

Inhaled Glucocorticoids during Pregnancy and Offspring Pediatric Diseases

A National Cohort Study

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Rationale: Glucocorticoid inhalation is the preferred asthma treatment during pregnancy. Previous studies on its safety focused on obstetric outcomes and offspring malformations.

Objectives: To determine whether glucocorticoid inhalation during pregnancy is a risk factor for offspring pediatric diseases.

Methods: We studied offspring (live singletons) of pregnant women suffering from asthma during pregnancy (prevalence = 6.3%; n = 4,083 mother-child pairs) from the Danish National Birth Cohort (births, 1996–2002; prospective data). We estimated the associations between use of inhaled glucocorticoids for asthma treatment during pregnancy (n = 1231; 79.9% budesonide, 17.6% fluticasone, 5.4% beclomethasone, and 0.9% other or unspecified glucocorticoids) and offspring diseases (International Classification of Diseases–10th Revision, diagnoses) during childhood. We conducted Cox or logistic regression analyses for each International Classification of Diseases–10th Revision category, controlling for use of non-glucocorticoid-containing inhalants, and confirmed results by addressing confounding by treatment indication using propensity score.

Measurements and Main Results: Offspring median age at end of follow-up was 6.1 (range, 3.6–8.9) years. Glucocorticoid inhalation was not associated with offspring disease risk in most categories, except for offspring endocrine, metabolic, and nutritional disorders (hazard ratio, 1.84; 95% confidence interval, 1.13–2.99). When repeating analyses with the major subgroup that used budesonide only, association estimates were of similar magnitude.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Inhaled glucocorticoids are the preferred treatment of asthma during pregnancy. Inhaled glucocorticoids are not associated with pregnancy complications, obstetric outcomes, or offspring malformations.

What This Study Adds to the Field

This study adds knowledge on potential long-term consequences of the use of inhaled glucocorticoids during pregnancy for offspring health. Data are mostly reassuring, supporting the use of glucocorticoid inhalants during pregnancy: glucocorticoids are not related to the offspring's risk of most diseases but may be a risk factor for offspring endocrine and metabolic disturbances, which should be considered further.

Conclusions: Regarding most disease categories, data are reassuring, supporting the use of inhaled glucocorticoids during pregnancy. In line with animal data, glucocorticoid inhalation during pregnancy may be a risk factor for offspring endocrine and metabolic disturbances, which should be considered further.

Keywords: antenatal; corticosteroids; inhaled; prenatal exposure delayed effects; programming

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Asthma is a common medical complication in pregnancy (1). Between 1997 and 2001, asthma affected 3.7–8.4% of all pregnant women in the United States (2). In Nordic countries, the point prevalence of asthma in adults ranges between 2% and 5% (3), whereas in Denmark the prevalence of current asthma in women of childbearing age has been reported to be 8.1% (4). Adequate treatment of asthma is important for maternal health and fetal maturation (5). The American National Asthma Education and Prevention Program has recommended inhaled corticosteroids as the preferred therapy for managing persistent asthma during pregnancy (5), which is in line with the recommendations in Nordic countries, set forth by the Nordic consensus report on asthma management (3). Indeed, the efficacy of corticosteroid inhalation in asthma treatment is well recognized (6). Findings from cohort studies and randomized trials suggest that inhaled corticosteroids used at clinically relevant doses in pregnant women are related to neither impaired obstetric outcomes nor an increased risk of offspring congenital malformations (5, 7–13). However, the focus of these studies was on a narrow range of short-term adverse outcomes in the offspring, and long-term systemic effects of

corticosteroid inhalation cannot be ruled out (14). These considerations together with the trend toward preferred use of inhaled corticosteroids during pregnancy make it important to extend follow-up time and to cover a larger spectrum of offspring diseases, because the potential negative effects of inhaled corticosteroids on the developing fetus continue to be of significant concern to patients and healthcare professionals (15). Animal studies suggest that intrauterine exposure to glucocorticoids has long-term effects on offspring physiology, including the brain, hypothalamic-pituitary-adrenal (HPA) axis, and cardiovascular and metabolic function (16).

