Asthma During Pregnancy and Clinical Outcomes in Offspring: A National Cohort Study

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**ABBREVIATIONS**

- CI—confidence interval
- DNBC—Danish National Birth Cohort
- HPA—hypothalamic-pituitary-adrenal
- HR—hazard ratio
- ICD-10—International Classification of Diseases, 10th Revision

Dr Tegethoff conceptualized and designed the study, carried out the statistical analyses, interpreted data, drafted the initial manuscript, critically reviewed the manuscript, and obtained funding; Dr Olsen acquired data, interpreted data, critically reviewed the manuscript, and obtained funding; Mr Schaffner carried out the statistical analyses, interpreted data, and critically reviewed the manuscript; Dr Meinlschmidt conceptualized and designed the study, carried out the statistical analyses, interpreted data, critically reviewed the manuscript, and obtained funding; and all authors approved the final manuscript as submitted.

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**WHAT’S KNOWN ON THIS SUBJECT:** Asthma is a common medical complication during pregnancy that is associated with an increased risk of adverse obstetric outcomes.

**WHAT THIS STUDY ADDS:** This study adds knowledge on potential long-term consequences of maternal asthma during pregnancy for offspring health, demonstrating that maternal asthma during pregnancy is linked to a wide spectrum of offspring diseases during childhood.

**BACKGROUND AND OBJECTIVE:** Maternal asthma is a common pregnancy complication, with adverse short-term effects for the offspring. The objective was to determine whether asthma during pregnancy is a risk factor of offspring diseases.

**METHODS:** We studied pregnant women from the Danish National Birth Cohort (births: 1996–2002; prospective data) giving birth to live singletons (n = 66 712 mother-child pairs), with 4145 (6.2%) women suffering from asthma during pregnancy. We estimated the associations between asthma during pregnancy and offspring diseases (International Classification of Diseases, 10th Revision diagnoses from national registries), controlling for potential confounders and validating findings by secondary analyses.

**RESULTS:** Offspring median age at end of follow-up was 6.2 (3.6–8.9) years. Asthma was associated with an increased offspring risk of infectious and parasitic diseases (hazard ratio [HR] 1.34; 95% confidence interval [CI] 1.23–1.46), diseases of the nervous system (HR 1.43; CI 1.18–1.73), ear (HR 1.33; CI 1.19–1.48), respiratory system (HR 1.43; CI 1.34–1.52), and skin (HR 1.39; CI 1.20–1.60), and potentially (not confirmed in secondary analyses) of endocrine and metabolic disorders (HR 1.26; CI 1.02–1.55), diseases of the digestive system (HR 1.17; CI 1.04–1.32), and malformations (odds ratio 1.13; CI 1.01–1.26), but not of neoplasms, mental disorders, or diseases of the blood and immune system, circulatory system, musculoskeletal system, and genitourinary system.

**CONCLUSIONS:** To the best of our knowledge, this is the first comprehensive study of the associations between asthma during pregnancy and a wide spectrum of offspring diseases. In line with previous data on selected outcomes, asthma during pregnancy may be a risk factor for numerous offspring diseases, suggesting that careful monitoring of women with asthma during pregnancy and their offspring is important. Pediatrics 2013;132:1–9
Asthma is a frequently occurring medical condition in pregnancy, affecting up to 8% of all pregnant women and women of childbearing age. A recent meta-analysis, including 40 publications from cohort studies, showed that maternal asthma was associated with an increased risk of low birth weight, small for gestational age, preterm delivery, and preeclampsia. Moreover, in a cohort including >40,000 pregnancies, maternal asthma during pregnancy was related to an increased risk of any congenital malformation in pregnancy was related to an increased risk of any congenital malformation in the offspring, and, specifically, to an increased risk of malformations of the nervous system, respiratory system, and digestive system. Maternal asthma during pregnancy was also shown to play a role in cardiac malformations in the offspring. However, the focus of these previous studies was on short-term adverse outcomes in the offspring, whereas long-term effects of maternal asthma on child health remain largely unknown. First studies on a narrow range of selected diseases suggest that maternal asthma during pregnancy is associated with an increased risk of asthma, bronchiolitis, atopic dermatitis, and autism spectrum disorder in the offspring during childhood, which is in line with animal models documenting intrauterine susceptibility to hypoxia-induced damage. These findings, together with the high prevalence of maternal asthma during pregnancy, make it important to further put a focus on follow-up time extended beyond the perinatal period and to cover a larger spectrum of offspring diseases.

