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Use of corticosteroids during pregnancy and risk of asthma in offspring: a nationwide Danish cohort study

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ABSTRACT

Objective: To examine whether in utero exposure to local and systemic corticosteroids is associated with asthma development in offspring.

Design: Cohort study.

Setting: Denmark.

Participants: We included all singletons born alive in Denmark between 1996 and 2009. Data on maternal corticosteroid use, asthma in offspring and covariates were obtained from medical registries.

Main outcome measures: We compared asthma risks of children prenatally exposed to corticosteroids and of children of former corticosteroid users with that of unexposed children. We computed absolute risks and used proportional-hazards regression to compute adjusted HRs (aHRs). Using logistic regression we compared exposed children with unexposed siblings in a 'within-mother-between-pregnancy' analysis. Adjustment addressed varying length of follow-up.

Results: We identified 877 778 children, 3.6% of whom were prenatally exposed to systemic (n=5327) or local (n=24 436) corticosteroids. A total of 105 677 children developed asthma during follow-up with a 10-year risk of 18.4% among the exposed and 13.5% among the unexposed. The aHR was 1.54 (95% CI 1.45 to 1.65) for systemic use, 1.45 (95% CI 1.40 to 1.50) for local use and 1.32 (95% CI 1.30 to 1.34) for former use. The adjusted OR of the 'within-mother-between-pregnancy' analysis was 1.11 (95% CI 0.98 to 1.25).

Conclusions: These population-based data do not support a strong causal association between maternal corticosteroid use during pregnancy and increased asthma risk in offspring.

Strengths and limitations of this study

- The strengths of the study are the large population size, the long and complete follow-up and the use of data from medical databases with no risk of recall bias and minimal risk of selection bias.
- The limitations are misclassification of exposure status, the fact that prescription dispensations may be an imperfect measure of disease and unmeasured confounding.

INTRODUCTION

Asthma has become the most common chronic lower respiratory tract disease of childhood, with an estimated prevalence of 5% to 20% among children aged 13–14 in industrialised countries.[1] The causes of asthma are largely unknown; however, genetics and maternal factors such as smoking and high body mass index (BMI) have been reported as risk factors.[2–4] Furthermore, use of paracetamol, proton pump inhibitors (PPIs), cyclooxygenase (COX) inhibitors and antibiotics during pregnancy also has been associated with asthma in offspring.[5–8] Proposed pathophysiological mechanisms underlying asthma development include alterations in the developing immune system[9] which may be affected by maternal corticosteroid intake.[10]

Corticosteroids are potent anti-inflammatory drugs used during pregnancy for conditions such as asthma and inflammatory bowel disease (IBD). Reported fetal side effects include altered development of the hypothalamic-pituitary-adrenal axis and abnormal organ function.[11–13] A Canadian study found that antenatal corticosteroid therapy used to induce fetal lung maturation was associated with childhood asthma (adjusted OR (aOR)=1.23 (95% CI 1.06 to 1.44)).[14]

We included oral corticosteroids and injections (systemic use). Nasal sprays, eyedrops, eardrops, local treatment in the mouth, inhalation corticosteroids, intestinal foams and suppositories were included as local use. Creams, over-the-counter medication (nasal spray and creams) and in-hospital administered corticosteroids were excluded.

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Given the widespread use of corticosteroids it is of major public health and clinical importance to gain knowledge about the effects of corticosteroid therapy on the fetus during the entire pregnancy. To the best of our knowledge, no studies to date have investigated the association between maternal corticosteroid therapy at any time during pregnancy and asthma in offspring. We therefore conducted a cohort study based on nationwide Danish medical registries, to examine the association between maternal corticosteroid therapy during pregnancy and the postnatal period and risk of asthma in the offspring.

METHODS

Setting and study population

This nationwide cohort study included all singletons born alive in Denmark from 1 January 1996 until 31 December 2009. The children and their parents were identified through the Danish Medical Birth Registry (DMBR), which stores data on all births in Denmark since 1973.[15 16] We used the civil registration number (CRN), a unique 10-digit personal identifier issued to every Danish citizen at birth or upon immigration,[15] to perform unambiguous linkage between registries. In Denmark, the National Health Service provides tax-supported healthcare to all residents and refunds a portion of patient expenditures for a wide range of prescribed drugs, including corticosteroids.

