

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

Marion Tegethoff, Jørn Olsen, Emmanuel Schaffner and Gunther Meinlschmidt
Pediatrics; originally published online August 5, 2013;
DOI: 10.1542/peds.2012-3686

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/early/2013/07/31/peds.2012-3686>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



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

AUTHORS: Marion Tegethoff, PhD,^a Jørn Olsen, MD, PhD,^{b,c} Emmanuel Schaffner, MSc,^{d,e} and Gunther Meinlschmidt, PhD^{f,g,h}

Divisions of ^aClinical Psychology and Psychiatry, ^dApplied Statistics in Life Sciences, and ^fClinical Psychology and Epidemiology, Department of Psychology, University of Basel, Basel, Switzerland; ^bDepartment of Epidemiology, School of Public Health, University of California at Los Angeles, Los Angeles, California; ^cThe Danish Epidemiology Science Centre, Department of Epidemiology, Institute of Public Health, University of Aarhus, Aarhus, Denmark; ^eBiostatistics and Computational Sciences, Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland; ^gResearch Department of Psychobiology, Psychosomatics, and Psychotherapy, Clinic of Psychosomatic Medicine and Psychotherapy, LWL University Hospital and School of Medicine, Ruhr-University Bochum, Bochum, Germany; and ^hNational Centre of Competence in Research "Swiss Etiological Study of Adjustment and Mental Health," Basel, Switzerland

KEY WORDS

antenatal, child, prenatal exposure delayed effects, prenatal, programming

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.

(Continued on last page)



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.

abstract



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,¹ affecting up to 8% of all pregnant women and women of childbearing age.^{2,3} 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.⁴ Moreover, in a cohort including >40 000 pregnancies, maternal asthma during 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.⁵ Maternal asthma during pregnancy was also shown to play a role in cardiac malformations in the offspring.⁶ 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,^{7,8} bronchiolitis,⁹ atopic dermatitis,¹⁰ and autism spectrum disorder¹¹ in the offspring during childhood, which is in line with animal models documenting intrauterine susceptibility to hypoxia-induced damage.¹² 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 2002.¹³ 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 invited 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.¹⁴ Moreover, multiples themselves are a heterogeneous group, for example, regarding number of placentas and cygocity, reflecting heterogeneous maternal-fetal physiology, with poorer outcome in higher-order pregnancies.^{14,15} The well-established associations between intrauterine conditions and long-term health also may be different in multiples and singletons.¹⁶

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.^{17,18} 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),¹⁹ 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 (eg, epilepsy, asthma, and febrile seizures, with positive predictive values of 81%, 85%, and 93%, respectively).^{20–24} Diagnoses, based on the Danish version of the *ICD-10*,²⁵ 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 models²⁸ 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.²⁹ 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,³⁴ general maternal health, to account for potential comorbid conditions that are frequently observed in asthma patients,^{35,36} smoking,³⁷ and infant gender,^{38,39} with the categories indicated in Table 1. We obtained information on offspring gender and maternal age at delivery from the Danish Medical Birth Registry,⁴⁰ and on socioeconomic status, parity, smoking during pregnancy, and general maternal health from the interviews taken at 12 and 30 weeks' gestation and at 6 months postpartum. Because 3453 singletons were born to mothers who contributed >1 pregnancy to the study, we calculated all SEs using the clustered sandwich estimator to correct for possible dependence between health outcomes in infants born to the same mother.⁴¹

All tests were 2-tailed and we set the level of significance at .05. In addition, we

