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Use of glucocorticoids during pregnancy and risk of attention-deficit/hyperactivity disorder in offspring: a nationwide Danish cohort study

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ABSTRACT

Objective Prenatal exposure to excess endogenous glucocorticoid (GC) has been linked to attention-deficit/hyperactivity disorder (ADHD). We investigated whether prenatal exposure to exogenous GC is associated with ADHD.

Design Nationwide cohort study.

Setting A cohort of 875 996 singletons born alive between 1996 and 2009 in Denmark. Data were obtained from national registries.

Exposures We identified children exposed prenatally to GCs, children unexposed prenatally and born to maternal former users, and children unexposed and born to maternal never users.

Main outcome measures We compared ADHD risk in children prenatally exposed to GCs and in children of former GC users with risk in unexposed children of never users. We computed cumulative incidence at 10 years of age and adjusted HRs (aHRs). In addition, we compared exposed children with unexposed siblings in a sibling design.

Results We identified 875 996 children, among whom 5319 were prenatally exposed to systemic GCs and 36 780 to local/inhaled GCs. Cumulative incidences of ADHD at 10 years of age were 2.65% in prenatally exposed children and 2.03% in unexposed children of never users. At the general population level, prenatal exposure was associated with ADHD compared with unexposed, with aHR of 1.43(95% CI 1.24 to 1.65) for systemic exposure and 1.23 (95% CI 1.15 to 1.31) for local/inhaled exposure. However, our former user analysis (aHR of 1.25 (95% CI 1.20 to 1.29)) and sibling design (aHR of 1.03 (95% CI 0.87 to 1.20)) indicated that these findings were due to confounding.

Conclusion This study provides no evidence of a causal association between prenatal exposure to GCs and risk of ADHD.

Strengths and limitations of this study

- ► This study was a large nationwide population-based study with long and virtually complete (≈ 95%) follow-up.
- ► We conducted a sibling analysis that allowed us to adjust for family-related factors, such as genetic and socioeconomic factors.
- ► We were limited by our lack of data on actual maternal use of glucocorticoids, as we used prescription redemption as a proxy for this information. This could have led to misclassification of exposure status.
- ► Attention-deficit/hyperactivity disorder is diagnosed based on criteria evaluating, for example, impulsiveness, inattention and hyperactivity. Assessment of these behaviours can be prone to interindividual judgement among physicians.

INTRODUCTION

Glucocorticoids (GCs) are anti-inflammatory agents used commonly since the 1950s to treat asthma, rheumatic diseases and other autoimmune diseases.[1] GC (mainly cortisol) is also synthesised endogenously in humans. Besides, having effects on the inflammatory system cortisol plays an important role in maintaining cardiovascular and metabolic homoeostasis especially during physiological or psychological stress. Hence, cortisol is also known as a stress hormone.[2] Exogenous GCs used in treatment regimens (both systemic and local formulations) are absorbed to the blood stream. Thus, exogenous GCs have the potential to affect human systems in similar ways as endogenous cortisol.[3]

GCs (both exogenous and endogenous) are known to cross the placental barrier and thus have the potential to affect fetal development.[4] Both animal and human studies have found that prenatal GC exposure can cause behavioural changes and increased anxiety levels in offspring.[5–8] A suggested explanation is 'fetal programming', a concept that describes the fetus' physiological adaptation to the characteristics of the intrauterine environment.[9] It is hypothesised that this environment has long-lasting effects on a child's health.[10]

