FACULTY OF HEALTH SCIENCE; AARHUS UNIVERSITY

# Use of Corticosteroids during Pregnancy and in the Postnatal Period and Risk of Asthma in Offspring: A Nationwide Danish Cohort Study.

*Research Year Report*

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## PREFACE

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## List of abbreviations:

| | |
|---|---|
| ACS | Antenatal Corticosteroid Therapy |
| ATC | Anatomical Therapeutic Chemical Classification System |
| BMI | Body Mass Index |
| CD | Crohn's Disease |
| CI | Confidence Interval |
| COPD | Chronic Obstructive Pulmonary Disease |
| COX | Cyclooxygenase Inhibitors |
| CPR | Civil Personal Registration |
| CRS | Civil Registration System |
| DM | Diabetes Mellitus |
| DMBR | Danish Medical Birth Registry |
| DNRP | Danish National Registry of Patients |
| ER | Emergency Room |
| HR | Hazard Ratio |
| IBD | Inflammatory Bowel Disease |
| ICD | International Classification of Diseases |
| OR | Odds Ratio |
| PPI | Proton Pump Inhibitors |
| RMPS | Danish registry of Medicinal Product Statistics |
| UC | Ulcerative Colitis |

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**Abstract**

*Background*

We examined maternal use of local and systemic corticosteroids during pregnancy and the postnatal period and risk of asthma in offspring.

*Material and Methods*

We conducted a cohort study including all live-born singletons born in Denmark between 1 January 1996 and 31 December 2009, with follow-up through 2010. Data on maternal corticosteroid use, asthma in offspring (hospital diagnosis and/or prescriptions for anti-asthma medication), and covariates were obtained from population-based medical registries. We computed absolute risk of asthma and used Cox proportional hazards regression to compute hazard ratios (aHRs) comparing children pre- or postnatally exposed to corticosteroids with unexposed children. Furthermore, we used logistic regression to compare exposed children with unexposed siblings, "within-mother-between-pregnancy", to address possible confounding from genetic and environmental factors.

*Results*

We identified 877,778 children and 31,759 (3.6%) were prenatally exposed to systemic (n=5,325) or local (n=26,434) corticosteroids. A total of 105,677 (8.3%) children developed asthma. The 10-year asthma risk was 18.4% for exposed children and 13.5% for unexposed. The corresponding aHR was 1.44 (95% CI:1.35-1.54). Results were similar when examining local corticosteroids. We found no increased risk of asthma in the "within-mother-between-pregnancy" analysis [adjusted odds ratio = 0.95 (95% CI:0.89-1.02)].

*Conclusions*

A positive association between prenatal exposure to corticosteroids and increased risk of asthma in offspring was not replicated in a "within-mother-between-pregnancy" analysis. This indicates confounding of the overall analyses by genetics, underlying disease or shared environmental risk factors.

Keywords: asthma, glucocorticoids, pregnancy, cohort study, prenatal exposure, delayed effects.

## Introduction

In recent decades asthma has become the most common childhood chronic lower respiratory disease worldwide (1), with an estimated prevalence of 5% to 20% among children in industrialized countries (2, 3). The causes of asthma are largely unknown, but genetics (4) and maternal factors such as smoking (5) and high body mass index (BMI) (6) are among reported risk factors. Maternal use of medications during pregnancy, such as paracetamol (7), proton pump inhibitors (PPIs) (8), cyclooxygenase (COX) inhibitors (9) and antibiotics (10), has also been associated with an increased risk of asthma in offspring.

Corticosteroids are potent anti-inflammatory drugs used by some women during pregnancy for various diseases, such as asthma and inflammatory bowel disease (IBD), despite maternal and fetal side effects (11, 12, 13).

A study found that antenatal corticosteroid (ACS) therapy used to induce fetal lung maturation is associated with childhood asthma [aOR = 1.23 (95% CI: 1.06-1.44)] (14).

To our knowledge, no studies have investigated the association between maternal corticosteroid therapy at any time during pregnancy and asthma in offspring. We therefore conducted a nationwide cohort study, based on Danish medical registries, to examine the association between maternal corticosteroid therapy during pregnancy, and in the postnatal period, and risk of asthma in offspring.

## Methods

*Setting and study population*

This nationwide cohort study included all singletons live-born in Denmark from January 1, 1996 until December 31, 2009. Mothers were identified through the Danish Medical Birth Registry (DMBR), which covers all births in Denmark since 1973 (15, 16). We used the civil registration number (CPR-number), a unique ten-digit personal identifier, provided to every Danish citizen at birth or upon immigration (17) to perform unambiguous linkage of registries. The National Health Service provides tax-supported health care to all Danish residents and refunds a portion of patient expenditures for a wide range of prescribed drugs, including corticosteroids.

