levels 2 and 3 for analysis because only 61 participants (14 SABs) had level 3 severity. Cox models were fit using gestational age as the time scale to estimate hazard ratios (HRs) for SAB and their 95% confidence intervals (CIs). Participants entered the risk set on the date of their first positive pregnancy test, or, if those data were not available, at 4 weeks of gestation (the median gestational age at first positive pregnancy test among all women with available data). Participants were censored if/when they had a termination (n=25) or were lost to follow-up (n=762), or at 20 weeks' gestation. We used the Andersen-Gill data structure to account for potential bias due to left truncation [15,16].

Potential confounders were selected *a priori* based on a directed acyclic graph (Supplemental Figure 1) and a literature review. Models were adjusted for maternal age (<25, 25–29, 30–34, ≥35 years); BMI (<25, 25–29, ≥30 kg/m^2); race/ethnicity (white and non-Hispanic versus non-white and/or Hispanic); current smoking (yes versus no); education (≤12, 13–15, 16, ≥17 years); household income (< versus ≥$50,000 USD per year); region of residence (Northeast, South, Midwest, or West in the US; Canada); number of primary care visits in the past year; type of health insurance (private versus other (*e.g.* out-of-pocket payments or Medicaid)); physical activity (MET-hours/week); alcohol intake (drinks/week); caffeine intake (mg/day); sugar-sweetened beverage intake (drinks/week); daily use of multivitamins or folic acid supplements (yes versus no); parity (parous versus nulliparous); physician-diagnosed endometriosis (yes versus no), uterine leiomyomata (yes versus no), diabetes (yes versus no), polycystic ovarian syndrome (yes versus no), depression or anxiety (yes versus no), and allergic rhinitis (yes versus no). We calculated BMI as weight (kg) divided by height squared (m^2), and total metabolic equivalents of task of physical activity using the Compendium of Physical Activities [17]. We stratified our analyses by timing of gestation (<8 vs. ≥8 weeks' gestation) because later losses are less likely to be attributable to chromosomal abnormalities [10]. In addition to its clinical relevance, this analysis also addresses the proportional hazards assumption by assessing the extent to which the HR changes over time. We also evaluated potential effect modification by history of SAB (yes versus no), maternal age (<30 versus ≥ 30 years), BMI (<25 versus ≥ 25 kg/m^2), and age at asthma diagnosis (<18 versus ≥ 18 years). We then excluded women with pregnancies conceived using fertility treatment, as the etiology of SAB might differ among these women. Finally, we conducted an analysis that evaluated medication type. For this analysis, we fit separate models for each medication type: short-acting β-agonists, inhaled corticosteroids, inhaled corticosteroids in combination with long-acting β-agonists, and leukotriene receptor antagonists. For each medication exposure, we adjusted for the same covariates as the primary analysis and fit models additionally adjusted for asthma status.

We multiply-imputed missing values for covariates and gestational age at SAB using the fully conditional specification method. Missingness ranged from 0.03% (caffeine consumption) to 2.8% (income) for all covariates except health insurance, which was imputed for 48.3% of participants (we added this variable to questionnaires in 2018). Gestational age at SAB was imputed for 5% of participants. Date of first positive pregnancy test was missing for 54% of participants because we added this variable to questionnaires in 2018. All analyses were performed using SAS statistical software (version 9.4, SAS Institute).

Results

Among 6,325 participants included in this analysis, 1,069 (16.9%) reported having ever been diagnosed with asthma at baseline and 1,208 (19.1%) experienced an incident SAB. On average, participants reported their first positive pregnancy test at 4.0 weeks' gestation (IQR: 3.7–4.4 weeks). Compared with participants without a history of asthma, those with asthma reported greater healthcare utilization and comorbidities (Table 1). Participants with more severe asthma reported a greater number of primary care visits in the past year and were more likely to report histories of SAB, subfertility or infertility, and polycystic ovarian syndrome.

61.8% of women with asthma were categorized as having level 0 severity (*i.e.*, they reported using no asthma medications in past four weeks), while 21.7%, 10.8%, and 5.7% were categorized as having levels 1, 2, and 3, respectively. From baseline to conception, most women (81.0%) had no change in severity. Women with severity level 1 at baseline were slightly more likely to have worsened severity (23.2%) than improved severity (15.9%) at the follow-up most recent to conception, but women with severity level 2 at baseline were equally likely to have worsened (5.7%) or improved (5.7%) severity during follow-up.