TABLE 1 Sample Characteristics According to Maternal Asthma During Pregnancy

	All Mother-Child Pairs	No Asthma	Asthma
<i>n</i> (% of total group)	66 712 (100.0)	62 567 (93.8)	4145 (6.2)
Discrete variables, <i>n</i> (%) ^a			
Maternal age, y			
<27	13 744 (20.6)	12 604 (20.1)	1140 (27.5)
27–29	18 005 (27.0)	16 938 (27.1)	1067 (25.7)
30–32	16 634 (24.9)	15 666 (25.0)	968 (23.3)
>32	18 329 (27.5)	17 359 (27.7)	970 (23.4)
Parity			
Primiparous	29 848 (44.7)	27 885 (44.6)	1963 (47.4)
Multiparous	34 434 (51.6)	32 381 (51.8)	2053 (49.5)
Unknown	2430 (3.6)	2301 (3.7)	129 (3.1)
General maternal health			
Very good	33 698 (50.5)	32 310 (51.6)	1388 (33.5)
Average	28 309 (42.4)	26 073 (41.7)	2236 (53.9)
Bad	2293 (3.4)	1899 (3.0)	394 (9.5)
Unknown	2412 (3.6)	2285 (3.7)	127 (3.1)
Socioeconomic status			
High	32 840 (49.2)	30 985 (49.5)	1855 (44.8)
Medium	23 481 (35.2)	22 002 (35.2)	1479 (35.7)
Low	5281 (7.9)	4806 (7.7)	475 (11.5)
Unknown	5110 (7.7)	4774 (7.6)	336 (8.1)
Smoking during pregnancy			
Yes	17 170 (25.7)	15 949 (25.5)	1221 (29.5)
No	47 256 (70.8)	44 448 (71.0)	2808 (67.7)
Unknown	2286 (3.4)	2170 (3.5)	116 (2.8)
Infant gender			
Boys	34 056 (51.1)	31 850 (50.9)	2206 (53.2)
Girls	32 656 (49.0)	30 717 (49.1)	1939 (46.8)

^a May not total 100 due to rounding.