The purpose of this study was to assess the associations between use of glucocorticoid inhalants because of 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 and Exposures

This study is based on prospective data from the Danish National Birth Cohort, including births between 1996 and 2003. Details on the cohort have been described elsewhere (17, 18). In brief, participants gave written informed consent and the Danish National Committee for Biomedical Research Ethics, Copenhagen, approved the study on behalf of all committees in the country. About 50% of all general practitioners in the country took part in the recruitment and they invited women when they came for their first pregnancy visit around weeks 6–12 of pregnancy, and 60% of the invited women participated. Follow-up interviews were repeatedly performed during and after pregnancy, and additionally, diagnoses during childhood were based on medical registries (for details, see later).

We considered as eligible all pregnancies with asthma with live singleton birth outcome. We excluded multiple births, because the intrauterine physiology underlying maternal–fetal transmission differs between multiples and singletons and multiple pregnancies have a significant risk of complications (19). Moreover, multiples themselves are a heterogeneous group, for example regarding number of multiples, number of placentas, and cygosity, reflecting heterogeneous maternal–fetal physiology, with poorer outcome in higher-order pregnancies (19, 20). The well-established associations between intrauterine conditions and long-term health also may be different in multiples and singletons (21).

Women were considered to have asthma during pregnancy if asthma occurred at any time during the current pregnancy. We obtained information on maternal asthma and asthma therapy with glucocorticoid-containing inhalants during current pregnancy from computer-assisted interviews taken around 12 and 30 weeks gestation and at 6 months postpartum. Women were asked if they suffered or had suffered from asthma during pregnancy, if the asthma had been diagnosed by a doctor, and if they had a lifetime history of asthma. It has recently been documented that the agreement of case ascertainment by patient self-report and physician diagnosis was high ($\kappa = 0.83$) (22). Indeed, additional analysis of the study cohort revealed that 95.85% of women reporting lifetime asthma had received this diagnosis by a doctor. Furthermore, women were asked whether they had used any kind of inhalants for asthma treatment during pregnancy. Women identified the drugs from a list of 26 asthma inhalation medications available in Denmark, or they stated the name of their medications.

Outcome Measures

Information on children's diseases derived from the Danish National Hospital Register, which contains information on all inpatients and outpatients in Danish hospitals and provides reporting of diagnoses, the validity of which has been studied for several diseases (23–27). Hospital diagnoses, based on the Danish version of the ICD-10 (28), were divided into dichotomous diagnostic categories according to Chapters 1–17 of the ICD-10. Additionally, we used as outcome a dichotomous overall category (“any disease”), indicating whether any disease of any diagnostic category was present (see also 17).

Statistical Analyses

We estimated the associations between use of glucocorticoid inhalants for asthma treatment during pregnancy and the offspring's disease risk by conducting separate Cox proportional hazard regression for diagnostic categories 1–14 and “any disease,” whereas logistic regression was used for diagnostic categories 16 and 17. To obtain less confounded estimates, we stratified the analyses, thereby allowing for separate baseline hazard functions for each stratum, for several potential predictors of child health, selected *a priori*, which might confound or suppress effects, including socioeconomic status (29) based on the mother's occupation (30), parity (31), maternal age (32), general maternal health (33), and adjusted for infant sex and use of any non-glucocorticoid-containing inhalant for asthma treatment (34, 35), with the categories indicated in Table 1.

We repeated the analyses on the association between glucocorticoid inhalants for asthma treatment during pregnancy and offspring health using propensity scores (36, 37) to control for confounding by indication for treatment with glucocorticoid inhalants.

The risk of adverse effects may vary with different types of glucocorticoid inhalation because of differences in first-pass metabolism and absorption from the airways and differences in pharmacokinetics after absorption (6, 38). Most women in this study used budesonide ($n = 983$; 79.9%). Therefore, we repeated the analyses comparing offspring of mothers using only budesonide as glucocorticoid inhalation for asthma treatment during pregnancy and offspring of mothers not using any type of glucocorticoid inhalation.

For details on the statistical analyses, see the online supplement.

RESULTS

Study Cohort Descriptives

Of 65,085 mother–child pairs with live singleton pregnancies and complete data on offspring diagnoses, maternal asthma status, and treatment with glucocorticoid-containing inhalants, 61,002 had no asthma during pregnancy (93.7%) and 4,083 had asthma during pregnancy and were included as eligible in the analysis (6.3%) (Figure 1 and Table 1). Median age at end of follow-up was 6.1 years (range, 3.6–8.9 yr).