The purpose of this study was to assess the associations between asthma during pregnancy and the offspring's risk of a wide range of diseases, categorized according to major chapters of the International Classification of Diseases, 10th Revision (ICD-10), during early childhood.

METHODS

Study Cohort

Briefly, this study is based on prospectively collected data from the Danish National Birth Cohort (DNBC), including births between 1996 and 2002. The Danish National Committee for Biomedical Research Ethics, Copenhagen, approved the study on behalf of all committees in the country. All participants gave written informed consent. Women were included when they had their first pregnancy visit between 6 and 12 weeks' gestation. Approximately 50% of all general practitioners in the country took part in the recruitment, and 60% of the invited women participated, so that finally 101,042 women could be enrolled in the DNBC. Computer-assisted interviews with mothers were performed repeatedly during and after pregnancy. Through linkage to medical registries, information on offspring diseases was continuously recorded. We considered as eligible all pregnancies in the DNBC with live singleton births. We excluded multiple births, as the intrauterine physiology underlying maternal-fetal transmission differs between multiples and singletons and multiple pregnancies have a significant risk of complications. Moreover, multiples themselves are a heterogeneous group, for example, regarding number of placentas and cygoty, reflecting heterogeneous maternal-fetal physiology, with poorer outcome in higher-order pregnancies. The well-established associations between intrauterine conditions and long-term health also may be different in multiples and singletons.

Asthma

Information on maternal asthma (“yes,” “no”) is based on computer-assisted interviews taken at ∼12 and 30 weeks' gestation and at 6 months postpartum. A mother was considered to have asthma during pregnancy if self-reported asthma of any type had occurred at any time during the current pregnancy, without further specification according to previously suggested asthma definitions. Women were asked if they had a lifetime history of asthma, if a doctor had diagnosed the asthma, and if they were suffering/had suffered from asthma during pregnancy. The agreement of case ascertainment by patient self-report and physician diagnosis has been shown to be high (κ: 0.83), and additional analysis of the study cohort revealed that 95.85% of women reporting lifetime asthma had received this diagnosis by a doctor.

Child Diseases

We obtained information on children’s diseases from the Danish National Hospital Register containing information on all inpatients and outpatients in Danish hospitals. The validity of the diagnoses in the registry has been studied for several diseases (e.g., epilepsy, asthma, and febrile seizures, with positive predictive values of 81%, 85%, and 93%, respectively). Diagnoses, based on the Danish version of the ICD-10, were classified into dichotomous diagnostic categories according to chapters 1 to 17 of the ICD-10. In addition, we used as outcome a dichotomous overall category (“any disease”), indicating whether any disease of any diagnostic category was present (see also refs 26 and 27).

Statistical Analyses

To estimate the associations between asthma during pregnancy and the offspring’s risk of disease, we conducted separate Cox proportional hazards regression models for each of the diagnostic categories 1 to 14 and “any disease.” In each regression model, we used the first diagnosis in the category as outcome measure. Data on timing of competing events, such as deaths and emigration, were not available in this data source, but these events were few in Denmark. Data on all children
without a diagnosis were censored at the end of follow-up (December 31, 2006), meaning these cases were considered as having no diagnosis until then. Age in days was used as the time variable. We evaluated the proportional hazards assumption by visually checking Schoenfeld residuals and using the test of Grambsch and Therneau.30

We used separate logistic regression models to assess the associations between asthma during pregnancy and the risk of conditions originating in the perinatal period (diagnostic category 16) and congenital malformations (diagnostic category 17) in the offspring, as these conditions are present around birth, and reasons for latency until diagnosis are likely unrelated to asthma during pregnancy.

To obtain less confounded estimates, we adjusted the analyses for several potential predictors of child health that might confound or suppress effects, selected a priori, including socioeconomic status31 based on the mother’s occupation (see ref 32), parity,33 maternal age at delivery and maternal age,34 general maternal health,35 smoking during pregnancy, and infant gender,38,39 with the categories indicated in Table 1. We dealt with loss to follow-up in the covariates. For statistical analyses for those with missing information, we selected a priori, including socioeconomic status.

We evaluated the results after adjusting P values corresponding to the 17 main tests for multiple comparisons using the Bonferroni method. We interpreted with caution all results that were statistically significant in the main (adjusted) analyses but not stable after either Bonferroni correction or secondary analyses (for details, see online supplemental information). We dealt with loss to follow-up and missing data by restricting analyses to mother-child pairs with complete and unambiguous data on asthma status during pregnancy, and by including an extra category in the analyses for those with missing information in the covariates. For statistical analyses, we used Stata/SE software, version 11.2 (Stata Corp, College Station, TX).