Corticosteroid use

Exposure to corticosteroids during pregnancy was defined as redemption of at least one maternal prescription for a systemic corticosteroid or at least two prescriptions for local corticosteroids 30 days before or during pregnancy. We established the start of pregnancies based on data on gestational age and birth date from the DMBR.

We further categorised prenatal exposure into exposure during the first trimester (the first 12 weeks of pregnancy) and during the remainder of pregnancy. Children exposed during the first trimester included children of mothers who had redeemed a prescription 30 days prior to pregnancy or in the first trimester. Former use was defined as redemption of corticosteroid prescriptions (for one systemic and/or two local corticosteroids) at any time prior to the 30 days before pregnancy.

In Denmark most local and all systemic corticosteroids are dispensed by prescription only. The Danish Registry of Medicinal Product Statistics (RMPS) maintains records on type of drug (according to the Anatomical Therapeutic Chemical (ATC) classification system) and date of prescription reimbursement for all prescribed medications dispensed from pharmacies nationwide. Information from the RMPS was also linked to our study subjects through the CRN. We did not have information on corticosteroids administered in hospital.

Asthma

Asthma in offspring was defined as an inpatient, outpatient or emergency room (ER) diagnosis of asthma and/or by redemption of at least two prescriptions for β-2-agonists and two prescriptions for inhaled corticosteroids. A similar algorithm, requiring only one prescription for a β-2-agonist and one prescription for an inhaled corticosteroid, has a positive predictive value of 80–100% in patients aged 5–45 years.[17] We obtained data on asthma diagnoses from the Danish National Registry of Patients (DNRP), coded according to WHO's *International Classification of Diseases* (ICD), 8th revision until the end of 1993 and 10th revision thereafter. The DNRP contains information on all inpatient discharges from non-psychiatric acute care hospitals since 1977. Both ER and outpatient specialist 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,[18] maternal smoking status,[19] maternal BMI (recorded from 2004 onward),[20] gender,[2] gestational age,[21] Apgar score,[22] birth order,[23] birth weight[24] and caesarean section.[25] From the RMPS we obtained information on maternal use of medications (paracetamol, PPI, COX inhibitors and antibiotics).[5–8] The DNRP was used to identify maternal asthma, maternal IBD (subdivided into ulcerative colitis and Crohn's disease (CD)), maternal diabetes, maternal chronic obstructive pulmonary disease and other maternal autoimmune diseases.[26] All relevant ICD and ATC codes are provided in online supplementary appendices 1 and 2, whereas stratification by maternal disease is provided in online supplementary appendix 3.

Statistical analysis

Offspring were followed from date of birth until date of asthma, death, emigration or the end of follow-up on 31 December 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 hazards regression was used to compute crude and adjusted HRs (aHRs) with 95% CI, comparing children exposed to corticosteroids during gestation, and children of mothers who were former corticosteroid users, with unexposed children. The analyses were adjusted for maternal age, maternal smoking status, maternal use of medication (paracetamol, PPIs, COX inhibitors and antibiotics), mode of delivery, gestational age, birth order, birth weight, gender and birth year. In an additional analysis we also adjusted for maternal BMI, for which we had data from 2004 onward. Analyses were repeated according to trimester of exposure. In a separate analysis we compared children exposed to corticosteroids postnatally with children wholly unexposed (during pregnancy and postnatally). Because Danish women are encouraged to breastfeed during the first postpartum year,[27] we used

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this timeframe to define the postnatal exposure period. We did a sensitivity analysis only including children who were given an asthma diagnosis (ie, excluding the medicine algorithm) as well as an analysis in which we started follow-up at the age of 5 years (a diagnosis of asthma can only be made with certainty from age 5),[28] both in order to exclude children with wheezing. Additionally, we moved the start of the exposure period from 30 days prior to pregnancy to 0 and 60 days, respectively, to evaluate if this was a sensible cut-off point.

Within-mother-between-pregnancy analysis

We conducted a 'within-mother-between-pregnancy' analysis, based on the assumption that siblings share genetic and environmental factors during their upbringing.[29] We identified families in which at least one sibling was exposed to corticosteroids anytime during gestation and at least one sibling was not. The unexposed siblings served as the reference cohort. Conditional logistic regression, adjusted for calendar period of birth and thereby addressing length of follow-up, was chosen over stratified Cox regression for this analysis. Logistic regression handled sibling pairs where both experienced the outcome more appropriately, all though results did not differ substantially from the stratified Cox regression. ORs with 95% CIs can be interpreted as estimates of relative risk. Model 1 was adjusted for birth period (1996–2000, 2001–2005 or 2006–2009), to account for differences in length of follow-up. Model 2, in addition, was adjusted for the same variables as in the main analysis including the general population comparison cohort. We also conducted a second 'within-parents-between-pregnancy' analysis restricted to full siblings, with the same parents.