reevaluated 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

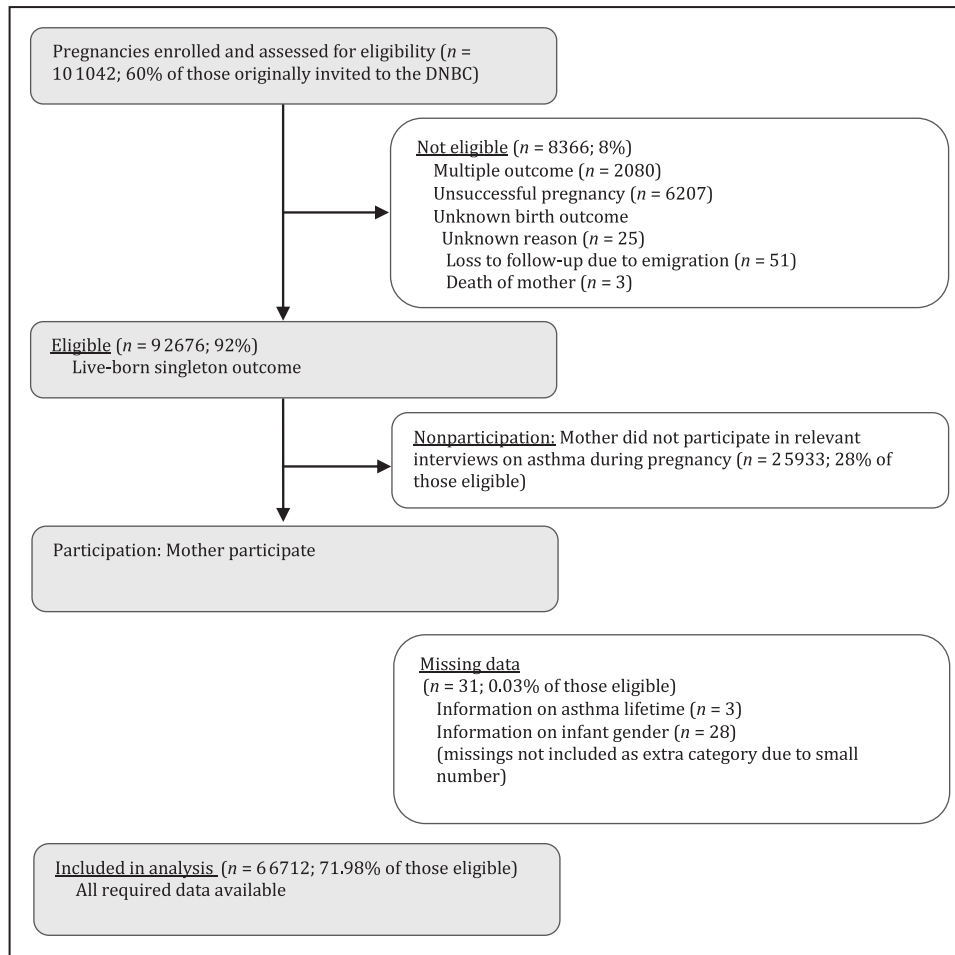
Study Cohort Descriptives

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.

TABLE 2 Cox Regression Models of Offspring Diseases Predicted by Asthma During Pregnancy

ICD-10 Category	No. Children With a Diagnosis	Crude ^a HR [95% CI]	Adjusted ^b HR [95% CI]
1. Infections, parasitic diseases	6754	1.42 [1.31–1.55]	1.34 [1.23–1.46]
2. Neoplasms	721	0.94 [0.69–1.28]	0.90 [0.66–1.23]
3. Diseases of blood, immune system	519	0.93 [0.64–1.35]	0.85 [0.58–1.23]
4. Endocrine, metabolic disorders	1194	1.33 [1.07–1.63]	1.26 [1.02–1.55]
5. Mental disorders	552	1.35 [1.00–1.83]	1.18 [0.87–1.60]
6. Diseases of nervous system	1296	1.51 [1.25–1.83]	1.43 [1.18–1.73]
7. Diseases of eye	1474	1.26 [1.04–1.53]	1.20 [0.99–1.46]
8. Diseases of ear	4398	1.41 [1.27–1.57]	1.33 [1.19–1.48]
9. Diseases of circulatory system	367	1.20 [0.81–1.78]	1.12 [0.76–1.68]
10. Diseases of respiratory system	12 592	1.51 [1.42–1.61]	1.43 [1.34–1.52]
11. Diseases of digestive system	4103	1.25 [1.11–1.40]	1.17 [1.04–1.32]
12. Diseases of skin	2519	1.43 [1.24–1.65]	1.39 [1.20–1.60]
13. Diseases of musculoskeletal system	3134	1.05 [0.91–1.21]	1.02 [0.89–1.18]
14. Diseases of genitourinary system	2271	1.16 [0.99–1.36]	1.10 [0.93–1.29]
Any	35 052	1.22 [1.18–1.27]	1.17 [1.13–1.22]

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.

TABLE 3 Logistic Regression Models of Offspring Diseases Predicted by Asthma During Pregnancy

ICD-10 Category	No. Children With a Diagnosis	Crude ^a OR [95% CI]	Adjusted ^b OR [95% CI]
16. Conditions originating in perinatal period	12 897	1.11 [1.03–1.20]	1.05 [0.97–1.14]
17. Malformations	5613	1.18 [1.06–1.31]	1.13 [1.01–1.26]

Odds ratios (OR) for the offspring's risk of having conditions originating in the perinatal period and malformations (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,⁴³ 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.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.^{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 factors⁶³ 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.³⁵ Indeed, if conditions such as psychopathologies are present during pregnancy, the offspring is at increased risk of adverse health outcomes.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 dis-

eases,²⁶ and that may either trigger or be triggered by asthma.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.³ Ongoing follow-up of children in the DNBC enables further research at later stages.

The rather low participation rate encountered in the DNBC¹³ was partly caused by a lack of participation by family doctors and partly by pregnant women who declined the invitation.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.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.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,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.^{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^{17,18}), 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,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,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,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 mis-

classification 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.