There was no association between history of asthma and increased SAB incidence (HR=0.98; 95% CI: 0.84, 1.14) (Table 2). Relative to no history of asthma, level 0 asthma was associated with lower SAB incidence (HR=0.82; 95% CI: 0.67, 1.01) but more severe asthma was associated with higher SAB incidence (level 1: HR=1.20; 95% CI: 0.91, 1.60) (levels 2–3: HR=1.31; 95% CI: 0.97, 1.78). When restricting the analysis to women with asthma, compared with women with level 0 asthma, the HR for severity level 1 was 1.44 (95% CI: 1.02, 2.03) and the HR for severity levels 2–3 was 1.62 (95% CI: 1.12, 2.33).

SABs occurred at a median of 6 weeks' gestation (IQR: 5–9 weeks). The percentage of SABs occurring before 8 weeks' gestation was similar for women with asthma (69.2%) and without asthma (64.7%), and across severity levels (0: 69.2%, 1: 67.3%, 2–3: 71.1%). HRs for the association between asthma, its severity, and SAB were generally consistent with the main analyses during <8 weeks' gestation (Table 3). Our results for ≥8 weeks' gestation were not consistent with a clear pattern and were based on small numbers of events. There was little evidence of effect modification by history of SAB, maternal age, BMI, or age at first asthma diagnosis (Table 3).

Among 5,880 participants who conceived without fertility treatment, there was no appreciable association between asthma history and SAB (HR=0.98; 95% CI: 0.84, 1.15) (Table 2). The HRs comparing levels 0, 1, and 2–3 with no history of asthma were 0.84 (95% CI: 0.68, 1.04), 1.10 (95% CI: 0.81, 1.49), and 1.39 (95% CI: 1.02, 1.89), respectively. In models evaluating medication type, use of short-acting β-agonists (HR=1.42; 95% CI: 1.06, 1.89) and use of inhaled corticosteroids (HR=1.32; 95% CI: 0.94, 1.87) were associated with greater SAB incidence (Supplemental Table 1). Use of inhaled corticosteroids in combination with long-acting β-agonists was associated with a slightly increased SAB incidence. There was no appreciable association for use of leukotriene receptor antagonists.

Discussion

In this prospective cohort study of couples trying to conceive, we evaluated associations between physician-diagnosed asthma, its severity, and SAB. We observed no appreciable association between history of asthma and SAB. However, women with severe asthma, based on preconception medication use, had a greater incidence of SAB compared with women who had never been diagnosed with asthma.

Previous studies of the relationship between maternal asthma and risk of SAB have been conducted primarily using administrative databases. In a study of 281,019 pregnancies in the United Kingdom, having asthma was associated with 10% higher odds of SAB [18]. Relative to women without asthma, having severe or uncontrolled asthma was associated 1.24 and 1.28 times the odds of SAB, respectively [18]. A study of 49,438 pregnancies in Québec evaluated asthma diagnosis, severity, and control in the year before SAB or the 20th week of gestation [8]. In the Québec study population, women with asthma had 1.41 times the odds of SAB compared with women without asthma. Among women with asthma, severity was not associated with SAB, but having uncontrolled symptoms was associated with 26% higher odds of SAB. Most recently, a study of over 4 million pregnancies in two US healthcare claims databases reported no appreciable association between asthma diagnosis, severity, or control and risk of SAB [9].

These studies had limitations. Administrative databases can only identify pregnancies for which medical care was sought, and women are less likely to seek clinical care for early SABs compared with later SABs. For example, in a Danish study comparing SAB reported in a population-based prospective cohort study with SAB recorded in the Hospital Discharge Register, reliance on the Hospital Discharge Register missed up to 30% of SABs [19]. In addition, women with asthma may be more likely to seek care for SAB since they are already under care for asthma, which would create a spurious association. It is also challenging to estimate gestational age at SAB in administrative databases. In the US study, for example, investigators assigned 90 days' gestation to all SABs [9]. A strength of the present study is its use of self-reported pregnancy and SAB. In PRESTO, participants report any recognized SABs and their timing regardless of whether the participant sought clinical care. Given that we studied a population of pregnancy planners who frequently use at-home pregnancy tests (nearly 100% of participants reported using at-home pregnancy tests), we ascertained SABs that occurred as early as 3 weeks' gestation. Administrative databases also tend to have limited data on potential confounders, especially lifestyle factors. In contrast, we adjusted for several potential confounders using self-reported data on demographic factors, lifestyle characteristics, and medical and reproductive history.

