



ORIGINAL ARTICLE

Pregnancy complications, treatment characteristics and birth outcomes in women with atopic dermatitis in Denmark

C.R. Hamann,^{1,2,3,*} A. Egeberg,^{1,2} A. Wollenberg,⁴ G. Gislason,⁵ L. Skov,^{1,2} J.P. Thyssen^{1,2}

¹Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

²Copenhagen Research Group for Inflammatory Skin (CORGIS), Hellerup, Denmark

³School of Health and Medical Science, Graduate Programme in Public Health and Epidemiology, University of Copenhagen, Copenhagen, Denmark

⁴Department of Dermatology and Allergy, Ludwig-Maximilian-University, Munich, Germany

⁵Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

*Correspondence: C.R. Hamann. E-mail: hamann511@gmail.com

Abstract

Background The risk of prenatal, obstetric and birth complications in mothers with atopic dermatitis (AD), along with treatment use during pregnancy, is unknown.

Objectives To examine the associations between prenatal, obstetric and birth complications in mothers with AD and describe the dermatologic care received during pregnancy.

Methods Mother-child pairs, in which the mother had a history of AD, were identified through the Danish Medical Birth Registry and matched 1 : 10 with non-AD pairs. Data on dermatologic treatment and prenatal, obstetric and birth complications were obtained through linkage via nationwide registers. Multiple logistic regression was performed.

Results We identified 10 668 births from 1997 through 2014 to women with AD. Women with a hospital/ambulatory contact for AD during pregnancy had increased topical corticosteroid and ultraviolet therapy use during pregnancy compared to prior. However, overall, women with AD received decreased dermatologic therapy during pregnancy compared to prior. In adjusted analysis, maternal AD was inversely associated with gestational diabetes [OR 0.79, 95% CI (0.68–0.92)], but positively associated with premature rupture of membranes [1.15 (1.05–1.27)] and staphylococcal neonatal septicemia [2.45 (1.33–4.49)]—albeit the latter was rare. These associations did not meet statistical significance in sub-analysis where body mass index data were available. No associations were found with preeclampsia, prematurity or non-staphylococcal neonatal septicaemia.

Conclusions Women with AD during pregnancy mainly used topical corticosteroids and ultraviolet therapy to control their disease. While premature rupture of membranes and staphylococcal neonatal septicaemia were over-represented in maternal AD, no associations were found with any other significant prenatal, obstetric or birth outcome.

Received: 6 May 2018; Accepted: 20 August 2018

Conflicts of interests

Dr. Thyssen has attended advisory boards for Roche and Sanofi-Genzyme and received speaker honorarium from LEO Pharma and Sanofi-Genzyme. Dr. Skov has received consultancy and/or speaker honoraria from Abbvie, Pfizer, Janssen-Cilag, Merck Sharp & Dohme and Leo Pharma and is a member of the advisory boards of Abbvie, Pfizer, Janssen-Cilag, Merck Sharp & Dohme, Eli Lilly, Celgene and Novartis. Dr. Egeberg has received research funding from Pfizer, Eli Lilly, the Danish National Psoriasis Foundation and the Kgl Hofbundtmager Aage Bang Foundation and honoraria as consultant and/or speaker from Almirall, Leo Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly, Novartis, Galderma and Janssen Pharmaceuticals. Dr Wollenberg is a consultant with honorarium for Almirall, Anacor, Astellas, Bioderma, Celgene, Chugai (travel grant), Galderma, Hans Karrer, Leo Pharma, L'Oreal, MEDA, MedImmune, Merck Sharp and Dohme, Novartis, Pierre Fabre, Pfizer, Regeneron and Sanofi-Adventis and he received research funding from Beiersdorf and Leo Pharma. Drs. Hamann and Gislason have no relevant interests to declare.

Funding source

None declared.

Introduction

Atopic dermatitis (AD) is a common chronic pruritic skin condition in adults,^{1,2} characterized by skin barrier impairment, a T-helper (Th) cell 2 skewed immune response and *Staphylococcus aureus* colonization.³ There is a little insight in the natural course of AD during pregnancy, and in particular the use of dermatologic therapy.^{4–8} Emollients and topical corticosteroids remain first-line recommended therapy for AD during pregnancy,⁹ while narrowband ultraviolet (UV) B therapy and cautious use of systemic corticosteroids represent alternatives when more aggressive therapy is needed.^{5,10,11} However, pregnancy does not improve the largely unfavourable risk-benefit ratio of long-term systemic steroid treatment for AD.¹⁰

Importantly, there is sparse knowledge about the risk of complications in pregnant AD patients,¹² although certain common complications of pregnancy, namely gestational diabetes and preeclampsia, have been proposed to alter the subsequent risk of developing AD in the offspring. However, since their baseline association with maternal AD during pregnancy is unclear, this prevents insight into possible causation.^{13,14} Moreover, selected diseases of pregnancy could be induced by medication used to treat AD, e.g. gestational diabetes from systemic use of prednisolone.

In this retrospective matched cohort study of pregnancies of women with a diagnosis of AD, we describe the dermatologic treatment they received during pregnancy and examine associations between maternal AD and common prenatal, obstetric and birth outcomes.

Methods

Data sources and study population

All Danish residents are given a unique personal identification number which allows for unambiguous cross-linkage of administrative and healthcare registries. The Danish Medical Birth Registry, established in 1968 contains health data on the prenatal, obstetric and perinatal care of all resident mother-child pairs in Denmark.¹⁵ The Danish National Patient Registry contains diagnosis codes, according to a modified version of the International Classification of Diseases (ICD) eighth and 10th revisions (the ninth revision was never implemented in Denmark), for visits to hospital- and university-based outpatient clinics, hospital admissions and emergency room visits throughout Denmark, as well as Nordic-specific (NOMESCO; Nordic Medico-Statistical Committee) codes for procedures performed and medications delivered in the hospital or ambulatory setting.¹⁶ The Registry of Medicinal Product Statistics contains Anatomical Therapeutic Chemical (ATC) classification codes for all prescriptions filled at Danish pharmacies.¹⁷

We identified all mother-child pairs in the Danish Medical Birth Registry from 1997 through 2014 where the mother had received a diagnosis of AD (ICD-8 691, ICD-10 L20) in the

Danish National Patient Registry prior to the birth of the child. These pairs were matched 1 : 10, by birth year, parity and maternal age at conception, with non-maternal-AD mother-child pairs from the Danish Medical Birth Registry. Mother-child pairs were stratified into mothers who had an ambulatory or hospital visit for AD during pregnancy or 24 months before the birth of the child. Approval for this study was obtained from the Danish Data Protection Agency (ref. 2007-58-0015, int. ref. GEH-2014-018, I-Suite 02736).