Cox Proportional Hazard Models and Logistic Regression Analyses

The results of the adjusted Cox and logistic regression analyses are presented in Tables 2 and 3. In women with asthma during pregnancy, use (vs. no use) of glucocorticoid inhalants was associated with a significantly increased risk for the first diagnosis of endocrine and metabolic disorders but not of diseases in any other category (Table 2).

When we repeated the adjusted regression analyses stratifying them for propensity score strata, the estimates were of similar magnitude as those presented in Tables 2 and 3. The increased risk of endocrine and metabolic disorders after glucocorticoid inhalation because of asthma during pregnancy was confirmed and even more pronounced (hazard ratio [HR], 1.84; 95% confidence interval [CI], 1.13–2.99). When using propensity score, glucocorticoid inhalation because of asthma during pregnancy was also related to an increased risk of diseases of the digestive system (HR, 1.54; 95% CI, 1.18–2.02).

Furthermore, repeating the adjusted regression analyses with budesonide-exposed mother–child pairs did not result in a relevant change of the magnitude of the estimates presented in Tables 2 and 3; the HR of endocrine and metabolic diseases was 1.72 (95% CI, 1.07–2.77).

When the adjusted analyses were repeated using only the women's first pregnancies in the cohort, the estimates were of similar magnitude as those presented in Tables 2 and 3.

Finally, when repeating the adjusted regression analyses controlling for further potential confounders (see online supplement),

TABLE 1. SAMPLE CHARACTERISTICS ACCORDING TO ASTHMA GC INHALATION OF THE MOTHER DURING PREGNANCY

	All Included Mother–Child Pairs	GC Inhalation during Pregnancy	No GC Inhalation during Pregnancy
N (% of all included mother–child pairs)	4,083	1,231 (30.1)	2,852 (69.9)
Discrete Variables: N (%)*			
Maternal age, yr			
<27	1,123 (27.5)	243 (19.7)	880 (30.9)
27–29	1,047 (25.6)	317 (25.8)	730 (25.6)
30–32	957 (23.4)	326 (26.5)	631 (22.1)
>32	956 (23.4)	345 (28)	611 (21.4)
Parity			
Primiparous	1,933 (47.3)	551 (44.8)	1,382 (48.5)
Multiparous	2,024 (49.6)	637 (51.8)	1,387 (48.6)
Unknown	126 (3.1)	43 (3.5)	83 (2.9)
General maternal health			
Very good	1,368 (33.5)	355 (28.8)	1,013 (35.5)
Average	2,201 (53.9)	677 (55)	1,524 (53.4)
Bad	390 (9.6)	157 (12.8)	233 (8.2)
Unknown	124 (3)	42 (3.4)	82 (2.9)
Socioeconomic status			
High	1,830 (44.8)	606 (49.2)	1,224 (42.9)
Medium	1,459 (35.7)	407 (33.1)	1,052 (36.9)
Low	465 (11.4)	112 (9.1)	353 (12.4)
Unknown	329 (8.1)	106 (8.6)	223 (7.8)
Infant sex			
Male	2,169 (53.1)	668 (54.3)	1,501 (52.6)
Female	1,914 (46.9)	563 (45.7)	1,351 (47.4)
Type of GC inhalation because of asthma [†]			
Beclomethasone		67 (5.4)	—
Budesonide		983 (79.9)	—
Fluticasone		217 (17.6)	—
Unspecified		11 (0.9)	—
Use of other (non-GC) asthma inhalation			
Yes	2,119 (51.9)	921 (74.8)	1,198 (42)
No	1,964 (48.1)	310 (25.2)	1,654 (58)
Continuous Variables: Median (interquartile range)			
Duration of use of GC inhalation during pregnancy, wk		33 (27–36)	—

Definition of abbreviation: GC = glucocorticoid.

*Percentages may not total 100 because of rounding, if not otherwise specified.

[†] Percentages do not total 100 because of use of multiple types of GC medication.

there was no relevant change of the magnitude of the estimates presented in Tables 2 and 3.

Exploratory case–control analyses revealed that cases with a diagnosis in the most common subcategory of “metabolic disorders,” compared with control subjects, were more likely to be exposed to maternal glucocorticoid inhalation during pregnancy (43.94% vs. 29.92%; $P = 0.012$), and that cases with the most common diagnosis of “volume depletion,” compared with control subjects, were more likely to be exposed to maternal glucocorticoid inhalation during pregnancy (42.55% vs. 30.00%; $P = 0.047$) (39).