In contrast with previous studies, we observed that participants with asthma severity level 0 had a lower rate of SAB compared with those who had no history of asthma. The unadjusted risks of SAB were 15.7% and 19.2% in the two groups, respectively, indicating a small absolute difference. The mechanism by which mild asthma severity might reduce incidence of SAB is unclear. While some women in this group may have had pediatric asthma that resolved, results were similar among women diagnosed in adulthood and those diagnosed in childhood. The unexpected association may also reflect some residual confounding by health-seeking behavior or environmental factors such as air pollution or allergens. This finding could also be due to chance.

The association between asthma severity and SAB could be driven by underlying immunologic pathways. Inflammation plays an important role in the development and maintenance of pregnancy [20], and chronic airway inflammation is a central component of asthma – an otherwise heterogeneous condition [13,21]. Dysregulation of inflammatory homeostasis among asthmatic women may influence risk of SAB. It has also been hypothesized that asthma and preterm birth share a common etiology leading to hyperreactivity of the bronchial airways and hypercontractility of the uterine smooth muscle [22,23]. This shared mechanism could affect SAB. Alternatively, these associations may be attributable to use of asthma medications. Results from our analysis of medication type indicate an increased rate of SAB associated with recent use of short-acting β-agonists or inhaled corticosteroids. However, these findings could be due to confounding by indication (i.e., underlying disease severity and symptom control). Guidelines issued by the American College of Obstetricians and Gynecologists conclude that the risks of uncontrolled asthma outweigh any potential harms of treatment, and that women should continue using their asthma medications throughout pregnancy to optimize symptom control and ensure optimal oxygen flow to fetus [24].

In this study, we could not evaluate symptom control, which made it impossible to separate the effects of medication from symptoms. The observed association between asthma severity and SAB could be confounded by symptoms, as asthma exacerbations may reduce oxygen flow to the embryo or fetus. Hypoxia during exacerbations represents a possible mechanism by which asthma increases risk of SAB [8,25], and women with more severe asthma are more likely to have exacerbations during pregnancy [26]. Future research might consider symptom control in the context of a preconception cohort with comprehensive ascertainment of early SAB. Study limitations include potential misclassification of asthma diagnosis and severity. Notably, 17% of study participants reported a history of asthma diagnosis, which is higher than the percentage of adult US women who reported currently living with asthma in 2018 (10%) [1]. We may have observed a high proportion with a history of asthma if some participants were diagnosed during childhood but outgrew their symptoms since then. However, results were similar between women diagnosed in childhood versus adulthood. Misclassification of asthma severity may have arisen because we did not collect data on medication dosage. However, we implemented broad categories for analysis (*i.e.*, asthma diagnosis without medication use; short-acting β-agonists only; inhaled corticosteroids, inhaled corticosteroids in combination with long-acting β-agonists, and/or leukotriene receptor antagonists), which reduces potential misclassification. Moreover, there was some variability in the length of time between exposure ascertainment and conception (median = 28 days; IQR: 11–49 days), which may have introduced misclassification of preconception asthma severity. However, we would expect any bias to be minimal, as most women had little change in asthma severity during follow-up. Misclassification of medication use is also possible: self-report might underestimate exposure due to imperfect recall or unwillingness to report. However, we expect high accuracy of self-report in this population because we collect data on medication use only in the last four weeks. In addition, we cannot rule out the possibility of residual confounding. Unmeasured characteristics such as exposure to air pollution, seasonal variation in asthma severity (e.g., due to allergies), or infection may have biased our effect estimates. Lastly, the findings of this study may not be generalizable to all reproductive-aged women. Our study population primarily includes women with a male partner who were planning a pregnancy, and who volunteered for and enrolled in the study through the internet. PRESTO participants report higher socioeconomic status on average compared with the general population. While we expect the biological mechanisms of the studied relationships to be consistent across reproductive-aged women, these results should be confirmed in other populations.