Baseline characteristics and treatments

Maternal adult asthma was assessed using a validated algorithm that includes two filled prescriptions of anti-asthmatic medications.¹⁸ Maternal type 2 diabetes (T2D) was determined if the mother had at least one filled prescription of a non-insulin antidiabetic drug (A10B) or ever had a T2D code registered (E11). Maternal hypertension was assessed using a validated diagnostic algorithm that uses a combination of at least two filled anti-hypertensive prescriptions in different anti-hypertensive classes within a 90 day period or a registered hypertension diagnosis (I1).^{19,20} Maternal body mass index (BMI; only available 2004–2014), smoking status, parity and number of visits to midwife and physician were recorded in the Danish Medical Birth Registry. The use of topical corticosteroids (TCS; D07), grouped into four potency classes from I to IV based on the ATC classification system,²¹ calcineurin inhibitors (D11), systemic corticosteroids (H02) and other immunomodulatory medications [methotrexate (L04AX03), (BWAH115) azathioprine (L04AX01), (BWHB83), cyclosporine (L04AD01), (BOHJ20), and mycophenolate mofetil (L04AA06), (BOHJ22)], was assessed during pregnancy and during a time period immediately preceding pregnancy, the duration of which was matched with the length of pregnancy on a case by case basis. Oral antiviral medications [aciclovir (J05AB01), famciclovir (J05AB09), valaciclovir (J05AB11) and penciclovir (J05AB13)], dicloxacillin (J01CF01) and antihistamine (R06) use was also assessed during and prior to pregnancy. Ultraviolet therapy was assessed by procedural code (BNGA). Maternal socioeconomic position was determined on the basis of average household gross annual income for the 5-year period prior to the birth of the child. Maternal residency urbanization level was assessed using established methods.²²

Outcome measures

Outcomes obtained from the Danish Medical Birth Registry included (i) obstetric outcomes (primary birth diagnosis, placental abruption, premature rupture of membranes, preterm premature rupture of membranes); and (ii) birth outcomes (neonatal septicaemia, stillbirth, gestational age at birth and weight at birth). The Danish National Patient Registry was used to examine (iii) prenatal outcomes and included hypertensive diseases of pregnancy (O10–O15), gestational diabetes (O244),

pruritic urticarial papules and plaques of pregnancy (PUPPP; O268G, O268H) and pemphigoid gestationis (O264). Many validation studies have confirmed that the validity of these outcome measures is high.^{23–27}

Statistical analysis

Means and standard deviations for continuous variables and frequencies and percentages for categorical variables were used to describe baseline characteristics. The Pearson chi-square test was performed to compare baseline and treatment characteristics between AD groups and controls. McNemar's test was used to compare changes in treatment characteristics within the same group in different time frames. The Cochran–Armitage test for trend was used to assess for trends across control and AD groups. Sub-analysis by first-born vs. non-first-born child was also performed. To assess the associations between maternal AD and prenatal, obstetric and birth outcomes, logistic regression was performed for each relationship using SAS version 9.4 (SAS Institute Inc. Cary, NC, USA). Continuous variables (i.e. gestational age, weight) were transformed into categorical outcomes according to World Health Organization guidelines.²⁸ Crude odds ratios (ORs) with 95% confidence intervals (CI) were calculated. ORs were also adjusted for socioeconomic position, smoking status, asthma, hypertension and T2D. Further sub-analysis with BMI added to the adjusted model was performed for the years in which BMI was recorded (2004–2014). Given the high number of outcomes Bonferroni correction was applied and *P*-values <0.00417 were considered statistically significant.

Results

Study population

We identified 10 668 births from 1997 through 2014 to women who had ever received a diagnosis of AD; 10 441 (97.9%) were successfully matched with controls. Of these 1064 (10.2%) had one or more ambulatory or hospital visits for AD in the 24 months prior to delivery [mean 1.6 visits, (standard deviation 1.8)]; of these 165 (1.5%) were inpatient hospital visits. There were 342 (3.2%) births in which the mother had an ambulatory or hospital visit for AD during pregnancy [1.6 visits, (1.2)]; of these 44 (13.8%) were inpatient hospital visits. More than half of studied births related to women who had had an ambulatory or hospital visit for AD after the age of 18 [5. 459 (52.3%)]. In this population of women with still active AD as an adult, the mean age of last recorded AD visit was 25.2 years (standard deviation 4.6). Overall mean age at last AD visit for all women with a history of AD was 16.7 years (standard deviation 10.2). Women with AD had a higher prevalence of asthma than controls (32.9% vs. 8.7%, *P* < 0.0001), more often lived in an urban environment (56.3% vs. 51.7%, *P* < 0.0001), and had a slightly increased prevalence of hypertension (3.6% vs. 3.1%,

P = 0.0100; Table 1). AD and non-AD women had similar prevalences of T2D, and in sub-analysis, a similar distribution of BMI. AD women had a slightly higher self-reported prevalence of smoking during pregnancy (13.2% vs. 12.0%, *P* = 0.0002). Apart from socioeconomic position and urbanization level, baseline/treatment statistics were similar for first-borns and non-firstborns.

Women with visits for AD during pregnancy were less obese and less underweight than the total AD population (Table 1). They had a similar prevalence of T2D compared to the rest of the AD population (0.9% vs. 1.7%, *P* = 0.2444), had a similar distribution of socioeconomic status, and more often lived in an urban environment (65.5% vs. 56.0%, *P* = 0.0007).

Treatment characteristics

While the number of visits to the obstetrician and midwife were similar across AD groups and controls, all dermatologic treatment markers were elevated in AD groups. In particular, we found an ascending relationship between topical and systemic medication use and AD groups, with the overall AD group having the lowest usage of these medications and women who had ambulatory or hospital visits during pregnancy having highest levels of treatment (Table 2). For example, TCS prescriptions were filled during 31.0% of AD pregnancies, 59.2% of pregnancies in which the mother had a visit for AD within 24 months and 83.4% of pregnancies in which the mother had a visit for AD during pregnancy, compared with 6.0% in controls (*P*_{trend} < 0.001). Group II and III topical steroids, mid-potency, were most commonly used and accounted for 84.8% of TCS used in AD pregnancies and 83.0% in control pregnancies.

Oral corticosteroids were filled during 1.9% of AD pregnancies, 5.2% of pregnancies in which the mother had a visit for AD within 24 months and 9.4% of pregnancies in which the mother had a visit for AD during pregnancy, compared with 0.6% in controls (*P*_{trend} < 0.001). Similarly, dicloxacillin was filled during 1.9% of AD pregnancies, 6.9% of pregnancies in which the mother had a visit for AD within 24 months and 14.1% of pregnancies in which the mother had a visit for AD during pregnancy, compared with 0.5% in controls (*P*_{trend} < 0.001).