REFERENCES

1. Bakhireva LN, Schatz M, Jones KL, Chambers CD; Organization of Teratology Information Specialists Collaborative Research Group. Asthma control during pregnancy and the risk of preterm delivery or impaired fetal growth. *Ann Allergy Asthma Immunol.* 2008; 101(2):137–143
2. Skadhaug LR, Baelum J, Siersted HC, et al. [The occurrence of asthma among young adults. A population-based study in five west Danish counties]. *Ugeskr Laeger.* 2005;167(6):648–651
3. Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: estimates from national health surveys. *Ann Epidemiol.* 2003;13(5):317–324
4. Murphy VE, Namazy JA, Powell H, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG.* 2011; 118(11):1314–1323
5. Blais L, Kettani FZ, Elftouh N, Forget A. Effect of maternal asthma on the risk of specific congenital malformations: a population-based cohort study. *Birth Defects Res A Clin Mol Teratol.* 2010;88(4):216–222
6. Lin S, Herdt-Losavio M, Gensburg L, Marshall E, Druschel C. Maternal asthma, asthma medication use, and the risk of congenital heart defects. *Birth Defects Res A Clin Mol Teratol.* 2009;85(2):161–168
7. Martel MJ, Rey E, Malo JL, et al. Determinants of the incidence of childhood asthma: a two-stage case-control study. *Am J Epidemiol.* 2009;169(2):195–205
8. Martel MJ, Rey E, Beauchesne MF, et al. Control and severity of asthma during pregnancy are associated with asthma incidence in offspring: two-stage case-control study. *Eur Respir J.* 2009;34(3):579–587
9. Carroll KN, Gebretsadik T, Griffin MR, et al. Maternal asthma and maternal smoking