*Corticosteroid use*

In Denmark most local and all systemic corticosteroids are dispensed by prescription only. The Danish registry of Medicinal Product Statistics (RMPS) records type of drug according to the Anatomical Therapeutic Chemical (ATC) classification system and the date of prescription reimbursement on all prescribed medications dispensed from pharmacies nationwide. Exposure to corticosteroids was defined as at least one redeemed prescription for a systemic corticosteroid or at least two redeemed

prescriptions for local corticosteroids 30 days before or during pregnancy. In sensitivity analyses we changed the start of the exposure window from 30 days before pregnancy to 60 and 0 days before pregnancy, respectively. Pregnancy was defined as the first day of the last menstrual period and until delivery.

*Asthma*

Asthma in offspring was defined as an inpatient, outpatient or Emergency Room (ER) diagnose of asthma and/or by redemption of prescriptions on beta-2-agonists and inhaled corticosteroids on two separate occasions. This algorithm has a positive predictive value (PPV) of 80% to 100% in patients 5-45 years of age (18). We obtained data on asthma diagnoses through the Danish National Registry of Patients (DNRP) coded according to the World Health Organization's International Classification of Diseases (ICD) eight revision until the end of 1993 and the tenth revision thereafter. The DNRP contains information on all inpatients discharges from non-psychiatric acute care hospitals since 1977. ER and outpatient clinic contacts were added in 1995 (15).

*Data on covariates*

We included a number of covariates identified as risk factors for asthma. From the DMBR we obtained information on maternal age at delivery (19), maternal smoking status (20), maternal BMI (recorded from 2004 and on) (21), gender (4), gestational age (22), Apgar score (23), birth order (24), birth weight (25) and caesarean section (26). From the RMPS we obtained information on maternal use of medications (paracetamol, PPI, COX inhibitors and antibiotics) (7, 8, 9, 10). The DNRP was used to identify maternal asthma, maternal inflammatory bowel disease (IBD) subdivided into ulcerative colitis (UC) and Crohn's disease (CD), maternal diabetes (DM), maternal chronic obstructive pulmonary disease (COPD) (27), and other maternal autoimmune diseases, as well as respiratory distress syndrome (RDS) in offspring. All relevant ICD and ATC codes are provided in Appendices 1 and 2.

*Statistical analysis*

The children were followed from date of birth until date of asthma, death, emigration, or the end of follow up on December 31. 2010, whichever came first. We computed 2-year, 5-year, and 10-year risk of asthma according to corticosteroid exposure, considering death as a competing risk.

Cox proportional hazard regression was used to compute crude and adjusted hazard ratios (aHR) with 95% confidence intervals (95% CI), comparing children exposed to corticosteroids pre- or postnatally with children unexposed during those periods. As Danish women are encouraged to breastfeed during the first postpartum year, we used this time period to define the breastfeeding period.
Furthermore, we categorized prenatal exposure periods into first trimester (the first 12 weeks of pregnancy), and the remainder of pregnancy. Additionally, we stratified by maternal smoking, maternal age, maternal disease, birth weight, birth order, birth year and gestational age.
In additional analyses we restricted the definition of asthma to only include hospital-diagnosis of asthma. As a diagnosis of asthma can only be made with certainty from age 5 years onwards we also did an analysis starting follow up at age 5 years (28). Furthermore, we stratified by maternal pre-pregnancy BMI for children born from 2004 on. Finally, we conducted an analysis excluding mothers who themselves had a hospital diagnosis of asthma, in order to reduce any bias from genetic and environmental factors implicated in the development of asthma in offspring.

*Within-mother-between-pregnancy analysis*

We conducted a "within-mother-between-pregnancy" analysis, based on the assumption that siblings share DNA and environment during their upbringing (29). Our aim was to reduce bias from these factors. We identified families in which at least one sibling was exposed to corticosteroids anytime during gestation and at least one was not. The unexposed sibling served as the reference. Conditional logistic regression was used for this analysis. The computed outcome measure was odds ratios (ORs) with 95% confidence intervals (95% CIs). The crude estimate was adjusted for birth-period (1996-2000, 2001-2005, or 2006-2009). The adjusted estimate accounted for maternal age, maternal smoking status, maternal use of medication (paracetamol, PPIs, COX inhibitors, antibiotics), mode of delivery, gestational age, birth order, birth weight, gender and birth year. Similarly, we conducted a second "within-parents-between-pregnancy" analysis in which siblings had the same mother and father.