In the control and total AD population, oral medications were used less commonly in pregnancy compared to a matched period of approximately 9 months prior. However, in the population of women with an AD visit during pregnancy all oral medications, with the exception of antivirals, were used by a similar proportion of women during pregnancy compared with prior, e.g. systemic corticosteroids (10.7% in the 9 months prior to 9.4% during pregnancy, *P* = 0.5465). Similarly, in all AD groups, high potency TCS (group IV) were generally less commonly used during pregnancy compared to the approximate 9 months prior to pregnancy, while lower potency TCS (group I

Table 1 Baseline characteristics of control and atopic dermatitis (AD) populations

	Controls			AD diagnosis anytime prior to birth			AD within 24 months of birth		hospital/ambulatory visit within 24 months of birth		AD during pregnancy		hospital/ambulatory visit during pregnancy	
	First child	Non-first child	Overall	First child	Non-first child	Overall	First child	Non-first child	Overall	Non-first child	First child	Non-first child	Overall	Non-first child
Baseline statistics	<i>n</i> = 50796	<i>n</i> = 53614	<i>n</i> = 104410	<i>n</i> = 5053	<i>n</i> = 5388	<i>n</i> = 10441	<i>n</i> = 585	<i>n</i> = 479	<i>n</i> = 1064	<i>n</i> = 132	<i>n</i> = 187	<i>n</i> = 132	<i>n</i> = 319	<i>n</i> = 319
Maternal age at delivery, mean (SD)	27.9 (4.6)	31.8 (4.3)	29.9 (4.8)	28.2 (4.7)	31.8 (4.3)	29.9 (4.8)	28.1 (4.4)	31.7 (4.4)	29.7 (4.8)	31.8 (4.6)	28.5 (4.7)	31.8 (4.6)	29.9 (4.9)	29.9 (4.9)
Asthma	3729 (7.3)	5325 (9.9)	9054 (8.7)	1578 (31.2)	1860 (34.5)	3438 (32.9)	165 (28.2)	161 (33.6)	326 (30.6)	46 (34.9)	51 (27.3)	46 (34.9)	97 (30.4)	97 (30.4)
Hypertension	1350 (2.7)	1879 (3.5)	3229 (3.1)	154 (3.1)	217 (4.0)	371 (3.6)	15 (2.6)	22 (4.6)	37 (3.5)	7 (5.3)	6 (3.2)	7 (5.3)	13 (4.1)	13 (4.1)
Diabetes mellitus II	927 (1.8)	987 (1.8)	1914 (1.8)	83 (1.6)	92 (1.7)	175 (1.7)	9 (1.5)	6 (1.3)	15 (1.4)	0 (0)	3 (1.6)	0 (0)	3 (0.9)	3 (0.9)
Maternal BMI	<i>n</i> = 35444	<i>n</i> = 38027	<i>n</i> = 73471	<i>n</i> = 3512	<i>n</i> = 3818	<i>n</i> = 7330	<i>n</i> = 335	<i>n</i> = 264	<i>n</i> = 599	<i>n</i> = 73	<i>n</i> = 106	<i>n</i> = 73	<i>n</i> = 179	<i>n</i> = 179
<18.5 underweight	1810 (5.1)	1593 (4.2)	3403 (4.6)	148 (4.2)	170 (4.5)	318 (4.3)	12 (3.6)	8 (3.0)	20 (3.3)	≤3 (≤4.1)	≤4 (≤3.8)	≤3 (≤4.1)	6 (3.4)	6 (3.4)
18.5–24.9	22869 (64.5)	23171 (60.9)	46040 (62.7)	2244 (63.9)	2321 (60.8)	4565 (62.3)	211 (63.0)	173 (65.5)	384 (64.1)	55 (75.3)	72 (67.9)	55 (75.3)	127 (70.9)	127 (70.9)
25.0–29.9 overweight	6897 (19.5)	8226 (21.6)	15123 (20.6)	698 (19.9)	830 (21.7)	1528 (20.8)	74 (22.1)	52 (19.7)	126 (21.0)	10 (13.7)	19 (17.9)	10 (13.7)	29 (16.2)	29 (16.2)
≥30.0 obese	3668 (10.9)	5037 (13.2)	8905 (12.1)	422 (12.0)	497 (13.0)	919 (12.5)	38 (11.3)	31 (11.7)	69 (11.5)	≤6 (≤8.2)	≤11 (≤10.4)	≤6 (≤8.2)	17 (9.5)	17 (9.5)
Missing	15352	15587	30939	1541	1570	3111	250	215	465	59	81	59	140	140
Maternal smoking status														
Non-smoker	40045 (78.8)	43571 (81.3)	83616 (80.1)	3925 (77.7)	4282 (79.5)	8207 (78.6)	434 (74.2)	375 (78.3)	809 (76.0)	104 (78.8)	140 (74.9)	104 (78.8)	244 (76.5)	244 (76.5)
Stopped in 1st trimester	1438 (2.8)	695 (1.3)	2133 (2.0)	142 (2.8)	70 (1.3)	212 (2.0)	18 (3.1)	4 (0.8)	22 (2.1)	≤3 (2.3)	≤5 (≤2.7)	≤3 (2.3)	≤7 (≤2.2)	≤7 (≤2.2)
Stopped after 1st trimester	308 (0.6)	196 (0.4)	504 (0.5)	33 (0.6)	33 (0.6)	66 (0.6)	7 (1.2)	3 (0.6)	10 (0.9)	≤3 (2.3)	≤3 (≤1.6)	≤3 (2.3)	≤3 (≤0.9)	≤3 (≤0.9)
Active smoker throughout pregnancy	6114 (12.0)	6387 (11.9)	12501 (12.0)	647 (12.8)	734 (13.6)	1381 (13.2)	69 (11.8)	64 (13.4)	133 (12.5)	17 (12.9)	23 (12.3)	17 (12.9)	40 (12.5)	40 (12.5)
Smoking status unknown	2891 (5.7)	2765 (5.2)	5656 (5.4)	306 (6.1)	269 (5.0)	575 (5.5)	57 (9.7)	33 (6.9)	90 (8.5)	9 (6.8)	18 (9.6)	9 (6.8)	27 (8.5)	27 (8.5)
Parity														
1			50796 (48.7)			5053 (48.4)			585 (55.0)				187 (58.6)	187 (58.6)
2			41282 (39.5)			3835 (36.7)			345 (32.4)				94 (29.5)	94 (29.5)
3			10031 (9.6)			1196 (11.5)			95 (8.9)				23 (7.2)	23 (7.2)
≥4			2310 (2.2)			357 (3.4)			39 (3.7)				15 (4.7)	15 (4.7)
Maternal socioeconomic position														
Top quintile	5767 (11.4)	15148 (28.3)	20915 (20.0)	872 (17.3)	1183 (22.0)	2055 (19.7)	107 (18.3)	117 (24.4)	224 (21.1)	33 (25.0)	38 (20.3)	33 (25.0)	71 (22.3)	71 (22.3)
2nd quintile	7639 (14.8)	13291 (24.8)	20930 (20.0)	969 (19.2)	1171 (21.7)	2140 (20.5)	113 (19.3)	112 (23.4)	225 (21.2)	31 (23.5)	31 (16.6)	31 (23.5)	62 (19.4)	62 (19.4)
3rd quintile	9990 (19.7)	10790 (20.1)	20780 (19.9)	1031 (20.4)	1160 (21.5)	2191 (21.0)	111 (19.0)	100 (20.9)	211 (19.8)	28 (21.1)	34 (18.2)	28 (21.1)	62 (19.4)	62 (19.4)
4th quintile	11780 (23.2)	8930 (16.7)	20710 (19.8)	1148 (22.7)	1112 (20.6)	2260 (21.7)	132 (22.6)	99 (20.7)	231 (21.7)	23 (17.4)	41 (21.9)	23 (17.4)	64 (20.1)	64 (20.1)
Bottom quintile	15720 (31.0)	5455 (10.2)	21175 (20.3)	1033 (20.4)	762 (14.1)	1795 (17.2)	122 (20.9)	51 (10.7)	173 (16.3)	17 (12.9)	43 (23.0)	17 (12.9)	60 (18.8)	60 (18.8)
Maternal residency														
Urban	27807 (54.7)	26193 (48.9)	54000 (51.7)	3045 (60.3)	2833 (52.6)	5878 (56.3)	393 (67.2)	280 (58.5)	673 (63.3)	83 (62.9)	126 (67.4)	83 (62.9)	209 (65.5)	209 (65.5)
Intermediate	6980 (13.7)	8471 (15.8)	15451 (14.8)	660 (13.1)	827 (15.4)	1487 (14.2)	62 (10.6)	58 (12.1)	120 (11.3)	15 (11.4)	22 (11.8)	15 (11.4)	37 (11.6)	37 (11.6)
Rural	12202 (24.0)	14421 (26.9)	26623 (25.5)	1077 (21.3)	1355 (25.2)	2432 (23.3)	108 (18.5)	112 (23.4)	220 (20.7)	28 (21.2)	31 (16.6)	28 (21.2)	59 (18.5)	59 (18.5)
Remote	3637 (7.2)	4439 (8.3)	8076 (7.7)	260 (5.2)	364 (6.8)	624 (6.0)	21 (3.6)	29 (6.1)	50 (4.7)	6 (4.6)	8 (4.3)	6 (4.6)	14 (4.4)	14 (4.4)