- are associated with increased risk of bronchiolitis during infancy. *Pediatrics*. 2007;119(6):1104–1112
10. Martel MJ, Beauchesne MF, Malo JL, Rey E, Perreault S, Forget A, et al. Maternal asthma, its control and severity in pregnancy, and the incidence of atopic dermatitis and allergic rhinitis in the offspring. *J Pediatr*. 2009;155(5):707–713.e1
11. Croen LA, Grether JK, Yoshida CK, Odouli R, Van de Water J. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. *Arch Pediatr Adolesc Med*. 2005;159(2):151–157
12. Webster WS, Abela D. The effect of hypoxia in development. *Birth Defects Res C Embryo Today*. 2007;81(3):215–228
13. Olsen J, Melbye M, Olsen SF, et al. The Danish National Birth Cohort—its background, structure and aim. *Scand J Public Health*. 2001;29(4):300–307
14. Norwitz ER, Edusa V, Park JS. Maternal physiology and complications of multiple pregnancy. *Semin Perinatol*. 2005;29(5):338–348
15. Santema JG, Bourdrez P, Wallenburg HC. Maternal and perinatal complications in triplet compared with twin pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 1995;60(2):143–147
16. Morley R. Can we generalise from findings in twins? *Paediatr Perinat Epidemiol*. 2005;19(suppl 1):54–59
17. Löwhagen O. Diagnosis of asthma—a new approach. *Allergy*. 2012;67(6):713–717
18. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(suppl 5):S94–S138
19. Baumeister H, Kriston L, Bengel J, Härter M. High agreement of self-report and physician-diagnosed somatic conditions yields limited bias in examining mental-physical comorbidity. *J Clin Epidemiol*. 2010;63(5):558–565
20. Christensen J, Vestergaard M, Olsen J, Sidenius P. Validation of epilepsy diagnoses in the Danish National Hospital Register. *Epilepsy Res*. 2007;75(2–3):162–170
21. Andersen TF, Madsen M, Jørgensen J, Mellemkjær L, Olsen JH. The Danish National Hospital Register: A valuable source of data for modern health sciences. *Dan Med Bull*. 1999;46(3):263–268
22. Moth G, Vedsted P, Schiøtz PO. National registry diagnoses agree with medical records on hospitalized asthmatic children. *Acta Paediatr*. 2007;96(10):1470–1473
23. Vestergaard M, Obel C, Henriksen TB, et al. The Danish National Hospital Register is a valuable study base for epidemiologic research in febrile seizures. *J Clin Epidemiol*. 2006;59(1):61–66
24. Sørensen HT, Larsen BO. A population-based Danish data resource with possible high validity in pharmacoepidemiological research. *J Med Syst*. 1994;18(1):33–38
25. Danish National Board of Health. *Classification of Diseases. 10th revision*. Copenhagen: Munksgård; 1993
26. Tegethoff M, Greene N, Olsen J, Schaffner E, Meinlschmidt G. Stress during pregnancy and offspring pediatric disease: a national cohort study. *Environ Health Perspect*. 2011;119(11):1647–1652
27. Tegethoff M, Greene N, Olsen J, Schaffner E, Meinlschmidt G. Inhaled glucocorticoids during pregnancy and offspring pediatric diseases: a national cohort study. *Am J Respir Crit Care Med*. 2012;185(5):557–563
28. Cox DR. Regression models and life-tables. *J R Stat Soc Series B*. 1972;34:187–220
29. World Health Organization. *The World Health Report 2005*. Geneva: World Health Organization; 2005
30. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81(3):515–526
31. Gissler M, Rahkonen O, Järvelin MR, Hemminki E. Social class differences in health until the age of seven years among the Finnish 1987 birth cohort. *Soc Sci Med*. 1998;46(12):1543–1552
32. Bech BH, Nohr EA, Vaeth M, Henriksen TB, Olsen J. Coffee and fetal death: a cohort study with prospective data. *Am J Epidemiol*. 2005;162(10):983–990
33. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. *Int J Epidemiol*. 2001;30(6):1428–1437
34. Hassold T, Chiu D. Maternal age-specific rates of numerical chromosome abnormalities with special reference to trisomy. *Hum Genet*. 1985;70(1):11–17
35. Boulet LP, Boulay ME. Asthma-related comorbidities. *Expert Rev Respir Med*. 2011;5(3):377–393
36. Waters E, Doyle J, Wolfe R, Wright M, Wake M, Salmon L. Influence of parental gender and self-reported health and illness on parent-reported child health. *Pediatrics*. 2000;106(6):1422–1428
37. Hofhuis W, de Jongste JC, Merkus PJ. Adverse health effects of prenatal and postnatal tobacco smoke exposure on children. *Arch Dis Child*. 2003;88(12):1086–1090
38. Gissler M, Järvelin MR, Louhiala P, Hemminki E. Boys have more health problems in childhood than girls: follow-up of the 1987 Finnish birth cohort. *Acta Paediatr*. 1999;88(3):310–314
39. Washburn TC, Medearis DN Jr, Childs B. Sex differences in susceptibility to infections. *Pediatrics*. 1965;35:57–64
40. Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull*. 1998;45(3):320–323
41. Williams RL. A note on robust variance estimation for cluster-correlated data. *Biometrics*. 2000;56(2):645–646
42. Murphy VE, Gibson PG, Smith R, Clifton VL. Asthma during pregnancy: mechanisms and treatment implications. *Eur Respir J*. 2005;25(4):731–750
43. Aldrich CJ, Wyatt JS, Spencer JA, Reynolds EO, Delpy DT. The effect of maternal oxygen administration on human fetal cerebral oxygenation measured during labour by near infrared spectroscopy. *Br J Obstet Gynaecol*. 1994;101(6):509–513
44. Golan H, Kashtutsky I, Hallak M, Sorokin Y, Huleihel M. Maternal hypoxia during pregnancy delays the development of motor reflexes in newborn mice. *Dev Neurosci*. 2004;26(1):24–29
45. Golan H, Kashtutsky I, Hallak M, Sorokin Y, Huleihel M. Maternal hypoxia during pregnancy induces fetal neurodevelopmental brain damage: partial protection by magnesium sulfate. *J Neurosci Res*. 2004;78(3):430–441
46. Williams SJ, Hemmings DG, Mitchell JM, McMillen IC, Davidge ST. Effects of maternal hypoxia or nutrient restriction during pregnancy on endothelial function in adult male rat offspring. *J Physiol*. 2005;565(pt 1):125–135
47. Wu XM, Hu CP, Li XZ, et al. Asthma pregnancy alters postnatal development of chromaffin cells in the rat adrenal medulla. *PLoS ONE*. 2011;6(5):e20337
48. Clifton VL, Giles WB, Smith R, et al. Alterations of placental vascular function in asthmatic pregnancies. *Am J Respir Crit Care Med*. 2001;164(4):546–553
49. Murphy VE, Gibson PG, Giles WB, et al. Maternal asthma is associated with reduced female fetal growth. *Am J Respir Crit Care Med*. 2003;168(11):1317–1323
50. Schatz M, Dombrowski MP, Wise R, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network; National Heart, Lung, and Blood Institute. Spirometry is related to perinatal outcomes in pregnant women with asthma. *Am J Obstet Gynecol*. 2006;194(1):120–126