Conclusions

Asthma diagnosis itself was not associated with SAB, but greater asthma severity based on preconception medication use was associated with a higher incidence of SAB. However, we were unable to clarify whether the observed association was attributable to disease symptoms or the medications used to treat asthma. Given the existing evidence, consistent with recommendations from the American College of Obstetricians and Gynecologists, women with asthma who are planning a pregnancy should prioritize control of their symptoms [2,24].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations and acronyms,

BMI	body mass index
CI	confidence interval
HR	hazard ratio
IQR	interquartile range
kg	kilograms (kg)
m^2	$meters^2$
mg	milligrams
PRESTO	Pregnancy Study Online
RR	risk ratio
SAB	spontaneous abortion
US	United States

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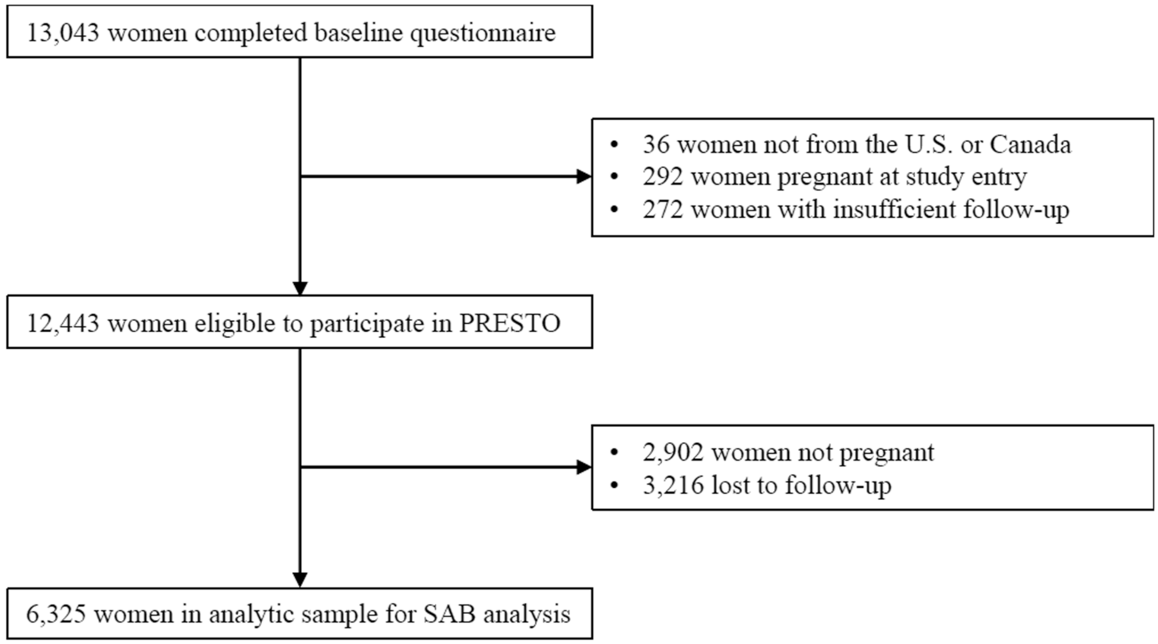

Figure 1.

PRESTO enrollment and eligibility criteria for analyses of spontaneous abortion, 2013–2020

Table 1.

Baseline characteristics of 6,325 PRESTO participants according to history of physician-diagnosed asthma (2013–2020)