Table 2 Treatment characteristics of control and atopic dermatitis (AD) populations

Controls		AD diagnosis anytime prior to birth			AD hospital/ambulatory visit within 24 months of birth			AD hospital/ambulatory visit during pregnancy		
First child	Non-first child	Overall	First child	Non-first child	Overall	First child	Non-first child	First child	Non-first child	Overall
<i>n</i> = 50796	<i>n</i> = 53614	<i>n</i> = 104410	<i>n</i> = 5053	<i>n</i> = 5388	<i>n</i> = 10441	<i>n</i> = 585	<i>n</i> = 479	<i>n</i> = 187	<i>n</i> = 132	<i>n</i> = 319
5.1 (2.0)	4.7 (2.0)	4.9 (2.0)	5.1 (2.1)	4.8 (2.0)	4.9 (2.1)	5.3 (2.0)	4.79 (1.9)	5.2 (1.9)	5.2 (1.8)	5.2 (1.8)
2.7 (1.0)	2.6 (1.0)	2.7 (1.0)	2.7 (1.0)	2.6 (1.0)	2.7 (1.0)	2.8 (1.0)	2.7 (0.9)	2.8 (1.1)	2.8 (0.8)	2.8 (1.0)
physician mean (SD)										
Use of topical corticosteroids										
Group I										
During pregnancy	427 (0.8)	801 (0.8)	279 (5.5)	259 (4.8)	538 (5.2)	77 (13.2)	56 (11.7)	51 (27.3)	26 (19.7)	77 (24.1)
Within 9 months of pregnancy	374 (0.7)	815 (0.8)	254 (5.0)	256 (4.8)	510 (4.9)	81 (13.9)	60 (12.5)	27 (14.4)	19 (14.4)	46 (14.4)
Group II										
During pregnancy	1576 (3.1)	3061 (2.9)	833 (16.5)	829 (15.4)	1662 (15.9)	216 (36.9)	164 (34.2)	111 (59.4)	76 (57.6)	187 (58.6)
Within 9 months of pregnancy	1570 (3.1)	3349 (3.2)	794 (15.7)	767 (14.2)	1561 (15.0)	217 (37.1)	143 (29.9)	61 (32.6)	41 (31.1)	102 (32.0)
Group III										
During pregnancy	1196 (2.4)	1657 (2.5)	914 (18.1)	1013 (18.8)	1927 (18.5)	262 (44.8)	192 (40.1)	118 (63.1)	91 (68.9)	209 (65.5)
Within 9 months of pregnancy	1955 (3.9)	4224 (4.1)	1179 (23.3)	1310 (24.3)	2489 (23.8)	308 (52.7)	248 (51.8)	85 (45.5)	63 (47.7)	148 (46.4)
Group IV										
During pregnancy	180 (0.4)	403 (0.4)	114 (2.3)	126 (2.3)	240 (2.3)	24 (4.1)	28 (5.9)	16 (8.6)	7 (5.3)	23 (7.2)
Within 9 months of pregnancy	385 (0.8)	798 (0.8)	179 (3.5)	234 (4.3)	413 (4.0)	36 (6.2)	55 (11.5)	10 (5.4)	17 (12.9)	27 (8.5)
Total										
During pregnancy	3070 (6.0)	6289 (6.0)	1577 (31.2)	1658 (30.8)	3235 (31.0)	360 (61.5)	270 (56.4)	157 (84.0)	109 (82.6)	266 (83.4)
Within 9 months of pregnancy	3872 (7.6)	8282 (7.9)	1794 (35.5)	1926 (35.8)	3720 (35.6)	393 (67.2)	317 (66.2)	119 (63.6)	84 (63.6)	203 (63.6)
Use of topical calcineurin inhibitors										
During pregnancy	23 (0.1)	56 (0.1)	58 (1.2)	59 (1.1)	117 (1.1)	16 (2.7)	16 (3.3)	7 (3.7)	6 (4.6)	13 (4.1)
Within 9 months of pregnancy	119 (0.2)	223 (0.2)	190 (3.8)	190 (3.5)	380 (3.6)	62 (10.6)	40 (8.4)	18 (9.6)	11 (8.3)	29 (9.1)
Use of systemic corticosteroids										
During pregnancy	316 (0.6)	631 (0.6)	100 (2.0)	102 (1.9)	202 (1.9)	28 (4.8)	27 (5.6)	18 (9.6)	12 (9.1)	30 (9.4)
Within 9 months of pregnancy	753 (1.5)	1595 (1.5)	265 (5.2)	302 (5.6)	567 (5.4)	67 (11.5)	60 (12.5)	18 (9.6)	16 (12.1)	34 (10.7)
Use of systemic non-corticosteroid immunomodulators										
During pregnancy	41 (0.1)	96 (0.1)	11 (0.2)	13 (0.2)	24 (0.2)	5 (0.9)	0 (0)	≤3 (≤1.6)	0 (0)	≤3 (≤0.9)
Within 9 months of pregnancy	79 (0.2)	156 (0.2)	28 (0.8)	37 (0.7)	75 (0.7)	13 (2.2)	12 (2.5)	4 (2.1)	0 (0)	4 (1.3)