51. Barker DJ, Osmond C, Simmonds SJ, Wield GA. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. *BMJ*. 1993;306(6875):422–426
52. Hofman PL, Regan F, Jackson WE, et al. Premature birth and later insulin resistance. *N Engl J Med*. 2004;351(21):2179–2186
53. Chung KF, Barnes PJ. Cytokines in asthma. *Thorax*. 1999;54(9):825–857
54. Dame JB, Juul SE. The distribution of receptors for the pro-inflammatory cytokines interleukin (IL)-6 and IL-8 in the developing human fetus. *Early Hum Dev*. 2000; 58(1):25–39
55. Dahlgren J, Nilsson C, Jennische E, et al. Prenatal cytokine exposure results in obesity and gender-specific programming. *Am J Physiol Endocrinol Metab*. 2001;281(2): E326–E334
56. Ashdown H, Dumont Y, Ng M, Poole S, Boksa P, Luheshi GN. The role of cytokines in mediating effects of prenatal infection on the fetus: implications for schizophrenia. *Mol Psychiatry*. 2006;11(1):47–55
57. Lim RH, Kobzik L. Transplacental passage of interleukins 4 and 13? *PLoS ONE*. 2009;4(3): e4660
58. Aaltonen R, Heikkinen T, Hakala K, Laine K, Alanen A. Transfer of proinflammatory cytokines across term placenta. *Obstet Gynecol*. 2005;106(4):802–807
59. Priftis KN, Papadimitriou A, Nicolaidou P, Chrousos GP. Dysregulation of the stress response in asthmatic children. *Allergy*. 2009;64(1):18–31
60. Tegethoff M, Pryce C, Meinlschmidt G. Effects of intrauterine exposure to synthetic glucocorticoids on fetal, newborn, and infant hypothalamic-pituitary-adrenal axis function in humans: a systematic review. *Endocr Rev*. 2009;30(7):753–789
61. Blais L, Beaudesne MF, Lemiere C, Elftouh N. High doses of inhaled corticosteroids during the first trimester of pregnancy and congenital malformations. *J Allergy Clin Immunol*. 2009;124(6):1229–1234.e4
62. Barne M, Brashier B, Kodgule R, Apte K, Salvi S. Is it really time to reconsider use of inhaled corticosteroids for control of asthma in pregnancy? *Am J Respir Crit Care Med*. 2012;185(12):1327–1328, author reply 1327–1328
63. Kauffmann F, Demenais F. Gene-environment interactions in asthma and allergic diseases: challenges and perspectives. *J Allergy Clin Immunol*. 2012;130(6):1229–1240; quiz 1241–1222
64. Van den Bergh BR, Mulder EJ, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neurosci Biobehav Rev*. 2005;29(2):237–258
65. Chida Y, Hamer M, Steptoe A. A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis. *Psychosom Med*. 2008; 70(1):102–116
66. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology*. 2006;17(4):413–418
67. Wolke D, Waylen A, Samara M, et al. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *Br J Psychiatry*. 2009;195(3):249–256
68. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax*. 2006;61(2):169–176
69. Bedard PL, Krzyzanowska MK, Pintilie M, Tannock IF. Statistical power of negative randomized controlled trials presented at American Society for Clinical Oncology annual meetings. *J Clin Oncol*. 2007;25(23): 3482–3487
70. Levine M, Ensom MH. Post hoc power analysis: an idea whose time has passed? *Pharmacotherapy*. 2001;21(4):405–409
71. Enriquez R, Griffin MR, Carroll KN, et al. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol*. 2007;120(3):625–630
72. Stausberg J, Lehmann N, Kaczmarek D, Stein M. Reliability of diagnoses coding with ICD-10. *Int J Med Inform*. 2008;77(1):50–57
73. Tegethoff M, Greene N, Olsen J, Meyer AH, Meinlschmidt G. Maternal psychosocial stress during pregnancy and placenta weight: evidence from a national cohort study. *PLoS ONE*. 2010;5(12):e14478
74. Tegethoff M, Greene N, Olsen J, Meyer AH, Meinlschmidt G. Maternal psychosocial adversity during pregnancy is associated with length of gestation and offspring size at birth: evidence from a population-based cohort study. *Psychosom Med*. 2010;72(4): 419–426
75. Tegethoff M, Raul JS, Jamey C, Khelil MB, Ludes B, Meinlschmidt G. Dehydroepiandrosterone in nails of infants: a potential biomarker of intrauterine responses to maternal stress. *Biol Psychol*. 2011;87(3): 414–420