DISCUSSION

In this population-based cohort study, 65,085 mother–child pairs were followed-up in real time from early pregnancy into childhood; maternal use of glucocorticoid inhalation because of asthma during pregnancy was not related to an increased risk of most diseases, except for endocrine and metabolic disorders during childhood, compared with offspring of mothers with asthma without glucocorticoid inhalation during pregnancy, taking into consideration potential confounding by treatment indication. The findings were stable when repeating analyses with budesonide inhalation only, the most common type of glucocorticoid inhalation in this sample. Our results are mostly reassuring regarding the use of glucocorticoid inhalation during pregnancy,

whereas they suggest taking a closer look at its relevance for endocrine and metabolic disturbances during childhood.

Our results are mostly in line with previous human studies on short-term reproductive failures after glucocorticoid inhalation during pregnancy that have not shown any strong association with fetal adrenal function (40), obstetric outcomes, and malformations (5, 7, 13), whereas other studies on long-term consequences are as yet lacking. In contrast, systemic glucocorticoid injection during human pregnancy has been linked to immune (41), cardiovascular (42), and neurologic (43) function. Because we focused on inhalation that limits systemic drug exposure (7), in the present study, the threshold to exert nonendocrinologic and nonmetabolic deleterious effects may not have been reached, supporting the usefulness of glucocorticoid inhalation during pregnancy. Further possible reasons are differences in treatment indication, type, dose, and frequency of glucocorticoid administration. Furthermore, as outcomes, we used clinical diagnoses instead of the potentially more sensitive physiologic or subclinical measures, which have been used in the previously mentioned studies on glucocorticoid injection. Moreover in the present study, in some diagnostic categories (e.g., neoplasms, diseases of blood and immune system, and diseases of the circulatory system) the number of cases was rather small, resulting in imprecise estimation of hazard ratios. Hence, firm conclusions concerning effects of glucocorticoid inhalation in these categories cannot be drawn at the current stage.