Analyses were performed using SAS (V.9.2; SAS Inc, Cary, North Carolina, USA). The study was approved by the Danish Data Protection Agency (record no. 2013-41-1790).

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)

Characteristics	Corticosteroid use during pregnancy, n (%)	No corticosteroid use during pregnancy, n (%)
All	31 759 (100)	846 019 (100)
Age at giving birth (years)		
<25	2363 (7.4)	119 386 (14.1)
25–29	9306 (29.3)	295 693 (35.0)
30–34	12 819 (40.4)	295 891 (35.0)
35–39	6170 (19.4)	116 104 (13.7)
≥40	1 101 (3.5)	18 945 (2.2)
Use of other drugs during pregnancy		
Antibiotics	14 817 (46.7)	297 906 (35.2)
Paracetamol	554 (1.7)	5367 (0.6)
PPIs	887 (2.8)	10 238 (1.2)
NSAIDs/Coxibs	2384 (7.5)	35 412 (4.2)
Smoking during pregnancy		
No	25 391 (80.0)	653 391 (77.2)
1–10 cigarettes/day	3908 (12.3)	120 435 (14.2)
11–20 cigarettes/day	1150 (3.6)	35 206 (4.2)
>20 cigarettes/day	173 (0.5)	4962 (0.6)
Missing	1137 (3.6)	32 025 (3.8)
Chronic disease		
Inflammatory bowel disease (IBD)	1037 (3.3)	5097 (0.6)
Crohn's disease (CD)	251 (0.8)	1775 (0.2)
Ulcerative colitis (UC)	655 (2.1)	2793 (0.3)
Both	131 (0.4)	529 (0.1)
Chronic obstructive pulmonary disease (COPD)	178 (0.6)	2159 (0.3)
Maternal diabetes mellitus (type 1)	116 (0.4)	2865 (0.3)
Maternal diabetes mellitus (type 2)	120 (0.4)	2355 (0.3)
Asthma	4431 (14.0)	38 662 (4.6)
Maternal body mass index (BMI) *		
Low	553 (1.7)	16 854 (2.0)
Normal	8846 (27.9)	204 289 (24.1)
Overweight	3131 (9.9)	68 411 (8.1)
Obese and severe obesity	1716 (5.4)	38 215 (4.5)

*Data on maternal BMI were only available from 2004 onward.
NSAIDS, non-steroidal anti-inflammatory drugs; Coxibs, cyclooxygenase inhibitors.

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RESULTS

Descriptive data

We identified 877 778 children born alive in Denmark from 1 January 1996 until 31 December 2009. Overall 31 759 children (3.6%) were prenatally exposed to corticosteroids and 5325 of their mothers (0.6%) used systemic corticosteroids (of these, 3800 redeemed one prescription and 1525 redeemed two or more prescriptions). Local corticosteroids were used by 26 434 mothers (3.0%) during pregnancy. Mothers who used corticosteroids during pregnancy were older than non-users, and used other drugs more frequently during pregnancy (table 1). Children exposed to corticosteroids during gestation were more frequently delivered by caesarean section than unexposed children (table 2).

Asthma in offspring

Median follow-up time was 5.8 years for exposed and 7 years for unexposed children. The absolute risk of asthma among exposed children was 9.5%, 15.1% and 18.4% after 2, 5 and 10 years of follow-up, respectively. Corresponding estimates among unexposed children were 6.8%, 10.9% and 13.5%.

Prenatal exposure to systemic corticosteroids was associated with asthma (aHR=1.54 (95% CI 1.45 to 1.65)). This estimate was highest among children of mothers who redeemed only one prescription for corticosteroids, compared to children of mothers who redeemed two or more. The aHR was 1.32 (95% CI 1.30 to 1.34) for children of former users of corticosteroids. Maternal corticosteroid use during the breastfeeding period was also associated with increased risk of asthma in offspring compared with never use (aHR=1.19 (95% CI 1.15 to 1.23)).