Table 2 Continued

	Controls			AD diagnosis anytime prior to birth			AD hospital/ambulatory visit within 24 months of birth			AD hospital/ambulatory visit during pregnancy		
	First child	Non-first child	Overall	First child	Non-first child	Overall	First child	Non-first child	Overall	First child	Non-first child	Overall
Ultraviolet therapy												
During pregnancy	12 (<0.1)	13 (<0.1)	25 (<0.1)	29 (0.6)	37 (0.7)	66 (0.6)	25 (4.3)	27 (5.6)	52 (4.9)	12 (6.4)	16 (12.1)	28 (8.8)
Within 9 months of pregnancy	26 (0.1)	13 (<0.1)	39 (<0.1)	31 (0.6)	31 (0.6)	62 (0.6)	26 (4.4)	17 (3.6)	43 (4.0)	≤3 (≤1.6)	≤3 (≤2.2)	4 (1.3)
Anti-viral use												
During pregnancy	590 (1.2)	482 (0.9)	1072 (1.0)	77 (1.5)	75 (1.4)	152 (1.5)	15 (2.6)	12 (2.5)	27 (2.5)	4 (2.1)	4 (3.0)	8 (2.5)
Within 9 months of pregnancy	1225 (2.4)	940 (1.8)	2165 (2.1)	182 (3.6)	143 (2.7)	325 (3.1)	29 (5.0)	24 (5.0)	53 (5.0)	9 (4.8)	8 (6.1)	17 (5.3)
Dicloxacillin use												
During pregnancy	272 (0.5)	276 (0.5)	548 (0.5)	85 (1.7)	116 (2.2)	201 (1.9)	36 (6.2)	37 (7.7)	73 (6.9)	26 (13.9)	19 (14.4)	45 (14.1)
Within 9 months of pregnancy	707 (1.4)	858 (1.6)	1565 (1.5)	212 (4.2)	242 (4.5)	454 (4.4)	76 (13.0)	57 (11.9)	133 (12.5)	21 (11.2)	20 (15.2)	41 (12.9)
Antihistamine use												
During pregnancy	1713 (3.4)	1892 (3.5)	3605 (3.5)	648 (12.8)	623 (11.6)	1271 (12.2)	117 (20.0)	92 (19.2)	209 (19.6)	50 (26.7)	35 (26.5)	85 (26.7)
Within 9 months of pregnancy	2222 (4.4)	2455 (4.6)	4677 (4.5)	941 (18.6)	815 (15.1)	1756 (16.8)	185 (31.6)	119 (24.8)	304 (28.6)	55 (29.4)	34 (25.8)	89 (27.9)

Green indicates a statistically significant increase in treatment use from prior to pregnancy to pregnancy. Yellow indicates no significant change in treatment use. Red indicates a statistically significant decrease in treatment use from prior to pregnancy to pregnancy.

and II) were generally more commonly used during pregnancy compared to prior, although the changes did not always meet statistical significance. In the group of women who had an AD visit during pregnancy, the use of any TCS increased from prior to pregnancy into pregnancy (63.6–83.4%, $P < 0.001$) as did UV therapy (1.3–8.8%, $P < 0.001$). Topical calcineurin inhibitors were less commonly used in all groups from prior to pregnancy into pregnancy.

Prenatal, obstetric and birth outcomes

Few outcomes were associated with maternal AD status. Children born to women with AD had similar birth weights to those born to controls [mean 3444 g (standard deviation 615 g) compared with 3473 g (612 g)] and were born at similar gestational ages [39.6 weeks (14.9 days) compared with 39.6 weeks (14.6 days)]. An inverse association was found with the development of gestational diabetes [OR 0.79, 95% CI (0.68–0.92), $P = 0.0020$], even after controlling for T2D and the use of systemic corticosteroids during pregnancy (Table S1, Figure 1). Positive associations were found with premature rupture of membranes [PROM; 1.15 (1.05–1.27), $P = 0.0031$] and staphylococcal neonatal septicaemia [2.45 (1.33–4.49), $P = 0.0039$]. However, no association was found with neonatal Group B streptococcal septicaemia [1.21 (0.65–2.24), $P = 0.5471$]. In a sub-analysis on all mother-child pairs from 2004 to 2014, where adjustment for BMI was possible, these associations remained consistent but became non-significant after Bonferroni correction: neonatal staphylococcal septicaemia (1.41 [0.59–3.42] $P = 0.4417$), PROM (1.13 [0.102–1.25] $P = 0.0189$), gestational diabetes [0.82 (0.69–0.97) $P = 0.0171$]. For all other outcomes, results from the sub-analysis where BMI adjustment was possible were consistent with initial analyses. Maternal AD was not associated with PUPPP or pemphigoid gestationis.

Discussion

Main findings

Women with a history of AD had overall decreased use of topical and systemic medication during pregnancy compared to the period prior. However, women with a hospital or ambulatory visit for AD during pregnancy had elevated TCS use compared to the period before pregnancy and maintained the same degree of systemic antibiotic and corticosteroid use during pregnancy. UV therapy was used among all AD groups, and was particularly escalated in the AD group with visits during pregnancy. There was no clear relationship between maternal AD and hypertensive diseases of pregnancy, however, a negative association with gestational diabetes was found. Significant associations were also observed between maternal AD and neonatal staphylococcal septicaemia as well as premature rupture of membranes suggesting that skin barrier deficiency in AD women may affect the risk of these conditions, albeit the absolute risk was low.