Analyses were performed using SAS® (v 9.2; SAS Inc, Cary, NC). The study was approved by the Danish Data Protection Agency (record no. 2011-41-6465).

**Results**

*Descriptive data*

We identified 877,778 children born alive in Denmark from January 1, 1996 until December 31, 2009. Overall 31,759 (3.6%) children were prenatally exposed to corticosteroids and 5,325 (0.6%) of the mothers used systemic corticosteroids (3,800 redeemed 1 prescription, 1,525 redeemed 2 or more

prescriptions). Local corticosteroids were used by 26,434 (3.0%) mothers during pregnancy. Mothers using corticosteroids during pregnancy were older than non-users, and they more frequently used other drugs during pregnancy (table 1). More children exposed to corticosteroids during gestation were delivered by Caesarean section than unexposed children (table 2). A total of 6,134 (0.7%) women suffered from inflammatory bowel disease (IBD) [2,026 from Crohn's disease (CD), 3,448 from ulcerative colitis (UC) and 660 from both]. Also, 2,337 (0.3%) women suffered from chronic obstructive pulmonary disease (COPD). The prevalence of type 1 and type 2 diabetes mellitus (DM) in women was similar. A total of 94,976 (10.8%) women suffered from one of the chronic or autoimmune diseases listed in Appendix 3.

*Asthma in offspring*

The maximum follow-up time was 15 years (median of 7.0 years for unexposed children and 5.8 years for exposed). The absolute risk of asthma among unexposed children was 6.8%, 10.9% and 13.5% after 2, 5 and 10 years of follow up, respectively. For exposed children the corresponding estimates were 9.5%, 15.1%, and 18.4%.

We observed an increased risk of asthma in children who were prenatally exposed to systemic corticosteroid therapy during pregnancy [aHR = 1.44 (95% CI: 1.35-1.54)]. Results were similar for children whose mothers used local corticosteroid therapy during pregnancy (Table 3). When stratifying the analyses according to various indications for corticosteroid treatment during pregnancy, an association between all maternal indications and asthma in children was observed, except for maternal IBD (Table 4). There was no increased risk of asthma in children exposed to corticosteroids and born very prematurely (weeks 19-29), while birth from week 30 and later yielded results similar to those of the main analysis (results not shown). Risk of asthma did not vary substantially between exposures in the different trimesters (Table 5).

Results did not change when asthma was strictly defined as a hospital diagnosis of asthma, when starting follow-up at age 5, or with additional adjustment for maternal BMI (results not shown). When the exposure period was changed to the first year after birth, we observed an increased risk of asthma in offspring [aHR = 1.20 (95% CI: 1.16-1.23)].

Finally, changing the exposure period from 30 days prior to pregnancy to 0 days and 60 days prior to pregnancy, did not change the estimates (data not shown).

*Sibling comparison*

The "within-mother-between-pregnancy" analysis showed no increased risk of asthma in siblings exposed to corticosteroids, compared to unexposed siblings (Table 6). Restricting this analysis to children with the same mother and father, instead of just the same mother, did not change the estimates substantially [aOR = 0.92 (95% CI: 0.89-1.00)].

## Discussion

We observed an overall increased risk of asthma in offspring prenatally exposed to corticosteroids, compared to unexposed children, similarly for children exposed postnatally. The estimates stayed unaltered when subjected to changes in asthma definition, time of exposure during gestation and starting follow-up at age 5 years. However, in the "within-mother-between-pregnancy" analysis we found no increased risk of asthma in the exposed sibling compared to the unexposed sibling.

To our knowledge, no previous studies have investigated use of corticosteroids at any time during pregnancy and risk of asthma in offspring. However, corresponding to estimates in our main analyses one study by Pole et al. reported that antenatal corticosteroid therapy administered just prior to birth was associated with an increased risk of asthma in the offspring (14), but the study did not include exposure to other medications or report a "within-mother-between-pregnancy" analysis.

Children of the same mother share a number of genetic and environmental factors, and by comparing siblings some unmeasured confounding will be accounted for. For this reason we conducted the "within-mother-between-pregnancy" analysis, which did not show an increased risk of asthma in the sibling exposed to corticosteroids during gestation, compared to the unexposed sibling. Although maternal use of corticosteroids may have various effects on the fetus (30, 31, 32) our data, based on this analysis, does not provide evidence that prenatal exposure to corticosteroids increases the risk of asthma. It should, however, be noted that the sibling design may also be confounded to some extent. Frisell T et al. recently published a paper questioning whether sibling design studies are always preferable for comparing exposed and unexposed siblings (33). They argued that any difference in confounding factors or measurement error between siblings would bias the estimate more than such differences between non-siblings. Thus if measurement error (*e.g.* misclassification of exposure status) is present, our estimates would be biased towards the null.