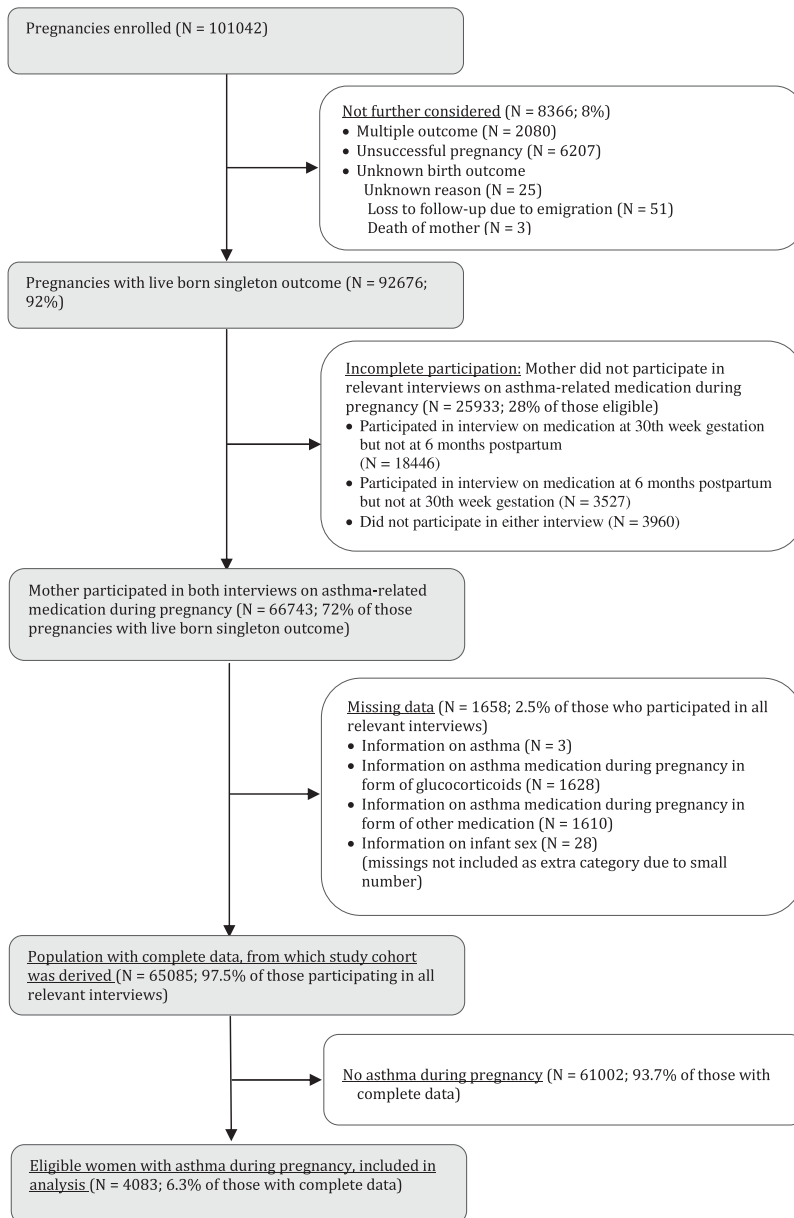


Figure 1. Flowchart of study participants.

With regard to endocrine and metabolic disorders, our results are in line with numerous animal studies demonstrating that intrauterine exposure to glucocorticoids has long-term effects on endocrine and metabolic function, including changes in HPA function, glucose–insulin homeostasis, pancreatic development, and fat metabolism (44). However, because these animal studies did not use inhalation as type of administration, comparisons should be drawn with caution.

Several mechanisms potentially linking glucocorticoid inhalation during pregnancy and endocrine and metabolic disorders in offspring should be considered. A proportion of the inhaled glucocorticoids that enter the systemic circulation may cross the placenta and enter the fetus (6, 45). Human evidence for the early presence of the glucocorticoid receptor (approved symbol is NR3C1) in the fetus (46) indicates that glucocorticoids may take effect in the fetus by the glucocorticoid receptor and lead to persistent derangements in endocrine and metabolic control (47, 48), even though recent evidence suggests that inhaled glucocorticoids do not exert effects on glucocorticoid-regulated pathways in the fetus (49). Alternatively, synthetic

glucocorticoids may affect maternal physiology, with secondary effects on the fetus. Indeed, glucocorticoid inhalation influences, among others, maternal HPA activity (14), which may play a role in endocrine and metabolic alterations in the offspring (50).

Our study has important strengths, including prospective data collection for a total of 65,085 mother–child pairs; linkage of a comprehensive medical registry with complete and medically verified diagnoses; and control for potential bias by confounding by indication for treatment with glucocorticoid inhalants, using propensity scores. By controlling for non-glucocorticoid-containing inhalants and other types of asthma medication, we took into account potential confounding by treatment-related asthma severity. However, residual or uncontrolled confounding cannot be completely excluded. Therefore, our finding of increased risk of endocrine and metabolic diseases in the offspring needs replication in an independent dataset. Our findings have clinical and public health relevance, because asthma is a common serious medical problem to complicate pregnancy, with glucocorticoid inhalation as recommended treatment (1, 2, 5).

TABLE 2. COX REGRESSION MODELS OF OFFSPRING DISEASES PREDICTED BY GLUCOCORTICOID INHALATION DURING PREGNANCY*

ICD-10 Category	No. of Children with a Diagnosis	Crude HR (95% CI) [†]	P	Adjusted HR (95% CI) [‡]	P
1. Infections, parasitic diseases	565	0.97 (0.81–1.16)	0.746	0.91 (0.75–1.11)	0.361
2. Neoplasms	41	0.56 (0.26–1.21)	0.141	0.54 (0.25–1.17)	0.118
3. Diseases of blood, immune system	29	1.63 (0.78–3.43)	0.193	1.54 (0.69–3.41)	0.290
4. Endocrine, metabolic disorders	93	1.54 (1.01–2.34)	0.045	1.62 (1.03–2.54)	0.036
5. Mental disorders	44	1.31 (0.71–2.42)	0.382	1.31 (0.71–2.44)	0.392
6. Diseases of nervous system	116	0.80 (0.53–1.22)	0.302	0.79 (0.51–1.23)	0.296
7. Diseases of eye	107	0.86 (0.56–1.32)	0.490	0.80 (0.52–1.23)	0.317
8. Diseases of ear	361	1.05 (0.84–1.31)	0.685	1.08 (0.86–1.37)	0.499
9. Diseases of circulatory system	26	1.23 (0.55–2.75)	0.618	1.35 (0.62–2.97)	0.453
10. Diseases of respiratory system	1,075	1.06 (0.93–1.21)	0.385	1.05 (0.91–1.20)	0.501
11. Diseases of digestive system	302	1.24 (0.98–1.58)	0.070	1.26 (0.98–1.63)	0.077
12. Diseases of skin	212	1.07 (0.80–1.43)	0.654	1.00 (0.73–1.38)	0.976
13. Diseases of musculoskeletal system	199	1.07 (0.80–1.45)	0.639	1.02 (0.74–1.40)	0.919
14. Diseases of genitourinary system	156	1.09 (0.78–1.53)	0.611	1.01 (0.71–1.44)	0.955
Any	2,443	1.03 (0.95–1.12)	0.437	1.05 (0.96–1.15)	0.242

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; ICD-10 = International Classification of Diseases–10th revision.