(Continued from first page)

www.pediatrics.org/cgi/doi/10.1542/peds.2012-3686

doi:10.1542/peds.2012-3686

Accepted for publication Jun 19, 2013

Address correspondence to Gunther Meinlschmidt, PhD, Division of Clinical Psychology and Epidemiology, Department of Psychology, University of Basel, Missionsstrasse 60/62, CH-4055 Basel, Switzerland. E-mail: gunther.meinlschmidt@unibas.ch

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2013 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: The Danish National Research Foundation established the Danish Epidemiology Science Centre, which initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from this foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation, and the Health Foundation. This project was financed by the German National Academic Foundation (to Dr Tegethoff), and the Swiss National Science Foundation, project numbers PZ00P1_137023 (to Dr Tegethoff) and 51A240_104890 as well as 100014_135328 (to Dr Meinlschmidt). The funding sources had no involvement in study design; in the collection, analysis, and interpretation of the data; in the writing of the report; and in the decision to submit the article for publication.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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

Marion Tegethoff, Jørn Olsen, Emmanuel Schaffner and Gunther Meinlschmidt
Pediatrics; originally published online August 5, 2013;
DOI: 10.1542/peds.2012-3686

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/early/2013/07/31/peds.2012-3686>

Supplementary Material

Supplementary material can be found at:
<http://pediatrics.aappublications.org/content/suppl/2013/07/31/peds.2012-3686.DCSupplemental.html>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://pediatrics.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://pediatrics.aappublications.org/site/misc/reprints.xhtml>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



Supplemental Information

METHODS: SECONDARY ANALYSES

To validate our findings, we performed further secondary analyses. First, we repeated the analyses including only the first pregnancy of each woman in the cohort, also to control for previous reproductive experiences.¹ Second, to account for potential bias by asthma self-report, we repeated the analyses including in the asthma group only women with doctor-diagnosed lifetime asthma reporting asthma during pregnancy. Third, 165 (3.98%) of 4145 women with asthma during pregnancy were identified as asthma during pregnancy cases due to the women's information given at the interview at 6 months postpartum. Therefore, to account for potential bias by differential recall and reverse causation, we repeated the analyses after allocating women to the asthma and no asthma during pregnancy groups based only on information derived from the interviews at 12 or 30 weeks' gestation. Fourth, as 2510 women with asthma during pregnancy reported use of asthma medication during pregnancy, we repeated all analyses after adjusting for the use of asthma medication during pregnancy, to account for potential bias by asthma medication and to give insight into the role of asthma medication in pediatric disease risk. We obtained information on asthma medication used at any time during the current pregnancy from computer-assisted interviews taken at ~12 and 30 weeks' gestation and at 6 months postpartum. Women were asked whether they had used any kind of inhalants, pills, or other types of asthma treatment during pregnancy; women identified the drugs from a list of asthma

medications available in Denmark, or they stated the name of their medications.