Bias and confounding

The strengths of our study include its large sample size and long and complete follow-up. Furthermore, the use of medical registries, in which data is not collected for research purposes, eliminates risk of selection and recall bias.

Potential misclassification of exposure status remains a study limitation since we do not know if and when mothers actually took the medication. Also we have no information on over the counter nasal sprays and corticosteroid containing creams. Similarly, we did not have information on corticosteroids given during hospitalization and did not know whether mothers at risk of preterm delivery were given corticosteroids in order to induce lung maturation in the fetus. This has been associated with asthma in offspring (14). However, patients prescribed systemic corticosteroids are likely to suffer from severe chronic disease and therefore also likely to use the medication. Furthermore, we cannot rule out some misclassification of children without actual asthma but with wheezing although using a validated algorithm for identifying asthma (18).

The risk of asthma was higher in exposed than unexposed children at the ages of 2, 5 and 10 years. In addition the median age at diagnosis was lower in exposed children. This might be due to a higher awareness of symptoms among mothers who themselves suffer from a chronic disease. They might be more prone than healthy mothers to take their children to the doctor. This could lead to differential misclassification, if children with milder symptoms and healthy mothers are less apt to be diagnosed.

Our main results are likely to be affected by unmeasured confounding from maternal alcohol consumption, socioeconomic status, diet, genetics and possible residual confounding from maternal smoking. The fact that the findings from our main analysis were not replicated in the "within-mother-between-pregnancy" analysis suggests that our main results were confounded. Besides unmeasured confounding, confounding by indication could also explain the association observed in our main results, as mothers who themselves had asthma would be at increased risk of genetically priming their offspring's susceptibility to this condition. However, analyses excluding mothers with asthma yielded similar results arguing against this conjecture.

The health consequences of withholding corticosteroids in pregnant women, in terms of poorly regulated disease, should be considered when assessing the implications of our results (34).

In conclusion, overall, prenatal exposure to both systemic and local corticosteroids was associated with an increased risk of asthma in offspring. However, since no association was observed in the "within-mother-between- pregnancy" analysis, these estimates are likely biased by unmeasured

confounding factors, such as genetic factors, underlying disease, or shared exposures in the environment such as diet.

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## Tables:

**Table 1. Characteristics of mothers of live born children from 1 January 1996 to 31 December 2009 in Denmark, according to corticosteroid drug use during pregnancy, N = 877 778.**

| | Corticosteroid use during pregnancy, n (%) | No corticosteroid use during pregnancy, n (%) |
|---|---|---|
| **All** | 31,759 (100) | 846,019 (100) |
| **Age** | | |
| **<25** | 2,363 (7.4) | 119,386 (14.1) |
| **25-29** | 9,306 (29.3) | 295,693 (35.0) |
| **30-34** | 12,819 (40.4) | 295,891 (35.0) |
| **35-39** | 6,170 (19.4) | 116,104 (13.7) |
| **≥40** | 1,101 (3.5) | 18,945 (2.2) |
| **Use of other drugs during pregnancy** | | |
| **Use of antibiotics** | 14,817 (46.7) | 297,906 (35.2) |
| **Use of paracetamol** | 554 (1.7) | 5,367 (0.6) |
| **Use of PPIs** | 887 (2.8) | 10,238 (1.2) |
| **Use of NSAIDs/Coxibs** | 2,384 (7.5) | 35,412 (4.2) |
| **Smoking during pregnancy** | | |
| **Non smokers** | 25,391 (80.0) | 653,391 (77.2) |
| **1-10 cigarettes per day** | 3,908 (12.3) | 120,435 (14.2) |
| **11-20 cigarettes per day** | 1,150 (3.6) | 35,206 (4.2) |
| **>20 cigarettes per day** | 173 (0.5) | 4,962 (0.6) |
| **Missing** | 1,137 (3.6) | 32,025 (3.8) |
| **Chronic disease** | | |
| **Inflammatory bowel disease (IBD)** | 1,037 (3.3) | 5,097 (0.6) |
| **Crohn's disease (CD)** | 251 (0.8) | 1,775 (0.2) |
| **Ulcerative colitis (UC)** | 655 (2.1) | 2,793 (0.3) |
| **Both** | 131 (0.4) | 529 (0.1) |
| **Chronic obstructive pulmonary disease (COPD)** | 178 (0.6) | 2,159 (0.3) |
| **Maternal Diabetes Mellitus (type 1)** | 116 (0.4) | 2,865 (0.3) |
| **Maternal Diabetes Mellitus (type 2)** | 120 (0.4) | 2,355 (0.3) |
| **Asthma** | 4,431 (14.0) | 38,662 (4.6) |
| **Maternal body-mass index (BMI)*** | | |
| **No BMI (before 2004)** | 16,427 (51.7) | 491,285 (58.1) |
| **Low (BMI: 15-18.4)** | 553 (1.7) | 16,854 (2.0) |
| **Normal (BMI: 18.5-24.9)** | 8,846 (27.9) | 204,289 (24.1) |
| **Overweight (BMI: 25-29.9)** | 3,131 (9.9) | 68,411 (8.1) |
| **Obese and severe obesity (BMI > 30)** | 1,716 (5.4) | 38,215 (4.5) |
| **Missing** | 1,086 (3.4) | 26,965 (3.2) |