Interpretation

Pregnancy is thought to worsen AD in approximately 50% of cases, but this impression is based on small data sets.^{4,6} In our large cohort of women with AD, there was a tendency towards reduced consumption of both topical and systemic medications during pregnancy when compared to the period prior. It is unclear if this decrease is due to the resolution of dermatitis, or rather a result of de-escalation of treatment over concern of medication risks during pregnancy. If the latter is the case, some patients' AD may have been undertreated during pregnancy and may explain why some patients' AD worsens during pregnancy. An increase in total TCS use and maintained use of systemic medications were observed in the group of AD women with a visit during pregnancy. Again, it is unclear from our data whether this increased topical therapy use during pregnancy is a result of initial under-treatment of AD in early pregnancy, a worsening of AD due to the natural Th2 skew of pregnancy, or a combination. Collectively, these data suggest that dermatologists treat AD during pregnancy with TCS, antibiotics, oral corticosteroids and escalation of UV therapy. However, the data do not necessarily reflect the best approach to AD care during pregnancy.^{10,11,29}

Previous studies suggested increased risk of AD in the offspring if their mothers experienced prenatal or obstetric complications.^{13,14} However, understanding the baseline associations between these complications and AD status is essential to avoid confounding. For example, there is evidence that neonatal sepsis may increase the risk of AD development in the offspring, but the trend is lost when family history of AD is accounted for.³⁰ In other words, the baseline associations between complications of pregnancy and maternal AD alter the interpretation of studies that show associations between these complications and the subsequent development of AD in the offspring—strong correlations between maternal AD and these complications would call into question previous results tying these complications to AD development in the offspring, while the absence of strong correlations would support these previous studies. In crude analysis, hypertensive diseases of pregnancy were more common in pregnancies to AD women compared to controls (5.1% vs. 4.4%), likely due to a higher prevalence of both previous hypertension and active smoking in the AD group.³¹ While the normal Th2 skew of pregnancy is lessened in the context of preeclampsia suggesting a possible protective benefit of AD and its Th2 predominance,³² no clear inverse association has been reported.^{33,34} We found an inverse association between gestational diabetes and maternal AD. The explanation for this inverse association is unclear, but is in line with the lower prevalence of T2D in adult AD patients in Denmark.³⁵ Additionally, the depression of this association in sub-analysis where BMI data were available suggests that differences in BMI distribution in AD vs. non-AD women may in part account for this association.

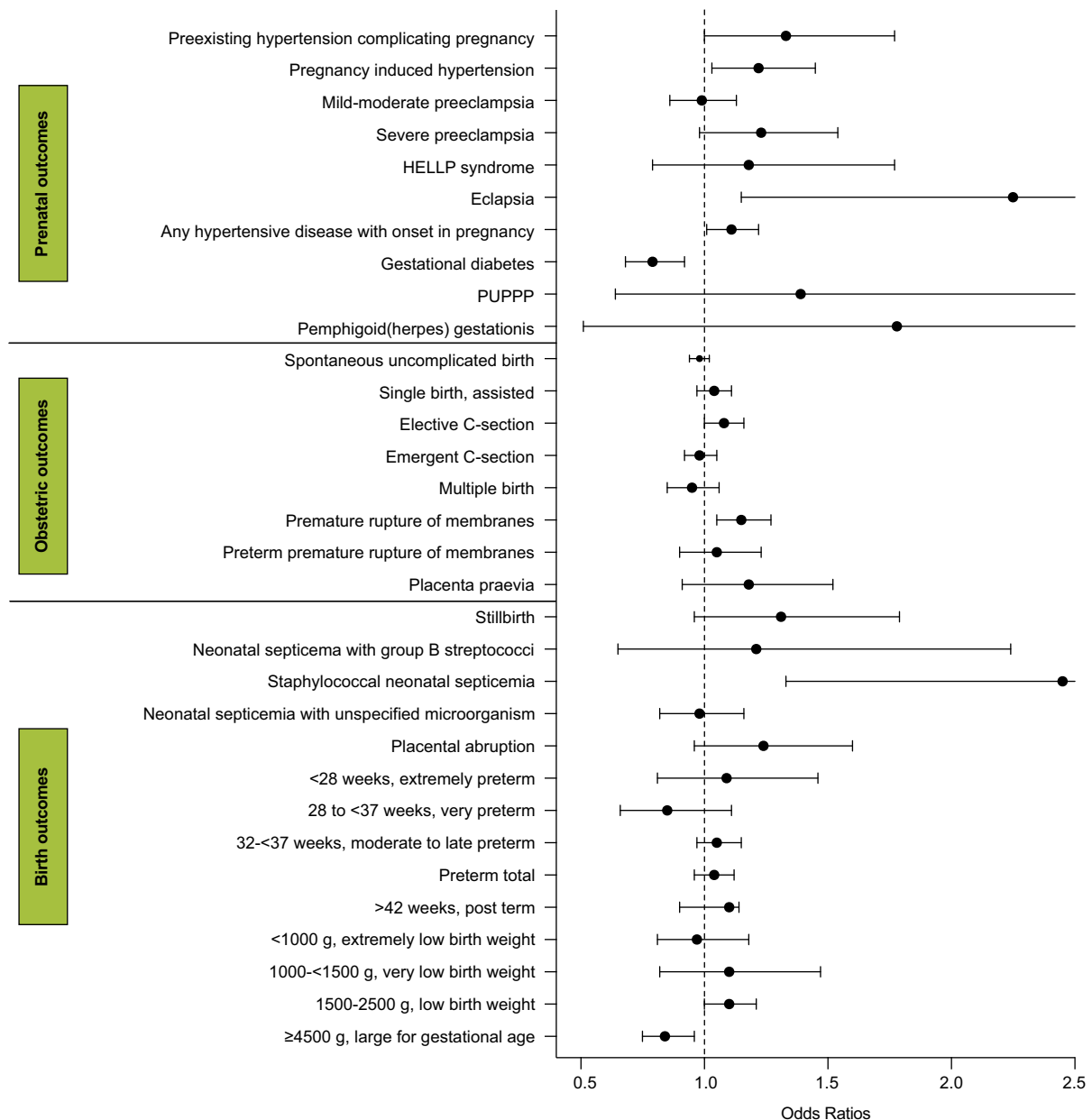


Figure 1 Forrest plot of adjusted odds ratios and 95% confidence intervals for associations between maternal atopic dermatitis and prenatal, obstetric and birth outcomes. After Bonferroni correction only the outcomes of gestational diabetes, premature rupture of membranes and staphylococcal neonatal septicaemia remained statistically significant.

Premature rupture of membranes (PROM) or spontaneous rupture of membranes prior to labour onset is a relatively common obstetric complication that is observed in up to 10% of normal births.^{36–38} We found an association, albeit weak, between PROM and maternal AD in both crude and adjusted analysis. However, the association did not meet statistical significance in sub-analysis. Over expression of

matrix metalloproteinase-9 (MMP-9) causing degradation of the extracellular matrix within the amniotic membrane has been suggested as a possible mechanism.^{39,40} MMP-9 has also been implicated as part of the pro-inflammatory milieu and serum MMP-9 is indeed elevated in AD patients.⁴¹ No other obstetric outcomes were clearly associated with maternal AD.

While the Th2 imbalance characteristic of AD, at least in theory, could enhance the natural Th2 protective skew of pregnancy,^{32,42} thereby potentially reducing risk of preterm labour or neonatal demise,⁴³ such data are limited and conflicting.^{33,34} Our analysis found no clear inverse associations between maternal AD and prematurity, low birth weight, stillbirth or more complicated birth. In fact, in crude analysis some birth and obstetric outcomes were worse in AD pregnancies, namely stillbirth (0.47% vs. 0.33%), prematurity (<37 weeks, 7.2% vs. 6.7%) and low birth weight (<2500 g, 6.4% vs. 5.8%). These associations were lost in adjusted analysis suggesting that AD patients' background risk factors, e.g. increased smoking, likely outweigh any potential benefit of a persistent or accentuated Th2 skew.