## RESULTS

### Study Cohort Descriptives

Complete information on maternal asthma status and offspring diagnoses was available for 66 712 mother-child pairs (71.98% of all eligible mother-child pairs in the DNBC, Fig 1). Of these, 4145 (6.2%) reported having asthma during pregnancy, whereas 62 567 (93.8%) reported having no asthma during pregnancy. Table 1 presents the characteristics of the total study sample and according to maternal asthma during pregnancy. Most of the women were older than 27 years, had a medium to high socioeconomic status, and average to very good general health; slightly more than half of the women were multiparous, and approximately one-fourth of the women reported smoking. Maximum time of follow-up was 8.9 years, with median age of offspring at end of follow-up being 6.2 years (range: 3.6–8.9 years).

### Cox Proportional Hazards Models and Logistic Regression Analyses

The results of the adjusted Cox and logistic regression analyses are presented...
in Tables 2 and 3. Asthma during pregnancy was associated with a significantly increased offspring risk for the first disease diagnosis in 8 of 16 diagnostic categories, including infectious and parasitic diseases; endocrine and metabolic disorders; diseases of the nervous system, ear, respiratory system, digestive system, and skin; as well as malformations, and a significantly increased offspring risk of having any disease. When P values were Bonferroni-adjusted, asthma during pregnancy was no longer associated with the offspring’s risk for endocrine and metabolic diseases and diseases of the digestive system. Results of the secondary analyses are reported in the online supplemental information.

DISCUSSION
We report findings based on 66,712 mother-child pairs who were followed up from early pregnancy into childhood in a population-based cohort study. Maternal asthma, as compared with no maternal asthma, during pregnancy was related to an increased risk of a wide range of diseases in the offspring during childhood, including infectious and parasitic diseases; diseases of the nervous system, ear, respiratory system, and skin; and potentially to endocrine and metabolic disorders, diseases of the digestive system, and malformations. To the best of our knowledge, this is the first study covering a wide spectrum of diseases during childhood to suggest that maternal asthma during pregnancy may be a risk factor of a wide range of pediatric diseases. This corroborates the clinical relevance of asthma during pregnancy with regard to long-term consequences emerging beyond the perinatal period, thereby further emphasizing that careful medical and obstetric monitoring of the asthmatic pregnant woman and her developing fetus and child are highly warranted. Yet, it should be noted that effect sizes were rather small to moderate (all adjusted hazard ratios [HRs] ≤1.43), indicating that each additional step of obstetric care should be well considered and dosed, thereby balancing its benefits with potential risks that might be induced by unjustified overrating of the role of asthma during pregnancy.

FIGURE 1
Flowchart of study participants.
Hazard ratios (HR) for the offspring having an initial diagnosis within the respective diagnostic category (outcomes) according to maternal asthma during pregnancy (predictor) (n = 66,712). Information on the children’s diagnoses were obtained from the database-linked Danish National Hospital Register, which contains information on all diagnoses of inpatients and outpatients in Danish hospitals. In each diagnostic category, we used the initial diagnosis.

a Crude model presented in support of transparency.

b All models adjusted for general maternal health, infant gender, maternal age, parity, smoking during pregnancy, and socioeconomic status.

Our results are in line with previous human studies on short-term reproductive failures after asthma during pregnancy, which have shown associations of asthma during pregnancy with adverse obstetric outcomes and congenital malformation,4–6 and extend knowledge to an overview of potential long-term consequences. Indeed, previous studies on long-term consequences of asthma during pregnancy with regard to selected child diseases also demonstrated an increased risk of asthma, bronchiolitis, atopic dermatitis, and autism spectrum disorder, in offspring of mothers with asthma.7–11