* Data on maternal BMI were only available from 2004 and forth.

**Table 2. Characteristics of children born in Denmark between 1 January 1996 and 31 December 2009, according to prenatal exposure to corticosteroids.**

| | Exposed to corticosteroids during pregnancy, n (%) | Not exposed to corticosteroids during pregnancy, n (%) |
|---|---|---|
| **Exposure period** | | |
| **Corticosteroid use 30 days prior to conception** | 2,246 (7.1) | |
| **Exposure during 1st trimester** | 7,297 (23.0) | |
| **Exposure during 2nd and 3rd trimester** | 22,216 (70.0) | |
| **Gestational age** | | |
| **19-29 weeks** | 96 (0.3) | 2,918 (0.3) |
| **30-36 weeks** | 1,402 (4.4) | 37,965 (4.5) |
| **37-41 weeks** | 27,686 (87.2) | 736,254 (87.0) |
| **42-48 weeks** | 2,418 (7.6) | 63,202 (7.5) |
| **Missing** | 157 (0.5) | 5,680 (0.7) |
| **Mode of delivery** | | |
| **Caesarean section** | 6,717 (21.2) | 148,607 (17.6) |
| **Respiratory distress syndrome (RDS)** | 1,218 (3.8) | 29,910 (3.5) |
| **Apgar score** | | |
| **<7** | 206 (0.7) | 5,828 (0.7) |
| **7-9** | 2,136 (6.7) | 55,853 (6.6) |
| **10** | 29,114 (91.7) | 774,315 (91.5) |
| **Missing** | 303 (1.0) | 10,023 (1.2) |
| **Birth weight** | | |
| **1500-2000 g** | 207 (0.7) | 6,003 (0.7) |
| **2000-2499 g** | 687 (2.2) | 18,565 (2.2) |
| **2500-2999 g** | 2,956 (9.3) | 86,449 (10.2) |
| **3000-5500 g** | 27,567 (86.8) | 723,099 (85.5) |
| **Misssing** | 342 (1.1) | 11,903 (1.4) |
| **Gender** | | |
| **Girl** | 15,236 (48.0) | 411,944 (48.7) |
| **Boy** | 16,523 (52.0) | 434,075 (51.3) |
| **Birth order** | | |
| **1** | 12,020 (37.9) | 365,101 (43.2) |
| **2** | 12,688 (40.0) | 314,768 (37.2) |
| **≥3** | 7,051 (22.2) | 166,150 (19.6) |
| **Birth year** | | |
| **1996-2000** | 9,881 (31.1) | 312,128 (36.9) |
| **2001-2005** | 11,254 (35.4) | 297,823 (35.2) |
| **2006-2009** | 10,624 (33.5) | 236,068 (27.9) |

**Table 3. Crude and adjusted hazard ratios (HRs) for asthma in children born in Denmark between 1996 and 2009, according to prenatal exposure to local or systemic corticosteroids at any time during gestation.**

| | N (%) | Crude HR (95% CI) | *Adjusted HR (95% CI) |
|---|---|---|---|
| **No corticosteroid use** | | 1.00 (ref) | 1.00 (ref) |
| **Systemic treatment:** | 5,325 (0.6) | 1.61 (1.51-1.72) | 1.44 (1.35-1.54) |
| **1 redeemed prescription** | 3,800 (0.4) | 1.61 (1.50-1.74) | 1.49 (1.38-1.61) |
| **≥2 redeemed prescriptions** | 1,525 (0.2) | 1.61 (1.43-1.82) | 1.32 (1.17-1.49) |
| **Local treatment:** | 26,434 (3.0) | 1.36 (1.32-1.40) | 1.36 (1.32-1.41) |

*Adjusted for maternal age, maternal smoking, maternal use of antibiotics, paracetamol, PPIs or anti-inflammatory drugs, mode of delivery, birth year, birth weight, gestational age, birth order and gender.