Maternal AD was associated with neonatal staphylococcal septicaemia, but not with neonatal septicaemia from other microorganisms. This observation suggests a biological pathomechanism as individuals with AD have higher rates of *S. aureus* colonization, both on lesional and non-lesional skin, and that both staphylococcal colonization and infection worsen AD severity.^{44,45} Additionally perineal staphylococcal colonization is common in AD patients,⁴⁶ and maternal staphylococcal colonization has been associated with neonatal staphylococcal colonization.⁴⁷ In the majority of neonatal staphylococcal septicaemia cases the mother had not received dicloxacillin during pregnancy or the 12 months prior. Importantly, the absolute number of cases in both groups was low which likely explains why the association was lost in the 2004–2014 sub-analysis.⁴⁸ This raises a possibility for a clinically important change in practice: surveillance and treatment of perineal staphylococcal colonization in pregnant women with AD, in the aim reduce neonatal staphylococcal septicaemia in the children of this group of women. However, more research is needed on this issue before a general recommendation can be made. It is also worth noting that while vaginal staphylococcal colonization does not likely alter risk for PROM,⁴⁹ PROM has been identified as a potential risk factor for neonatal septicaemia.^{50,51} Similarly, decreased utilization of dermatologic therapy during pregnancy by women with a history of AD may at least in theory influence burden of *S. aureus* colonization or infection.

Strengths and limitations

The use of the Danish national health registries allows for large-scale data gathering that encompasses both health data such as medication use and hospital/ambulatory visits but also socioeconomic data such as household income. All pregnancies recorded by residents of Denmark are included in the Danish Medical Birth Registry, a clear strength, however not all women with AD were included in our cohort, given that not all patients with AD receive care at a hospital-based clinic or clinic collecting data for the Danish National Patient Register. Additionally, given the study design, causation cannot be established. Our study did not account for dietary or activity-

based lifestyle factors or other possible residual confounders which may influence these associations. Information on AD severity was lacking. Lastly, only 319 women with AD were seen by a clinician during their pregnancy.

Conclusions

In this nationwide retrospective matched cohort study, we found associations between maternal AD and PROM and neonatal staphylococcal septicaemia (although the latter was rare), but an inverse association with gestational diabetes. However, these associations did not meet statistical significance in sub-analysis where BMI data were available. No association was found with hypertensive disease of pregnancy, stillbirth or prematurity. Topical and systemic therapies were more commonly used in pregnancies to women with AD compared to controls. Health care providers caring for patients with AD should be cognizant of these differences.

Acknowledgement

Dr. Thyssen is supported by an unrestricted grant from the Lundbeck Foundation.

Author contributions

Dr. Hamann had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hamann, Egeberg, Skov and Thyssen. Acquisition, analysis and interpretation of data: All authors. Drafting of the manuscript: Hamann, Egeberg and Thyssen. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Hamann. Obtained funding: None. Administrative, technical or material support: All authors. Study supervision: All authors.

References

- 1 Mortz CG, Andersen KE, Dellgren C, Barington T, Bindslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. *Allergy* 2015; **70**: 836–845.
- 2 Abuabara K, Yu AM, Okhovat JP, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: a systematic review and meta-analysis of longitudinal studies. *Allergy* 2018; **73**: 696–704.
- 3 Werfel T, Allam JP, Biedermann T *et al.* Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol* 2016; **138**: 336–349.
- 4 Kemmett D, Tidman M. The influence of the menstrual cycle and pregnancy on atopic dermatitis. *Br J Dermatol* 1991; **125**: 59–61.
- 5 Weatherhead S, Robson SC, Reynolds NJ. Eczema in pregnancy. *BMJ* 2007; **335**: 152–154.
- 6 Cho S, Kim HJ, Oh SH, Park CO, Jung JY, Lee KH. The influence of pregnancy and menstruation on the deterioration of atopic dermatitis symptoms. *Ann Dermatol* 2010; **22**: 180–185.
- 7 Bager P, Wohlfahrt J, Boyd H, Thyssen JP, Melbye M. The role of filaggrin mutations during pregnancy and postpartum: atopic dermatitis and genital skin diseases. *Allergy* 2016; **71**: 724–727.
- 8 Ambros-Rudolph CM, Mullegger RR, Vaughan-Jones SA, Kerl H, Black MM. The specific dermatoses of pregnancy revisited and reclassified: results of a retrospective two-center study on 505 pregnant patients. *J Am Acad Dermatol* 2006; **54**: 395–404.