	Never diagnosed with asthma	Ever diagnosed with asthma	*Asthma severity*			
			Severity Level 0	Severity Level 1	Severity Level 2	Severity Level 3
Number of Participants, N (%)	5,256 (83.1)	1,069 (16.9)	661 (10.5)	232 (3.7)	115 (1.8)	61 (1.0)
Gestational age at pregnancy recognition (weeks), mean (SD)[1]	4.2 (0.8)	4.3 (1.3)	4.3 (1.4)	4.3 (0.9)	4.3 (1.3)	3.9 (0.6)
Age (years), mean (SD)	30.0 (3.8)	29.6 (3.8)	29.5 (3.8)	29.5 (4.0)	30.0 (3.5)	30.9 (3.8)
Age at asthma diagnosis (years), mean (SD)	-	12.4 (8.2)	11.7 (7.4)	13.5 (9.0)	14.5 (10.2)	11.1 (8.7)
BMI (kg/m^2), mean (SD)	26.6 (6.6)	28.1 (7.1)	27.8 (7.2)	28.8 (7.1)	27.5 (6.5)	29.5 (6.4)
Race/ethnicity, %						
White, non-Hispanic	86.4	87.1	85.7	87.3	94.2	84.9
White, Hispanic	5.8	5.9	6.7	5.7	2.4	3.3
Black, non-Hispanic	2.2	2.1	2.4	2.2	0.0	3.6
Asian, non-Hispanic	1.9	1.3	1.4	1.4	0.0	1.4
Multiracial/other race	3.7	3.7	3.8	3.4	3.4	6.9
Current smoker, %	7.5	7.4	6.1	11.7	7.2	3.6
Education ≥ college degree, %	78.7	76.0	78.3	68.7	75.9	75.7
Annual household income < 50,000 USD, %	14.9	17.9	16.3	22.0	15.8	20.1
Region of residence, %						
Northeast	23.4	26.4	26.8	28.2	23.5	17.5
South	22.8	20.4	19.5	18.6	23.8	27.1
Midwest	22.3	23.3	21.4	25.8	28.5	23.1
West	15.8	14.9	16.8	12.5	14.4	10.5
Canada	15.7	14.9	15.5	14.9	9.9	21.8
Number of primary care visits in past year, %						
0	12.5	9.9	11.5	9.1	6.0	2.7
1 to 3	73.8	70.7	71.1	68.8	74.1	66.8
≥4	13.6	19.5	17.4	22.0	19.9	30.5
Private health insurance (among US residents only), %	93.0	92.2	93.2	88.2	94.5	93.1

	Never diagnosed with asthma	Ever diagnosed with asthma	*Asthma severity*			
			Severity Level 0	Severity Level 1	Severity Level 2	Severity Level 3
Physical activity (total MET-hrs/wk), mean (SD)	34.9 (25.1)	36.7 (25.3)	36.7 (25.7)	35.5 (24.4)	37.4 (23.4)	38.7 (27.6)
Alcoholic beverages (drinks/week), mean (SD)	3.1 (4.4)	3.1 (4.0)	2.9 (3.6)	3.3 (3.7)	3.7 (6.0)	3.3 (4.9)
Caffeine (mg/day), mean (SD)	120.8 (112.5)	125.3 (121.8)	124.3 (128.0)	123.6 (106.2)	143.9 (115.6)	118.5 (119.1)
Sugar sweetened beverages (drinks/week), mean (SD)	1.1 (3.2)	1.4 (3.2)	1.3 (3.0)	1.6 (3.8)	1.0 (2.5)	1.5 (3.5)
Daily use of multivitamins/folic acid, %	84.2	84.7	83.3	85.0	91.8	85.6
Reproductive characteristics and comorbidities, %						
Total number of menstrual cycles tried to conceive, median	5	5	5	5	6	7
Parous	32.7	32.6	35.4	29.8	26.7	26.6
History of SAB	24.8	25.6	26.0	26.2	17.9	37.4
History of subfertility or infertility[1]	13.1	14.7	14.8	16.1	9.1	19.5
Physician-diagnosed medical conditions:						
Endometriosis	2.3	4.7	4.2	6.6	5.1	5.5
Uterine leiomyomata	2.0	2.6	3.1	1.5	2.8	2.2
Polycystic ovarian syndrome	5.4	8.7	8.7	8.0	8.7	14.1
Diabetes	0.9	1.8	1.2	3.5	2.6	0.0
Depression	22.5	30.8	29.7	34.8	29.8	27.7
Anxiety	22.6	33.1	31.3	35.7	36.5	34.9
Allergic rhinitis	7.0	20.4	16.4	26.5	28.9	23.9

Abbreviations: BMI=body mass index; SAB=spontaneous abortion; SD=standard deviation; USD=United States dollar

Note: All characteristics, except age, are age-standardized at baseline.

[1] Among women with non-missing data for this variable.