**Table 4. Crude and adjusted hazard ratios (HRs) for asthma in offspring prenatally exposed to corticosteroids compared to offspring prenatally unexposed, according to maternal indications for corticosteroid treatment in terms of inflammatory bowel disease (IBD), asthma, or autoimmune disease.**

| | Crude HR (95%CI) | *Adjusted HR (95%CI) |
|---|---|---|
| Maternal disease: | | |
| IBD | 0.99 (0.80-1.21) | 0.94 (0.76-1.17) |
| No IBD | 1.51 (1.47-1.55) | 1.48 (1.44-1.52) |
| Asthma (ICD code or use of anti-asthma medication) | 1.29 (1.21-1.37) | 1.31 (1.23-1.40) |
| No asthma (ICD code or prescription) | 1.35 (1.31-1.40) | 1.33 (1.29-1.38) |
| Autoimmune disease | 1.51 (1.32-1.74) | 1.41 (1.22-1.62) |
| No autoimmune disease | 1.49 (1.45-1.53) | 1.47 (1.42-1.51) |

*Adjusted for maternal age, maternal smoking, maternal use of antibiotics, paracetamol, PPIs or anti-inflammatory drugs, mode of delivery, birth year, birth weight, gestational age, birth order and gender.

**Table 5. Crude and adjusted hazard ratios (HRs) for asthma in offspring prenatally exposed to corticosteroids according to trimester of exposure.**

| | N (%) | Crude HR (95%CI) | *Adjusted HR (95%CI) |
|---|---|---|---|
| Unexposed | 846,019 (96.38) | 1.00 (ref) | 1.00 (ref) |
| Corticosteroid use 30 days prior to conception | 2,246 (0.26) | 1.57 (1.42-1.74) | 1.45 (1.31-1.60) |
| Exposed during 1. trimester | 7,297 (0.83) | 1.65 (1.56-1.74) | 1.58 (1.50-1.67) |
| Exposed during 2nd or 3rd trimester | 22,216 (2.53) | 1.44 (1.39-1.49) | 1.43 (1.38-1.48) |

*Adjusted for maternal age, maternal smoking, maternal use of antibiotics, paracetamol, PPIs or anti-inflammatory drugs, mode of delivery, birth year, birth weight, gestational age, birth order and gender.

**Table 6. Crude and adjusted odds ratios (ORs) for asthma in children prenatally exposed to corticosteroids compared with unexposed siblings.**

| | N | *Crude OR (95%CI) | **Adjusted OR (95%CI) |
|---|---|---|---|
| Unexposed children (at least one sibling has been prenatally unexposed) | 5,957 | 1.00 (ref) | 1.00 (ref) |
| Exposed children (at least one sibling has been prenatally exposed) | 4,542 | 0.96 (0.90-1.02) | 0.95 (0.89-1.02) |

*Crude estimate was adjusted for birth year (1996-2000, 2001-2005, 2006-2009).

**Additionally adjusted for maternal age, maternal smoking status, maternal use of medication (paracetamol, PPIs, COX inhibitors, antibiotics), mode of delivery, gestational age, birth order, birth weight, gender and birth year.

**Appendix 1:**

ATC codes:

Local corticosteroids (min. 2 prescriptions):

A01AC (corticosteroids for local oral treatment)

A07EA (corticosteroids acting locally or intestinally)

C05AA (corticosteroids, vasoprotective agents for treatment of haemorrhoids/anal fissures for topical use)

G01B (anti-infectives/antiseptics in combination with corticosteroids, gynecological)

R01AD (corticosteroids, decongestants, and other nasal preparations for topical use)

S01BA (corticosteroids, plain, ophthalmological use)

S01BB (corticosteroids and mydriatics in combination)

S01CA (corticosteroids and anti-infectives in combination)

S01CB (corticosteroids/anti-infectives/mydriatics in combination)

S02B (corticosteroids, otological use)

S02C (corticosteroids and anti-infectives in combination, otological use)

S03B (corticosteroids, ophthalmologic and otologic preparations)

S03C (corticosteroids and anti-infectives in combination, ophthalmologic and otologic preparations)

Systemic corticosteroids (min. 1 prescription):

A11ED (vitamin B-complex with anabolic steroids)

A14A (anabolic steroids)

H02 (corticosteroids systemic use)

J01XC (steroid antibacterials for systemic use)

M01BA (anti-inflammatory/anti-rheumatic agents in combination with corticosteroids)

N02CB (corticosteroid derivatives, nervous system)

**Appendix 2**:

ICD-10 codes for asthma (after 1994): J45 (asthma), J46 (status asthmaticus), ICD-8 codes for asthma (before 1994): 493 (asthma).