Results were almost identical for children whose mothers used local corticosteroids during pregnancy compared with systemic use (table 3) and risk of asthma did not vary substantially according to trimester of exposure (results not shown). Estimates also did not

Table 2 Characteristics of 877 778 children born in Denmark between 1 January 1996 and 31 December 2009 according to prenatal exposure to corticosteroids

Characteristics	Exposed to corticosteroids during pregnancy, n (%)	Not exposed to corticosteroids during pregnancy, n (%)
Exposure period		
Corticosteroid use 30 days prior to conception	2246 (7.1)	
Exposure during first trimester	7297 (23.0)	
Exposure during second and third trimester	22 216 (70.0)	
Gestational age (weeks)		
19–29	96 (0.3)	2918 (0.3)
30–36	1402 (4.4)	37 965 (4.5)
37–41	27 686 (87.2)	736 254 (87.0)
42–48	2418 (7.6)	63 202 (7.5)
Missing	157 (0.5)	5680 (0.7)
Mode of delivery		
Caesarean section	6717 (21.2)	148 607 (17.6)
Respiratory distress syndrome	1218 (3.8)	29 910 (3.5)
Apgar score		
<7	206 (0.7)	5828 (0,7)
7–9	2136 (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 (g)		
1500–2000	207 (0.7)	6003 (0.7)
2000–2499	687 (2.2)	18 565 (2.2)
2500–2999	2956 (9.3)	86 449 (10.2)
3000–5000	27 567 (86.8)	723 099 (85.5)
Missing	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	7051 (22.2)	166 150 (19.6)
Birth year		
1966–2000	9881 (31.1)	312 128 (36.9)
2001–2005	11 524 (35.4)	297 823 (35.2)
2006–2009	10 624 (33.5)	236 068 (27.9)

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Table 3 Crude and adjusted 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	5325	1.73 (1.62 to 1.85)	1.54 (1.45 to 1.65)
1 redeemed prescription	3800	1.73 (1.61 to 1.87)	1.60 (1.48 to 1.72)
≥2 redeemed prescriptions	1525	1.73 (1.53 to 1.95)	1.42 (1.26 to 1.60)
Local treatment	26 434	1.45 (1.40 to 1.50)	1.45 (1.40 to 1.50)
Former maternal use	162 949	1.36 (1.34 to 1.38)	1.32 (1.30 to 1.34)

*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.

change when asthma was strictly defined as a hospital diagnosis of asthma (ie, not including asthma medication), when follow-up began at age 5, or with additional adjustment for maternal BMI (results not shown). Finally, changing the exposure period from 30 days prior to pregnancy to 0 and 60 days prior to pregnancy did not affect the estimates (data not shown).

Sibling comparison

The 'within-mother-between-pregnancy' analysis indicated a minor increase in asthma risk in siblings exposed to corticosteroids, compared to unexposed siblings (aOR=1.11 (95% CI 0.98 to 1.25)) (table 4). Restricting the analysis to children with the same parents, instead of just the same mother, did not change the estimates substantially, aOR=1.04 (95% CI 0.92 to 1.18).

DISCUSSION

The attenuated association in the 'within-mother-between-pregnancy' analysis, bordering on no association, strongly indicates the presence of confounding by family related or other factors in the analyses including a general population comparison cohort. This is further underlined by the positive association of former maternal corticosteroid use with asthma in offspring, and by comparable aHRs for local and systemic use. Thus, these population-based data do not support a strong causal association between exposure to corticosteroid therapy during gestation and increased asthma risk.

To the best of our knowledge, no previous studies have investigated the association between maternal corticosteroid use at any time during pregnancy and risk of asthma in offspring. A Canadian study by Pole *et al*[14] reported that corticosteroid therapy administered just prior to birth to induce fetal lung maturation was associated with increased risk of asthma in offspring, between 3 and 5 years of age (aHR 1.19 (95% CI 1.03 to 1.39)). But the risk was decreased after 8 years of age (aHR 0.74 (95% CI 0.54 to 1.03)). The indication of the corticosteroid therapy examined in the Canadian study, fetal lung maturation, is more closely related to asthma development than the maternal indications present in our study. This may hamper direct comparison of the results of the two studies.

Of the mothers diagnosed with asthma (43 093) only around 10% (4431) were in corticosteroid therapy during their pregnancy. This might be due to the fact that our definition of asthma does not take into account the different degrees of asthma, as mild asthma can be managed with β-2-agonists when symptoms occur. Another possible explanation might be that women could have enough medication for long periods of time, and thus does not redeem prescriptions during their pregnancy. We cannot, however, rule out the possibility of misclassification due to a wrong/hastily given diagnosis.