*HRs for the offspring having an initial diagnosis within the respective diagnostic category (outcomes) according to inhaled glucocorticoid use during pregnancy because of asthma (predictor) (N = 4,083). Information on the children's diagnoses was 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, the initial diagnosis was used.

[†]Crude model presented in support of transparency.

[‡]All models stratified for socioeconomic status, parity, maternal age, and general maternal health, and adjusted for infant sex. In addition, the glucocorticoid versus no glucocorticoid comparisons were adjusted for use of any non-glucocorticoid-containing inhalant for asthma treatment.

Furthermore, ongoing follow-up of children in this cohort makes it possible to add further findings at later stages. On the basis of (1) previous reports documenting that initial selection bias caused by nonparticipation does not place a major threat to the Danish National Birth Cohort (51), (2) the acceptable retention and follow-up rate in the present study, together with the fact that the validity of regression models is only marginally affected by selective drop-out (52), (3) the high percentage of complete data, and (4) 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.

One limitation of the present study is that we did not have information on the offspring's medical diagnoses given from general practitioners, meaning we probably missed less severe pathologies. Moreover, we did not have information on the daily inhalation doses, even though offspring disease risk might vary depending on the amount of glucocorticoids administered. To obtain such information from interviews is, however, hardly feasible in such a large cohort. Even though each organ system has a specific critical period in which it is most susceptible to intrauterine perturbations (53), we did not include data on timing of inhaled glucocorticoid exposure during pregnancy, because most women reported using glucocorticoid inhalants throughout most parts of pregnancy. Moreover, we did not repeat analyses including only mother–child pairs exposed to beclomethasone and fluticasone, respectively, because this would

have led to imprecise estimations and statistical assumption failures caused by small sample sizes and small numbers of events. Furthermore, we focused on glucocorticoid inhalation for asthma treatment during pregnancy rather than on other active ingredients (e.g., long-acting β -agonists) or on glucocorticoids administered by other routes of administration, because glucocorticoid inhalation has been recommended as the preferred asthma therapy during pregnancy and treatment indication for glucocorticoid inhalation is rather homogeneous. We did not exclude mother–child pairs in which maternal asthma treatment during pregnancy with inhaled glucocorticoids had been complemented with other active ingredients or with glucocorticoids administered by other routes of administration, because this again would have led to imprecise estimations and statistical assumption failures caused by a considerable reduction of sample size (>50%; see Table 1) and small numbers of events. However, we took into account potential bias by other types of medications (see above).

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 diseases (22). 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. Moreover, the prevalence of women suffering from asthma during pregnancy in this cohort (6.3%) is

TABLE 3. LOGISTIC REGRESSION MODELS OF OFFSPRING DISEASES PREDICTED BY GLUCOCORTICOID INHALATION DURING PREGNANCY*

ICD-10 Category	No. of Children with a Diagnosis	Crude OR (95% CI) [†]	P	Adjusted OR (95% CI) [‡]	P
16. Conditions originating in perinatal period	850	1.01 (0.86–1.19)	0.885	1.02 (0.86–1.22)	0.803
17. Malformations	390	1.09 (0.87–1.36)	0.456	1.08 (0.85–1.37)	0.519

Definition of abbreviations: CI = confidence interval; ICD-10 = International Classification of Diseases–10th revision; OR = odds ratio.

*ORs for the offspring's risk of having conditions originating in the perinatal period and malformations (outcomes) according to inhaled glucocorticoid use during pregnancy because of asthma (predictor) (N = 4,083). Information on the children's diagnoses was 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, the initial diagnosis was used.

[†]Crude model presented in support of transparency.