ICD-10 codes for Inflamatory Bowel Disease: K50 (Crohn's disease), K51 (ulcerative colitis), ICD-8 codes for IBD: 563.01, 563.02, 563.09 (Crohn's disease) and 563.19 (ulcerative colitis).

ICD-10 and ICD-8 codes for autoimmune diseases:
ICD-10: D59.0-1, ICD-8: 283.90-1 (Autoimmune hemolytic anemia)
ICD-10: D69.3, ICD-8: 287.10 (Autoimmune thrombocytopenic purpura (Werlhof))
ICD-10: D51.0, ICD-8: 281.00, 281.01, 281.08, 281.09 (Pernicious anaemia)
ICD-10: E27.1A, E27.2A, ICD-8: 255.10-11 (Addison's disease)
ICD-10: E05.0, ICD-8: 242.00, 242.01, 242.08, 242.09 (Graves disease)
ICD-10: E06.3, ICD-8: 244.01, 245.03 (Autoimmune thyroiditis (Hashimotos disease))
ICD-10: G35, ICD-8: 340 (Multiple sclerosis)
ICD-10: G70.0, ICD-8: 733.09 (Myasthenia gravis)
ICD-10: K74.3, ICD-8: 571.90 (Primary biliary cirrhosis)
ICD-10: K75.4 , ICD-8: 571.93 (Autoimmune hepatitis)
ICD-10: K83.0, ICD-8: 575 (Sclerosis cholangitis)
ICD-10: J84.1A, J84.1B, J84.1C, ICD-8: 517.01 (Idiopathic pulmonary fibrosis)
ICD-10: L10.0, L10.2, L10.4, L12.0, ICD-8: 694 (Pemphigus / pemphigoid)
ICD-10: L13.0, ICD-8: 693.00, 693.08-9 (Dermatitis herpetiformis)
ICD-10: L00, L51.2, L11, L13-14, ICD-8: 684.00 (Bullous disorders)
ICD-10: L40, M07.0-M07.3, ICD-8: 696.09, 696.10, 696.19 (Psoriasis)
ICD-10: L80, ICD-8: 709.01 (Vitiligo)
ICD-10: L94.0-1, ICD-8: 734.00-2, 734.08-9 (Scleroderma/morphea)
ICD-10: M35.1, ICD-8: (Mixed connective tissue disease (MCTD))
ICD-10: M34.0-9, ICD-8: 734.19, 695.49 (Lupus erythematosus (all subtypes))
ICD-10: M05, M06, G73.7D, I32.8A, I39.8E, ICD-8: 712.19, 712.29, 712.39, 712.59 (Rheumatoid arthritis)
ICD-10: M08, ICD-8: 712.09 (Juvenile Rheumatoid arthritis)
ICD-10: M10, ICD-8: 274 (Gout)
ICD-10: M07.3A, ICD-8: 696.09 (Psoriasis arthritis)
ICD-10: M45, ICD-8: 712.49 (Ankylosing spondylitis (Mb. Bechterew))

ICD-10: M33, ICD-8: 716.09, 716.19 (Polymyositis/dermatopolymyositis)

ICD-10: M32, G73.7C, N08.5A, N16.4B, ICD-8: 734.19 (Systemic lupus erythematosus)

ICD-10: M35.0, G73.7A, ICD-8: 734.90 (Sjögren's syndrome)

ICD-10: D86, G53.2, H22.1A, I41.8B, K77.8B, M63.3, ICD-8: 135.99 (Sarcoidosis)

ICD-10: M30.0, ICD-8: 446.09 (Polyarteritis nodosa)

ICD-10: M31.3, ICD-8: 446.29 (Wegener´s granulomatosis)

ICD-10: M31.5, M31.6, M35.3, ICD-8: 446.30, 446.31, 446.39 (Temporal arteritis / polymyalgia rheumatica)

ICD-10: D69.0B, M31.0B, ICD-8: 287.09 (Schönlein-Henoch purpura)

ICD-10: I77.6, L95, ICD-8:446.09 (Vasculitis/arteritis)

ICD-10: H20.0-1, ICD-8: 364 (Uveitis)