To determine whether the association between maternal asthma during pregnancy and offspring diseases differs between girls and boys and between smokers and nonsmokers, for exploratory purposes a posteriori, we additionally repeated the adjusted analyses modeling the corresponding interaction terms, and, if applicable, we repeated the adjusted analyses in the subgroups.

For exploratory purposes, we additionally repeated the adjusted analyses after controlling for further, a posteriori defined, potential confounders, including maternal diabetes² and hypertension³ during pregnancy, with the categories "yes," "no," and "unknown," to account for potential confounding by specific comorbid conditions.⁴ We received the corresponding information from the interviews taken at 12 and 30 weeks' gestation and at 6 months postpartum.

RESULTS: SECONDARY ANALYSES

When we repeated the adjusted analyses using only the women's first pregnancies in the cohort, levels of significance were comparable to those presented in Tables 2 and 3.

Levels of significance were also comparable to those presented in Tables 2 and 3 when we repeated the adjusted analyses including in the asthma group only women with doctor-diagnosed asthma. Only the asthma-associated risk of malformations was no longer significant (odds ratio [OR] 1.12, 95% confidence interval [CI] 1.00–1.26).

Furthermore, repeating the adjusted analyses, after allocating women to the asthma and no asthma during preg-

nancy groups based only on information derived from the interviews at 12 or 30 weeks' gestation, did not change the results, except for the asthma-related risk of diseases of the eye that reached statistical significance (hazard ratio [HR] 1.22, 95% CI 1.00–1.49). Likewise, when we repeated the adjusted analyses additionally adjusting for the use of asthma medication during pregnancy, levels of significance regarding the comparison between offspring of mothers with asthma without medication and offspring of mothers without asthma were comparable to those presented in Tables 2 and 3 for most disease categories. However, the asthma-associated risk for the first diagnosis in the categories "endocrine and metabolic disorders" (HR 1.16, 95% CI 0.84–1.59) and "malformations" (OR 1.14, 95% CI 0.97–1.34) was no longer significant, whereas the risk in the category "diseases of the eye" reached statistical significance (HR 1.35, 95% CI 1.02–1.81). In most categories, the disease risk did not differ significantly between offspring of mothers with asthma with versus without medication, but asthma medication was associated with a decreased risk of neoplasms in the offspring (HR 0.54, 95% CI 0.31–0.96).

The associations between maternal asthma during pregnancy and offspring diseases did not differ between girls and boys and between smokers and nonsmokers; only the association between maternal asthma and offspring diseases of the circulatory system differed between smokers and nonsmokers (HR 3.85, 95% CI 1.13–13.11), even though analyses in the subgroups were not significant (smokers: HR 0.42, 95% CI 0.14–1.30; nonsmokers: HR 1.45, 95% CI 0.94–2.24).

When we repeated the adjusted analyses additionally controlling for

maternal diabetes and hypertension during pregnancy, levels of significance

were comparable to those presented in Tables 2 and 3.

REFERENCES

1. Olsen J. Confounding by exposure history and prior outcome. *Epidemiology*. 2008;19(4):635–636, author reply 636
2. Aman J, Hansson U, Ostlund I, Wall K, Persson B. Increased fat mass and cardiac septal hypertrophy in newborn infants of mothers with well-controlled diabetes during pregnancy. *Neonatology*. 2011;100(2):147–154
3. Fatemeh T, Marziyeh G, Nayereh G, Anahita G, Samira T. Maternal and perinatal outcome in nulliparous women complicated with pregnancy hypertension. *J Pak Med Assoc*. 2010;60(9):707–710
4. Boulet LP, Boulay ME. Asthma-related comorbidities. *Expert Rev Respir Med*. 2011;5(3):377–393