If the observed associations between maternal asthma during pregnancy and offspring diseases are causal, there may be several potential underlying mechanisms explaining these links.42 First, low maternal oxygen supply is related to restricted fetal oxygenation, which has been associated with delays in the development of the nervous system,44 adverse neurodevelopmental outcomes,45 and impairment of vascular function46 in animals. Moreover, maternal asthma during pregnancy has been shown to result in dysfunction of bronchial relaxation in offspring rats via inhibition of epinephrine synthesis.47 Furthermore, maternal hypoxia has been shown to affect fetal growth, placental function, and length of gestation,48–50 and these birth outcomes have been linked with adverse health outcomes in numerous studies.51,52 Therefore, maternal hypoxia may, via restricted fetal oxygenation, result in multiple organ pathology that manifests in a wide range of offspring diseases. Second, cytokines play an important role in the inflammatory processes of the airways in asthma,53 and cytokine receptors are widely expressed in the human fetus from early gestation.54 Indeed, maternal exposure to cytokines during pregnancy was associated with adverse offspring outcome in rats,55 and the association between maternal infection during pregnancy and offspring deficits appears to be mediated by cytokines,56 even though the permeability of the placenta to cytokines remains unclear.57,58 Third, the hypothalamic-pituitary-adrenal (HPA) axis is another candidate mechanism linking maternal asthma during pregnancy with offspring diseases, as dysregulation of the HPA axis is a frequently observed feature of asthma59 and changes in intrauterine glucocorticoid exposure have been shown to take effect in the fetus.60 Fourth, one may speculate that asthma medication adversely affects the fetus. However, children of mothers with asthma taking asthma medication were at similar risk for diseases as children of mothers with asthma but without asthma medication, indicating that asthma medication does not play an important role in the offspring’s risk of diseases. Notably, the risk of neoplasms was even decreased in the offspring of mothers with asthma under medication. Moreover, there is considerable evidence mostly indicating that commonly used asthma medications, such as inhaled corticosteroids and inhaled short-acting β-agonists, do not increase the risk of adverse perinatal outcomes, even though high doses of inhaled corticosteroids have been associated with an increased prevalence of congenital malformations,61 but that
treatment with inhaled corticosteroids may actually be protective against outcomes such as low birth weight.\textsuperscript{42} Moreover, we recently reported reassuring data demonstrating that glucocorticoid inhalation during asthmatic pregnancy was not related to an increased risk of a wide range of offspring diseases during childhood, except for endocrine and metabolic disorders.\textsuperscript{27,62} This is in line with our here presented finding that the risk of endocrine and metabolic disorders was no longer significant when comparing offspring of mothers with asthma without medication and offspring of mothers without asthma, suggesting that endocrine and metabolic disorders are not a consequence of asthma per se.

The strengths of our study include the prospective data collection for a total of 66,712 mother-child pairs, linkage of a comprehensive medical registry with complete and medically verified diagnoses, accounting for bias by asthma medication and control for several potential confounders, even though residual or uncontrolled confounding cannot be excluded, including confounding by genetic factors\textsuperscript{63} or further specific comorbidities that have been observed in patients with asthma, including rhinitis, sinusitis, gastroesophageal reflux disease, obstructive sleep apnea, endocrine disorders, and mental disorders.\textsuperscript{35} Indeed, if conditions such as psychopathologies are present during pregnancy, the offspring is at increased risk of adverse health outcomes.\textsuperscript{64} However, comorbidities may well be mediators of the observed associations, meaning that, in this case, comorbidities are only triggered by asthma, and adjusting for mediators bears the risk of underestimation. The same is true for psychosocial factors during pregnancy that have been shown to be associated with a wide range of offspring diseases,\textsuperscript{26} and that may either trigger or be triggered by asthma.\textsuperscript{65}

Our findings have clinical and public health relevance, as asthma is a common serious medical problem to complicate pregnancy, with approximately up to 8% of pregnant women affected.\textsuperscript{3} Ongoing follow-up of children in the DNBC enables further research at later stages.

The rather low participation rate encountered in the DNBC\textsuperscript{13} was partly caused by a lack of participation by family doctors and partly by pregnant women who declined the invitation.\textsuperscript{66} Comparing data from DNBC participants with data from the source population based on all births in 2 well-defined geographical areas in Denmark, independent of the DNBC, revealed some sociodemographic and health-related differences between both groups, including among others in DNBC participants a modest overrepresentation of 25- to 35-year-old women, nonsmokers, and in vitro fertilization pregnancies, and a lower rate of small-for-gestational-age birth outcome.\textsuperscript{66} However, the effect of nonparticipation on selected exposure-risk associations, for example the association between in vitro fertilization and preterm birth, was negligible, indicating that initial selection bias caused by the relatively high rate of nonparticipation in the DNBC does not place a major threat to the external validity of DNBC studies.\textsuperscript{66} Moreover, on the basis of (1) the acceptable retention and follow-up rate in the current study, together with the fact that the validity of regression models is only marginally affected by selective drop-out,\textsuperscript{67} (2) the high percentage of complete data, and (3) completeness of diagnoses through linkage to the Danish National Hospital Register, we think it is unlikely that loss of mother-child pairs has introduced measurable selection bias.