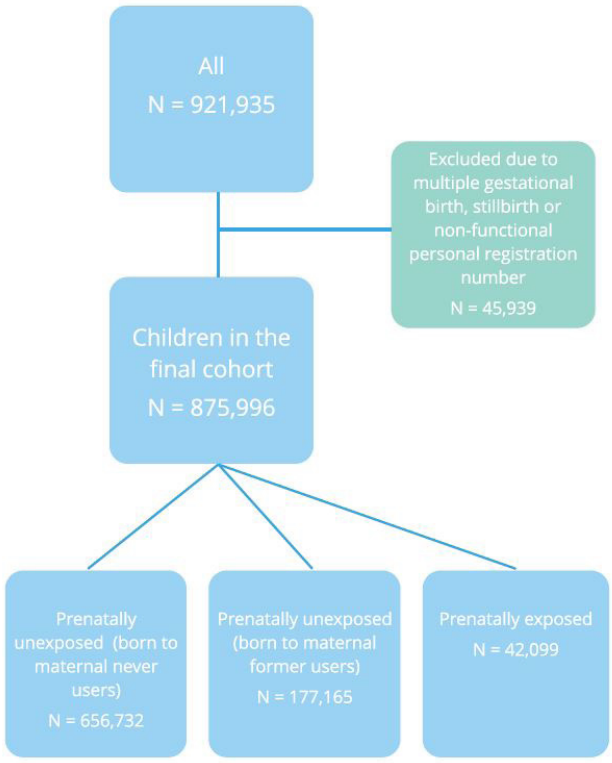

Figure 1 Children identified in the Danish Medical Birth Registry (1996–2009).

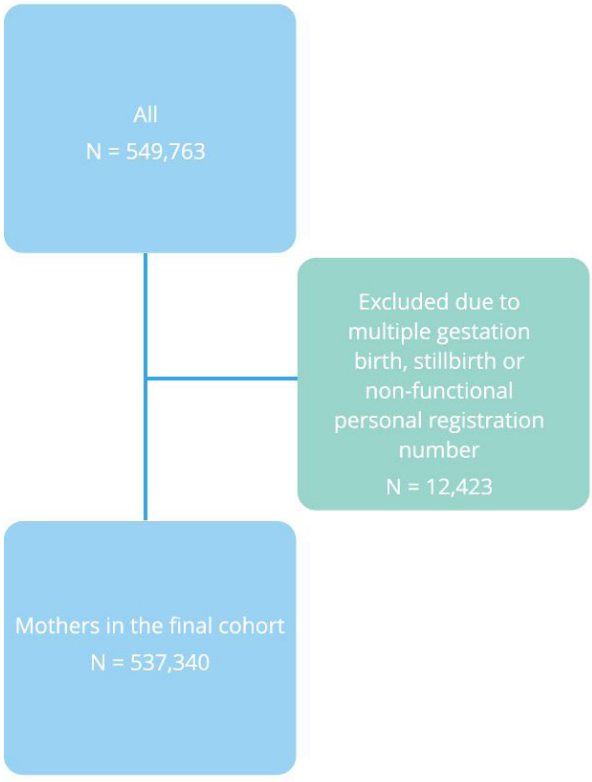

Figure 2 Mothers identified in the Danish Medical Birth Registry (1996–2009).

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterised by impulsiveness, inattention and hyperactivity. The incidence of childhood ADHD is increasing, with the current worldwide prevalence estimated at approximately 5%.[11] An important risk factor for ADHD is heritability.[12] Other proposed risk factors include preterm birth and prenatal exposure to smoking or alcohol.[13–16] However, knowledge on causal mechanisms underlying the development of ADHD still needs more investigation. There is little evidence available on the risk of ADHD following prenatal exposure to GCs. However, one study reported an association between maternal stress during pregnancy and increased risk of ADHD in offspring, possibly due to a stress-related increase in cortisol during pregnancy.[17] Few studies of women exposed to GCs because of impending preterm birth found an increased risk of adverse neuropsychiatric outcomes (eg, ADHD) among their offspring. However, preterm delivery in itself increases the risk of ADHD and other adverse outcomes in children.[18 19]

Some inflammatory diseases treated with GCs are also risk factors for adverse birth outcomes. For instance, IBD increases the risk of stillbirth, growth restriction and preterm delivery, and this risk increases if the disease is poorly managed.[20] Cessation of GC treatment during pregnancy thus is not possible for women with most chronic inflammatory diseases. This underscores the need for a better understanding of potential adverse neurodevelopmental outcomes after prenatal exposure to GCs.

Therefore, we conducted a cohort study on use of GCs during pregnancy and risk of ADHD in offspring.