- 9 Gelmetti C, Wollenberg A. Atopic dermatitis - all you can do from the outside. *Br J Dermatol* 2014; **170**(Suppl 1): 19–24.
- 10 Wollenberg A, Oranje A, Deleuran M et al. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol* 2016; **30**: 729–747.
- 11 Ring J, Alomar A, Bieber T et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol* 2012; **26**: 1045–1060.
- 12 Vaughan Jones SA, Hern S, Nelson-Piercy C, Seed PT, Black MM. A prospective study of 200 women with dermatoses of pregnancy correlating clinical findings with hormonal and immunopathological profiles. *Br J Dermatol* 1999; **141**: 71–81.
- 13 Kumar R, Ouyang F, Story RE et al. Gestational diabetes, atopic dermatitis, and allergen sensitization in early childhood. *J Allergy Clin Immunol* 2009; **124**: 1031–1038.e1031–1034.
- 14 Stokholm J, Sevelsted A, Anderson UD, Bisgaard H. Preeclampsia associates with asthma, allergy and eczema in childhood. *Am J Respir Crit Care Med* 2017; **195**: 614–621.
- 15 Bliddal M, Broe A, Pottgard A, Olsen J, Langhoff-Roos J. The Danish medical birth register. *Eur J Epidemiol* 2018; **33**: 27–36.
- 16 Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015; **7**: 449–490.
- 17 Gaist D, Sørensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997; **44**: 445–448.
- 18 von Bulow A, Kriegbaum M, Backer V, Porsbjerg C. The prevalence of severe asthma and low asthma control among Danish adults. *J Allergy Clin Immunol Pract* 2014; **2**: 759–767.
- 19 Olesen JB, Lip GY, Hansen ML et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011; **342**: d124.
- 20 Schmiegelow MD, Andersson C, Kober L et al. Associations between body mass index and development of metabolic disorders in fertile women—a nationwide cohort study. *J Am Heart Assoc* 2014; **3**: e000672.
- 21 Health NIO. WHO Collaborating Centre for Drug Statistics Methodology, 2017. URL <https://www.whooc.no/> (last accessed: 16 January 2018).
- 22 Kristensen IT, Kjeldsen C, Dalgaard T. Landdistriktskommuner-indikatorer for landdistrikt [Rural District Municipalities—Indicators for Rural District], 2006.
- 23 Olsen SF, Houshmand-Oregaard A, Granstrom C et al. Diagnosing gestational diabetes mellitus in the Danish National Birth Cohort. *Acta Obstet Gynecol Scand* 2017; **96**: 563–569.
- 24 Sneider K, Langhoff-Roos J, Sundtoft IB, Christiansen OB. Validation of second trimester miscarriages and spontaneous deliveries. *Clin Epidemiol* 2015; **7**: 517–527.
- 25 Thisted DL, Mortensen LH, Hvidman L, Rasmussen SC, Larsen T, Krebs L. Use of ICD-10 codes to monitor uterine rupture: validation of a national birth registry. *Eur J Obstet Gynecol Reprod Biol* 2014; **173**: 23–28.
- 26 Klemmensen AK, Olsen SF, Osterdal ML, Tabor A. Validity of preeclampsia-related diagnoses recorded in a national hospital registry and in a postpartum interview of the women. *Am J Epidemiol* 2007; **166**: 117–124.
- 27 Langhoff-Roos J, Rasmussen S, Sundhedsstyrelsen D; Sundhedsstyrelsen. Center for Evaluering og Medicinsk Teknologivurdering C. Validering af Landspatientregisteret (LPR) mhp. obstetrisk forskning og kvalitetssikring: - et kvalitetsudviklingsprojekt. Sundhedsstyrelsen, 2003.
- 28 Althabe F, Howson CP, Kinney M, Lawn J. Born too soon: The global action report on preterm birth. World Health Organization, Geneva, 2012.
- 29 Ring J, Alomar A, Bieber T et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol* 2012; **26**: 1176–1193.
- 30 Kopp MV, Semmler S, Ihorst G, Berner R, Forster J. Hospital admission with neonatal sepsis and development of atopic disease: is there a link? *Pediatr Allergy Immunol* 2005; **16**: 630–636.
- 31 Newman MG, Lindsay MK, Graves W. Cigarette smoking and pre-eclampsia: their association and effects on clinical outcomes. *J Matern Fetal Med* 2001; **10**: 166–170.
- 32 Saito S, Sakai M, Sasaki Y, Tanebe K, Tsuda H, Michimata T. Quantitative analysis of peripheral blood Th0, Th1, Th2 and the Th1: Th2 cell ratio during normal human pregnancy and preeclampsia. *Clin Exp Immunol* 1999; **117**: 550.
- 33 Seeger JD, Lanza LL, West WA, Fernandez C, Rivero E. Pregnancy and pregnancy outcome among women with inflammatory skin diseases. *Dermatology* 2007; **214**: 32–39.
- 34 Trønnes H, Wilcox AJ, Markestad T, Tollånes MC, Lie RT, Moster D. Associations of maternal atopic diseases with adverse pregnancy outcomes: a national cohort study. *Paediatr Perinat Epidemiol* 2014; **28**: 489–497.
- 35 Andersen YMF, Egeberg A, Gislason GH, Skov L, Knop FK, Thyssen JP. Adult atopic dermatitis and the risk of type 2 diabetes. *J Allergy Clin Immunol* 2017; **139**: 1057–1059.
- 36 Miller HC, Jekel JF. Epidemiology of spontaneous premature rupture of membranes: factors in pre-term births. *Yale J Biol Med* 1989; **62**: 241–251.
- 37 Ladfors L, Mattsson LA, Eriksson M, Milsom I. Prevalence and risk factors for prelabor rupture of the membranes (PROM) at or near-term in an urban Swedish population. *J Perinat Med* 2000; **28**: 491–496.
- 38 Lyons P, ed. Premature rupture of membranes. In *Obstetrics in Family Medicine: A Practical Guide*. Springer International Publishing, Cham, 2015: 65–70.
- 39 Romero R, Chaiworapongsa T, Espinoza J et al. Fetal plasma MMP-9 concentrations are elevated in preterm premature rupture of the membranes. *Am J Obstet Gynecol* 2002; **187**: 1125–1130.
- 40 Zuo G, Dong JX, Zhao FF, Chen Y. Expression of matrix metalloproteinase-9 and its substrate level in patients with premature rupture of membranes. *J Obstet Gynaecol* 2017; **37**: 441–445.
- 41 Devillers AC, van Toorenbergen AW, Klein Heerenbrink GJ, Mulder PG, Oranje AP. Elevated levels of plasma matrix metalloproteinase-9 in patients with atopic dermatitis: a pilot study. *Clin Exp Dermatol* 2007; **32**: 311–313.
- 42 Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a Th2 phenomenon? *Immunol Today* 1993; **14**: 353–356.
- 43 Fu Y, Lou H, Wang C et al. T cell subsets in cord blood are influenced by maternal allergy and associated with atopic dermatitis. *Pediatr Allergy Immunol* 2013; **24**: 178–186.
- 44 Saintive S, Abad E, C Ferreira D et al. What is the role of *Staphylococcus aureus* and herpes virus infections in the pathogenesis of atopic dermatitis? *Future Microbiol* 2017; **12**: 1327–1334.
- 45 Totte JE, van der Feltz WT, Hennekam M, van Belkum A, van Zuuren EJ, Pasmans SG. Prevalence and odds of *Staphylococcus aureus* carriage in atopic dermatitis: a systematic review and meta-analysis. *Br J Dermatol* 2016; **175**: 687–695.
- 46 Alsterholm M, Strombeck L, Ljung A et al. Variation in *Staphylococcus aureus* colonization in relation to disease severity in adults with atopic dermatitis during a five-month follow-up. *Acta Derm Venereol* 2017; **97**: 802–807.
- 47 Roca A, Bojang A, Camara B et al. Maternal colonization with *Staphylococcus aureus* and Group B streptococcus is associated with colonization in newborns. *Clin Microbiol Infect* 2017; **23**: 974–979.
- 48 Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis I. Background, goals, and general strategy. *J Clin Epidemiol* 1995; **48**: 1495–1501.
- 49 Veleminsky M, Tosner J. Relationship of vaginal microflora to PROM, pPROM and the risk of early-onset neonatal sepsis. *Neuro Endocrinol Lett* 2008; **29**: 205–221.
- 50 Seaward PG, Hannah ME, Myhr TL et al. International multicenter term PROM study: evaluation of predictors of neonatal infection in infants born to patients with premature rupture of membranes at term.

Premature Rupture of the Membranes. *Am J Obstet Gynecol* 1998; **179**(3 Pt 1): 635–639.

- 51 Schuchat A, Zywicki SS, Dinsmoor MJ *et al.* Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study. *Pediatrics* 2000; **105**: 21–26.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Crude and adjusted odds ratios and 95% confidence intervals for associations between maternal atopic dermatitis and prenatal, obstetric and birth outcomes.