[‡]All models stratified for socioeconomic status, parity, maternal age, and general maternal health, and adjusted for infant sex. In addition, the glucocorticoid versus no glucocorticoid comparisons were adjusted for use of any non-glucocorticoid-containing inhalant for asthma treatment.

virtually identical with the prevalence of asthma during pregnancy, based on medical records, in a recent large epidemiologic study (6.5%) (54). Besides the validity of self-report of asthma during pregnancy, the validity of self-reported medication use during pregnancy has been discussed and the best way to assess medication use during pregnancy has been a matter of debate. Some studies focused on whether the use of registry-based data on drug prescription or dispensing represents a useful approach to assess glucocorticoid use during pregnancy. Notably, the value of such data has been shown to be limited because of noncompliance (55). Therefore, interviews on drug use have been suggested as a useful alternative (55). Still, self-reported medication during pregnancy may be limited by recall bias (56). However, most importantly, it has been argued that differential recall is particularly relevant when data are retrospectively collected after the outcome disease is known by the subjects (57) and when drugs are used only for a short period of time (56); therefore, given that we used prospective data on medication that were collected as early as 30 weeks gestation and 6 months postpartum (i.e., predominantly before offspring disease outcomes were known) and given the fact that glucocorticoid inhalation was mainly used over a long period of time, we think that recall bias is rather unlikely.

Caution is warranted when interpreting the putative biologic meaning of the major findings, given the heterogeneity of the rationales behind the different ICD-10 categories (e.g., grouping by organ system and etiology). However, results of the exploratory case-control analyses provide the hypothesis that glucocorticoid inhalation during pregnancy may indeed predict the risk of more specific subcategories and diagnoses. Moreover, the ICD-10, with its high reliability at the category level (58), is the international standard diagnostic classification system of diseases, recommended for epidemiologic studies.

There is evidence from a long-term follow-up study that metabolic function can be impaired in adult offspring of mothers who received intramuscular injections of synthetic glucocorticoid during pregnancy (59). Further follow-up of our cohort will allow examining whether the observed impairments in endocrine and metabolic function persist into adulthood, and whether further offspring pathologies related to maternal glucocorticoid inhalation during pregnancy manifest at a later stage. With regard to generalizability of the findings to multiples, caution is warranted until results are confirmed in a sufficiently large sample of higher-order pregnancies.

If these findings are corroborated in independent data sources, other studies should focus on the role of the daily inhalation dose, the specific effects of beclomethasone and fluticasone, and the underlying mechanisms and pathways of the association between glucocorticoid inhalants during pregnancy and the offspring's risk of endocrine and metabolic disorders, such as epigenetic mechanisms, the HPA axis, placenta, and fetal development, which have recently been linked to early adversities (47, 60–62). Furthermore, they should analyze in detail long-term effects of intrauterine exposure to glucocorticoids on specific endocrine and metabolic pathologies, including laboratory results and biologic disease markers, evaluate the addition of long-acting β -agonists to inhaled glucocorticoids, and most importantly identify modifiable factors within this context to improve preventive approaches and interventions.

To the best of our knowledge, this is the first comprehensive study of the potential effects of glucocorticoid inhalation during pregnancy on offspring health, covering a large spectrum of pediatric diseases. Data on the use of glucocorticoid inhalants during pregnancy were mostly reassuring, supporting the use of glucocorticoid inhalation in women with asthma during pregnancy. However, the risk of endocrine and metabolic disorders in the

offspring of women using glucocorticoid inhalation during pregnancy needs further attention, as does the risk of diseases in diagnostic categories for which we only had small case numbers. Given the widespread use of glucocorticoid inhalation in the treatment of asthma, our findings should be considered to critically reappraise the long-term risks and benefits of glucocorticoid inhalation during pregnancy.

Author disclosures are available with the text of this article at www.atsjournals.org.

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**Inhaled glucocorticoids during pregnancy and offspring pediatric diseases:
A national cohort study**

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Online Data Supplement

Online Data Supplement: Additional information on statistical analyses

We estimated the associations between use of glucocorticoid inhalants for asthma treatment during pregnancy and the offspring's risk for the first diagnosis of a disease by conducting separate Cox proportional hazards regression models (1) for each of the diagnostic categories 1 to 14 and "any disease". 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 (2). Data on all other children were censored at the end of follow-up (December 31, 2006). Age in days was used as time variable. We evaluated the proportional hazards assumption by visually checking Schoenfeld residuals and the test of Grambsch and Therneau (3).