The study also has some limitations and our findings need replication in an independent dataset. One limitation is that we did not have information on asthma severity, including duration of asthma episodes, even though it could be hypothesized that the magnitude of disease risk may be lower in offspring of mothers with less severe asthma during pregnancy.\textsuperscript{4,68} Moreover, we were not able to operationalize asthma according to a specific definition (eg, taking into account key characteristics, such as inflammation, hyperresponsiveness, reversible airway obstruction, and respiratory symptoms\textsuperscript{17,19}), as the required information, including diagnostic test results or information on asthma subtypes, was not available from the interviews, and it is hardly feasible in a large cohort to assess such details. However, validation of self-reported asthma against physician diagnoses,\textsuperscript{19} together with the high percentage of women with asthma during pregnancy and a doctor-diagnosis of lifetime asthma in this study, allows to at least approach the definition of asthma according to the ICD-10. Another limitation is that interview questions had to be designed to fit the telephone condition and were only partially validated. Moreover, in the current study, in some diagnostic categories, the number of cases was notably smaller than in other categories, resulting in less precise estimation of HRs. However, post hoc power analyses, assuming small effect sizes defined as HR = 1.3, as suggested previously,\textsuperscript{69} revealed a statistical power of 94%, 85%, 87%, and 71% for the categories including <1000 cases with a diagnosis, namely neoplasms, diseases of the blood and immune system, mental disorders, and diseases of the circulatory system, respectively. Statistical power was >99% in all other categories. It should be noted that post hoc power analyses have been strongly criticized,\textsuperscript{70} and, therefore, conclusions
concerning potential effects of maternal asthma during pregnancy on the offspring’s disease risk in categories with small case numbers are less certain at the current stage. Finally, the validity of self-report of disease has been suspected to be a potential source of bias; however, it has recently been documented that there was a high agreement between self-reported asthma and physician-diagnosed asthma, with self-report of asthma having very high specificity (98.14%) and the highest sensitivity (94.99%) across a wide range of somatic disease.19 We were also able to ensure in our study cohort that 95.85% of the women reporting lifetime asthma had received this diagnosis by a doctor, and to demonstrate in our study sample that results mostly did not change when we repeated the analyses, including in the asthma group only women with doctor-diagnosed asthma. Moreover, the prevalence of women suffering from asthma during pregnancy in this cohort (6.2%) is virtually identical to the prevalence of asthma during pregnancy, based on medical records, in a recent large epidemiologic study (6.5%).71 Furthermore, asthma data were mostly collected before the outcome data, making differential misclassification unlikely, which was also confirmed by secondary analyses.

The putative biological conclusions of the findings should be drawn with caution, given the heterogeneity of the rationales behind the different ICD-10 categories (eg, grouping by organ system, etiology). However, the ICD-10 is the international standard diagnostic classification system of diseases and recommended for epidemiologic studies, with high reliability at the category level.72 The presented findings should be corroborated in a sufficiently large sample of higher-order pregnancies before generalizing them to multiples. As we did not have diagnostic information from general practitioners regarding child pathologies, we probably missed less-severe offspring diseases and the relation with asthma during pregnancy may be lower in these cases. Future follow-up of the cohort yields the potential to determine whether offspring of mothers suffering from asthma during pregnancy are also at increased risk for a wide range of pathologies during adulthood, and whether even further diseases will develop at a later stage. Provided that our findings are confirmed in independent data sources, future studies should focus on potential underlying mechanisms of the association between maternal asthma during pregnancy and the offspring’s disease risk, such as cytokines, the HPA axis, placenta, and fetal development, which have repeatedly been associated with early adversities.73–75 Moreover, future work should analyze long-term consequences of intrauterine exposure to maternal asthma with regard to specific pathologies within the disease categories for which an increased risk has been identified. Most importantly, modifiable factors within this relationship should be identified to improve both prevention and intervention.

CONCLUSIONS

This is, to the best of our knowledge, the first comprehensive study on the association of maternal asthma during pregnancy with offspring health, covering a wide spectrum of pediatric diseases. Our finding that offspring of mothers suffering from asthma during pregnancy are at an increased risk for a variety of diseases during childhood suggests that careful medical and obstetric monitoring of the asthmatic pregnant woman and her developing fetus and child are highly warranted, regardless of the causes for this association.

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