**Appendix 3:**

Stratification by maternal disease

| | All, 877,778 N (%) | Exposed, 31,759 N (%) | Unexposed, 846, 019 N (%) |
|---|---|---|---|
| Asthma (diagnosis) | 21,619 (2.5) | 2,469 (7.8) | 19,150 (2.3) |
| Asthma (diagnosis and/or use of anti-asthma medication) | 43,093 (4.9) | 4,431 (14.0) | 38,662 (4.6) |
| Chronic Obstructive Pulmonary Disease | 2,337 (0.3) | 178 (0.6) | 2,159 (0.3) |
| Diabetes Mellitus, Type 1 | 2,981 (0.3) | 116 (0.4) | 2,865 (0.3) |
| Diabetes Mellitus, Type 2 | 2,475 (0.3) | 120 (0.4) | 2,355 (0.3) |
| Ulcerative Colitis | 3,448 (0.4) | 655 (2.1) | 2,793 (0.3) |
| Crohn's Disease | 2,026 (0.2) | 251 (0.8) | 1,775 (0.2) |
| Autoimmune hemolytic anemia | 61 (0.0) | 12 (0.0) | 49 (0.0) |
| Autoimmune thrombocytopenic purpura | 460 (0.1) | 51 (0.2) | 409 (0.0) |
| Pernicious anaemia | 178 (0.0) | 14 (0.0) | 164 (0.0) |
| Addison's disease | 45 (0.0) | 34 (0.1) | 11 (0.0) |
| Grave's disease | 4,078 (0.5) | 241 (0.8) | 3,837 (0.5) |
| Autoimmune thyroiditis | 737 (0.1) | 48 (0.2) | 689 (0.1) |
| Multiple sclerosis | 1,154 (0.1) | 62 (0.2) | 1,092 (0.1) |
| Myasthenia gravis | 118 (0.0) | 11 (0.0) | 107 (0.0) |
| Primary biliary cirrhosis | 28 (0.0) | 7 (0.0) | 21 (0.0) |
| Autoimmune hepatitis | 63 (0.0) | 19 (0.0) | 44 (0.0) |
| Sclerosis cholangitis | 325 (0.0) | 23 (0.0) | 302 (0.0) |
| Idiopathic pulmonary fibrosis | 33 (0.0) | 6 (0.0) | 27 (0.0) |
| Pemphigus/pemphigoid | 19 (0.0) | 3 (0.0) | 16 (0.0) |
| Dermatitis herpetiformis | 103 (0.0) | 10 (0.0) | 93 (0.0) |
| Bullous disorders | 168 (0.0) | 14 (0.0) | 154 (0.0) |
| Psoriasis | 1,995 (0.2) | 135 (0.4) | 1,860 (0.2) |

| | | | |
|---|---|---|---|
| Vitiligo | 212 (0.0) | 13 (0.0) | 199 (0.0) |
| Scleroderma/morphea | 142 (0.0) | 12 (0.0) | 130 (0.0) |
| Mixed connective tissue disease | 47 (0.0) | 7 (0.0) | 40 (0.0) |
| Lupus erythematosus | 186 (0.0) | 33 (0.1) | 153 (0.0) |
| Rheumatoid arthritis | 1,498 (0.2) | 235 (0.7) | 1,263 (0.1) |
| Juvenile Rheumatoid arthritis | 767 (0.1) | 75 (0.2) | 692 (0.1) |
| Gout | 221 (0.0) | 9 (0.0) | 212 (0.0) |
| Psoriasis arthritis | 48 (0.0) | 3 (0.0) | 45 (0.0) |
| Ankylosing spondylitis | 245 (0.0) | 48 (0.2) | 197 (0.0) |
| Polymyositis/dermatopolymyositis | 68 (0.0) | 4 (0.0) | 64 (0.0) |
| Systemic lupus erythematosus | 439 (0.1) | 140 (0.4) | 299 (0.0) |
| Sjögrens syndrome | 135 (0.0) | 21 (0.1) | 114 (0.0) |
| Sarcoidosis | 1,083 (0.1) | 97 (0.3) | 986 (0.1) |
| Polyarteritis nodosa | 57 (0.1) | 8 (0.1) | 49 (0.0) |
| Wegeners granulomatosis | 25 (0.0) | 4 (0.0) | 21 (0.0) |
| Temporal arteritis/polymyalgia rheumatica | 17 (0.0) | 1 (0.0) | 16 (0.0) |
| Schönlein-Henoch purpura | 1,042 (0.1) | 40 (0.1) | 1,002 (0.1) |
| Vasculitis/arteritis | 156 (0.0) | 19 (0.1) | 137 (0.0) |
| Uveitis | 1,044 (0.1) | 224 (0.7) | 820 (0.1) |

*Adjusted for variables included in the analysis.

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