Table 2.

Associations between asthma diagnosis, its severity, and spontaneous abortion, among 6,325 PRESTO participants (2013–2020)

Asthma Status[1]	No. Participants	No. Spontaneous Abortions (%)	HR[2]	95% CI	HR[3]	95% CI
Never diagnosed with asthma	5,256	1,007 (19.2)	*ref*	-	*ref*	-
Ever diagnosed with asthma	1,069	201 (18.8)	1.00	0.86–1.17	0.98	0.84–1.14
Severity[4]						
Level 0	661	104 (15.7)	0.83	0.68–1.02	0.82	0.67–1.01
Level 1	232	52 (22.4)	1.23	0.93–1.62	1.20	0.91–1.60
Levels 2–3	176	45 (25.6)	1.36	1.01–1.84	1.31	0.97–1.78
Associations among participants who conceived without fertility treatment (N=5,880)						
Never diagnosed with asthma	4,889	946 (19.4)	*Ref*	-	*ref*	-
Ever diagnosed with asthma	991	190 (19.2)	1.02	0.87–1.19	0.98	0.84–1.15
Severity[4]						
Level 0	612	100 (16.3)	0.86	0.70–1.05	0.84	0.68–1.04
Level 1	218	46 (21.1)	1.15	0.85–1.55	1.10	0.81–1.49
Levels 2–3	161	44 (27.3)	1.47	1.09–1.99	1.39	1.02–1.89

Abbreviations: HR=hazard ratio, 95% CI= 95% Confidence Interval, SAB=spontaneous abortion.

[1]Hazard Ratios and 95% CIs were estimated using Cox models with gestational weeks as the time scale. We used the exact option to account for tied event times. Women with no history of asthma diagnosis were used as the reference group for all analyses, but separate models were fit to evaluate 1) diagnosis and 2) severity.

[2]Adjusted for maternal age at conception.

[3]Adjusted for age, body mass index, race/ethnicity, current smoking, education, income, type of health insurance, region, number of primary care visits in the past year, physical activity, alcohol intake, caffeine intake, sugar sweetened beverage intake, use of multivitamins or folic acid supplements, parity, endometriosis, uterine leiomyomata, diabetes, polycystic ovarian syndrome, depression/anxiety, and allergic rhinitis.

[4]Severity was based on self-reported medication use, according to stepwise treatment guidelines: Level 0 (asthma diagnosis without medication use); Level 1 (only short-acting β-agonists); Level 2 (inhaled corticosteroids or leukotriene receptor antagonists); Level 3 (inhaled corticosteroids in combination with long-acting β-agonists).

Table 3.

Stratified associations between asthma diagnosis, its severity, and spontaneous abortion, among 6,325 PRESTO participants (2013–2020)

Asthma Status[1]	No. Participants	No. SAB (%)	Adjusted HR[2]	95% CI	No. Participants	No. SAB (%)	Adjusted HR[2]	95% CI
	Gestation < 8 weeks'[4]				**Gestation ≥ 8 weeks'[5]**			
No Asthma	5,243	651 (12.4)	*ref*	-	4,301	356 (8.3)	*ref*	-
Asthma	1,066	139 (13.0)	1.05	0.87–1.27	869	62 (7.1)	0.86	0.65–1.13
Severity[3]								
Level 0	659	72 (10.9)	0.88	0.68–1.13	549	32 (5.8)	0.72	0.50–1.04
Level 1	232	35 (15.1)	1.24	0.87–1.75	186	17 (9.1)	1.15	0.70–1.90
Level 2–3	175	32 (18.3)	1.46	1.02–2.10	134	13 (9.7)	1.04	0.58–1.86
	No History of SAB				**History of SAB**			
No Asthma	3,953	705 (17.8)	*ref*	-	1,303	302 (23.2)	*ref*	-
Asthma	799	136 (17.0)	0.95	0.79–1.15	270	65 (24.1)	1.03	0.78–1.37
Severity[3]								
Level 0	493	69 (14.0)	0.79	0.61–1.01	168	35 (20.8)	0.89	0.62–1.27
Level 1	172	34 (19.8)	1.14	0.80–1.61	60	18 (30.0)	1.37	0.84–2.25
Level 2–3	134	33 (24.6)	1.36	0.95–1.94	42	12 (28.6)	1.20	0.65–2.20
	Age < 30				**Age ≥ 30**			
No Asthma	2,443	396 (16.2)	*ref*	-	2,813	611 (21.7)	*ref*	-
Asthma	543	95 (17.5)	1.07	0.85–1.35	526	106 (20.2)	0.89	0.72–1.11
Severity[3]								
Level 0	345	54 (15.7)	0.95	0.71–1.27	316	50 (15.8)	0.70	0.52–0.93
Level 1	123	25 (20.3)	1.27	0.84–1.91	109	27 (24.8)	1.16	0.78–1.72
Level 2–3	75	16 (21.3)	1.34	0.81–2.24	101	29 (28.7)	1.28	0.88–1.88
	BMI < 25 kg/m²				**BMI ≥ 25 kg/m²**			
No Asthma	2,727	497 (18.2)	*ref*	-	2,529	510 (20.2)	*ref*	-
Asthma	436	71 (16.3)	0.89	0.69–1.14	633	130 (20.5)	1.03	0.85–1.26
Severity[3]								
Level 0	285	37 (13.0)	0.70	0.50–0.98	376	67 (17.8)	0.89	0.69–1.16