We used separate logistic-regression models to assess the associations between use of glucocorticoid inhalants for asthma treatment during pregnancy and the risk of conditions originating in the perinatal period and congenital malformations in the offspring, as these conditions are present around birth, and reasons for latency until diagnosis are likely unrelated to use of glucocorticoid inhalants during pregnancy.

Since 143 singletons were born to mothers who contributed more than one pregnancy to the study, we calculated all standard errors using the clustered sandwich estimator to correct for possible dependence between health outcomes in infants born to the same mother (4).

To obtain less confounded estimates, we stratified the analyses, thereby allowing for separate baseline hazard functions for each stratum, for several potential predictors of child health, selected *a priori*, that might confound or suppress effects, including socioeconomic status (5) based on the mother's occupation (see (6)), parity (7), maternal age (8), general maternal health (9), and adjusted for infant sex and use of any non-glucocorticoid-containing inhalant for asthma treatment (10, 11), with the categories indicated in Table 1.

We repeated the adjusted analyses on the association between glucocorticoid inhalants for asthma treatment during pregnancy and offspring health using propensity scores (12, 13) to control for confounding by indication for treatment with glucocorticoid inhalants. We computed propensity scores for women with asthma during pregnancy by using logistic regression with the dependent variable being use of glucocorticoid inhalants during pregnancy and a variety of prognostic factors (covariates), including maternal smoking during pregnancy, numerous other maternal diseases (e.g. diabetes and allergy during pregnancy) and respective use of medication, maternal asthma treatment in form of pills or other non-inhalant medication, maternal asthma before pregnancy, maternal psychosocial stress during pregnancy, maternal disease burden and perceived health, paternal asthma and allergies, and many other variables (detailed list available on request). Individuals were categorized into nine strata according to their propensity scores, so that within each stratum, covariates in treated and untreated groups were approximately similarly distributed (14). Cox proportional hazards and logistic regression models were stratified for propensity score strata (15), excluding 59 cases outside the region of common support.

The risk of adverse effects may vary with different types of glucocorticoid inhalation due to differences in first-pass metabolism and absorption from the airways and differences in pharmacokinetics following absorption (16, 17). The majority of women in this study used budesonide ($n=983$; 79.9%). Therefore, we also repeated the adjusted analyses comparing

offspring of mothers using only budesonide as glucocorticoid inhalation for asthma treatment during pregnancy and offspring of mothers not using any type of glucocorticoid inhalation.

Finally, we repeated the adjusted analyses including only the first pregnancy of each woman in the cohort, also to control for previous reproductive experiences (18).

We additionally repeated the adjusted analyses after controlling for further, *a posteriori* defined, potential confounders, with the categories ‘yes’, ‘no’, ‘unknown’, if not otherwise specified in brackets, including maternal smoking during pregnancy, maternal diabetes during pregnancy, maternal gestational diabetes during pregnancy, pre-pregnancy obesity and gestational obesity (BMI, kg/m²: ≤30; > 30; unknown), as defined by (19), weight gain during pregnancy (continuous), maternal sleep problems during pregnancy, maternal allergy during pregnancy, paternal lifetime asthma, and paternal lifetime allergy.

Based on the results of the primary Cox regression analyses, we performed two exploratory case-control analyses with the most common specific subcategory (‘metabolic disorders’, *n* = 66 cases) and the most common specific diagnosis (‘volume depletion’, *n* = 47 cases) within the ICD-10 category ‘endocrine and metabolic disorders’ observed in the study cohort, as outcomes. Each time, we used all other offspring of mothers suffering from asthma during pregnancy as controls, as these are the closest to the source population with regard to exposure distribution (20). To test whether children with a diagnosis in the subcategory ‘metabolic disorders’ and whether children with the diagnosis ‘volume depletion’ were more likely than controls to be exposed to inhaled glucocorticoids *in utero*, cases and controls were compared using one-sided Fisher’s exact tests, with regard to maternal history of exposure to glucocorticoid inhalation during pregnancy.

We obtained information on offspring sex and maternal age at delivery from the Danish Medical Birth Registry (21), on socioeconomic status, parity, and general maternal health from the interview at 12 weeks gestation, on use of any non-glucocorticoid-containing inhalant for asthma treatment from the interview at 30 weeks gestation, and on further

covariates for the propensity score and the additional analyses from the interviews taken at 12 and 30 weeks gestation and at 6 months postpartum.

All tests were two-tailed, if not otherwise specified, and we set the level of significance at 0.05. 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 and glucocorticoid therapy 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 10.0).

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