The strengths of our study include its large sample size, long and complete follow-up and use of population-based medical registries. Thus, selection and recall biases were virtually eliminated. Furthermore, the availability of registry data on family relations made the 'within-mother-between-pregnancy' analysis possible.

Table 4 Crude and adjusted ORs for asthma in children prenatally exposed to corticosteroids compared with unexposed siblings.

	N	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Unexposed children (at least one sibling has been prenatally exposed)	5957	1.00 (ref)	1.00 (ref)
Exposed children (at least one sibling has been prenatally unexposed)	4542	1.12 (1.00 to 1.24)	1.11 (0.98 to 1.25)

Model 1: the estimate is adjusted for birth year (1996–2000, 2001–2005, 2006–2009).
Model 2: the estimate is additionally adjusted for maternal age, maternal smoking status, maternal use of medication (paracetamol, proton-pump inhibitors, cyclooxygenase inhibitors, antibiotics), mode of delivery, gestational age, birth order, birth weight, gender and birth year.

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The fact that we did not have information on over-the-counter medication (containing very low doses of corticosteroids) and in-hospital administered corticosteroids and the exclusion of topical corticosteroids is a potential source of bias. However, we have no reason to believe that this exposure was different between the exposed and the unexposed, and thus the use of these medications would have biased our results towards the null.

Potential misclassification of exposure to corticosteroids should be noted, since we only know that mothers redeemed the prescribed medication at a pharmacy. We had no data on actual drug use and dosage of the different types of drugs. However, corticosteroid treatment during pregnancy is followed quite closely by physicians, which increases compliance. Furthermore, we cannot rule out some misclassification of children with wheezing as asthma patients, as these children could have been given a diagnosis of asthma hastily or have redeemed more than two prescriptions for corticosteroids and β-2-agonists. We therefore used a validated algorithm and made it even stricter to identify asthma outcomes[17]; however, the validated algorithm was done for the prescription-based diagnosis. However, we cannot rule out that some children might have been misclassified if misdiagnosed. Despite this we do not believe that these potential sources of bias were able to conceal a strong causal association in the 'within-mother-between-pregnancy' analysis. Frisell *et al*[30] recently demonstrated that sibling designs are susceptible to random measurement error of exposures, leading to attenuation of association estimates. However, part of the analyses that were based on comparison with the general population comparison cohort further indicate the presence of confounding in this comparison. Thus, there was a positive association between former maternal use of corticosteroids and asthma in offspring and the aHRs for maternal use of local and systemic corticosteroids were virtually similar.

In conclusion, the aetiology of asthma likely involves common risk factors for maternal corticosteroid treatment and asthma in offspring, such as environmental or genetic factors. However, based on the 'within-mother-between-pregnancy' analysis, we do not consider prenatal exposure to corticosteroids to be a strong risk factor for asthma development, which may apply to immunosuppression during pregnancy in general.

Contributors HTS conceived the study. All authors contributed to the design of the study, the interpretation of the results, and the writing process. AB drafted the initial manuscript. TF performed the statistical analyses.

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Competing interests None.

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Data sharing statement No additional data are available.

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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)	2469 (7.8)	19 150 (2.3)
Asthma (diagnosis and/or use of anti-asthma medication)	43 093 (4.9)	4431 (14.0)	38 662 (4.6)
Chronic Obstructive Pulmonary Disease	2337 (0.3)	178 (0.6)	2159 (0.3)
Diabetes Mellitus, Type 1	2981 (0.3)	116 (0.4)	2865 (0.3)
Diabetes Mellitus, Type 2	2475 (0.3)	120 (0.4)	2355 (0.3)
Ulcerative Colitis	3448 (0.4)	655 (2.1)	2793 (0.3)
Crohn's Disease	2026 (0.2)	251 (0.8)	1775 (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	4078 (0.5)	241 (0.8)	3,837 (0.5)
Autoimmune thyroiditis	737 (0.1)	48 (0.2)	689 (0.1)
Multiple sclerosis	1154 (0.1)	62 (0.2)	1092 (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	1995 (0.2)	135 (0.4)	1860 (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	1498 (0.2)	235 (0.7)	1263 (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	1083 (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	1042 (0.1)	40 (0.1)	1002 (0.1)
Vasculitis/arteritis	156 (0.0)	19 (0.1)	137 (0.0)
Uveitis	1044 (0.1)	224 (0.7)	820 (0.1)

*Adjusted for variables included in the analysis.