Asthma Status[1]	No. Participants	No. SAB (%)	Adjusted HR[2]	95% CI	No. Participants	No. SAB (%)	Adjusted HR[2]	95% CI
Level 1	80	13 (16.3)	0.88	0.51–1.54	152	39 (25.7)	1.36	0.97–1.91
Level 2–3	71	21 (29.6)	1.72	1.09–2.70	105	24 (22.9)	1.10	0.73–1.67
	Age at first diagnosis < 18 years[6]				**Age at first diagnosis ≥ 18 years**			
No Asthma	5,256	1,007 (19.2)	*ref*	-	5,256	1,007 (19.2)	*ref*	-
Asthma	607	112 (18.5)	0.97	0.80–1.19	462	89 (19.3)	0.99	0.79–1.23
Severity[3]								
Level 0	391	60 (15.4)	0.80	0.61–1.04	270	44 (16.3)	0.85	0.62–1.15
Level 1	119	27 (22.7)	1.28	0.87–1.88	113	25 (22.1)	1.15	0.77–1.72
Level 2–3	97	25 (25.8)	1.37	0.91–2.05	79	20 (25.3)	1.25	0.79–1.95

Abbreviations: HR=hazard ratio, 95% CI= 95% Confidence Interval, SAB=spontaneous abortion, BMI=body mass index.

[1] HRs and 95% CIs were estimated using Cox models with gestational weeks as the time scale. We used the exact option to account for tied event times. Women with no history of asthma diagnosis were used as the reference group for all analyses, but separate models were fit to evaluate 1) diagnosis and 2) severity. Stratified models for age were adjusted for a continuous age variable and stratified models for BMI were adjusted for a continuous BMI variable.

[2] Adjusted for age, body mass index, race/ethnicity, current smoking, education, income, type of health insurance, region, number of primary care visits in the past year, physical activity, alcohol intake, caffeine intake, sugar sweetened beverage intake, use of multivitamins or folic acid supplements, parity, endometriosis, uterine leiomyomata, diabetes, polycystic ovarian syndrome, depression/anxiety, and allergic rhinitis.

[3] Severity was based on self-reported medication use, according to stepwise treatment guidelines: Level 0 (asthma diagnosis without medication use); Level 1 (only short-acting β-agonists); Level 2 (inhaled corticosteroids or leukotriene receptor antagonists); Level 3 (inhaled corticosteroids in combination with long-acting β-agonists).

[4] For the analysis of < 8 weeks' gestation, women who carried a pregnancy past this point were censored at 8 weeks. Women who entered the risk set at ≥ 8 weeks were excluded.

[5] For the analysis of ≥ 8 weeks' gestation, participants entered the risk set at 8 weeks' gestation (earliest), and those with a SAB before that were excluded.

[6] In analyses for "age at first diagnosis < 18 years," we excluded women who reported a first diagnosis at ≥ 18 years of age. In analyses for "age at first diagnosis ≥ 18 years," we excluded women who reported a first diagnosis at < 18 years of age.