METHODS

Setting

We conducted this cohort study in Denmark, which has 5.6 million inhabitants and approximately 65 000 births annually. The Danish healthcare system provides tax-supported health services to all residents, guaranteeing access to primary and secondary care free of charge. A unique central personal registration number (the civil registration number) is assigned to all Danish residents at birth by the Civil Registration System (CRS).[21] It is used in registries to record use of health services, allowing continuous population surveillance and permitting accurate and unambiguous linkage of information among relevant registries at the individual level.

Study population and design

We used the Danish Medical Birth Registry[22] to identify a cohort of all singletons born alive in Denmark from 1 January 1996 until 31 December 2009 (figure 1 and figure 2). The Danish Medical Birth Registry contains computerised records of all deliveries in Denmark since 1973. Each record includes the civil registration number of the mother, father and newborn, as well as multiple variables describing the delivery, the newborn and the

Table 1 Distribution of 42 099 prenatally exposed children according to time of exposure and type of administration

	n (%)
All	42 099
According to administration form	
All systemic treatment	5319 (12.6)
Systemic, low dose (1 redeemed prescription)	3797 (9.0)
Systemic, high dose (≥2 redeemed prescriptions)	1522 (3.6)
Local/inhaled	36 780 (87.4)
According to time of first exposure	
First-trimester exposure	11 702 (27.8)
Second-trimester and third-trimester exposure	27 484 (65.3)
≤30 days prior to pregnancy	2913 (6.9)

mother. The midwives or physicians overseeing the deliveries collect the data. Siblings born to the same mother were identified through the CRS. Thus it was possible to identify a sibling comparison cohort that was highly suitable for optimising adjustment for important potential family-related and genetic confounders. We also established a general population cohort to allow comparisons with unexposed children of never users.

Maternal GC use

Prenatal exposure to GCs was defined as maternal redemption of a prescription for at least one systemic GC and/or two redeemed prescriptions for a local GC or two redeemed prescriptions for an inhaled GC 30 days prior to or at any time during pregnancy. Prescriptions were identified through the Danish National Prescription Registry.[23] Since January 1994, this registry has recorded information on all prescriptions redeemed in Denmark, including the patient's civil registration number, the medication classification code (the Anatomical Therapeutic Chemical classification system of WHO) and the date of dispensing. Most local and all inhaled and systemic GCs, as well as all ADHD medications, are available only by prescription in Denmark. Pregnancy was defined as starting from the first day of the last menstrual period, according to the definition used by the Danish Medical Birth Registry. First-trimester exposure was defined as redemption of a prescription by the mother during the period 30 days prior to start of pregnancy up to 12 weeks after start of pregnancy; second-trimester and third-trimester exposure was defined as prescription redemption during the remainder of the pregnancy.[24] If the mother redeemed more than one prescription during pregnancy, the date of the first redemption for systemic GCs or the date of the second redemption for local/inhaled GCs was used to determine the time of first exposure. We defined maternal former users of GCs as women who had redeemed a prescription for one systemic GC and/or for two local or inhaled GCs up to 30 days prior to pregnancy. Never users were women who had never redeemed a prescription for GCs from 1994 and until birth.[25]

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

ADHD in offspring was defined as a diagnosis of ADHD by a physician or by redemption of a prescription for ADHD medication. We used the Danish Psychiatric Registry[26] and the Danish National Patient Registry (DNPR)[27] to identify children in the study population who had an inpatient or outpatient hospital diagnosis of ADHD. The Danish Psychiatric Registry contains computerised data on all admissions to psychiatric hospitals since 1969 and on outpatient contacts since 1995. The DNPR has tracked all inpatient stays at Danish public hospitals since 1977, and outpatient clinic and emergency room visits at all public hospitals since 1995. Data recorded in the DNPR and the Danish Psychiatric Registry include the patient's civil registration number, dates of admission and discharge or outpatient visit dates, and up to 20 discharge diagnoses for each contact, classified according to the Eighth Revision of the International Classification of Diseases until 1994 and the 10th Revision thereafter. Diagnosis and treatment of ADHD are also handled by psychiatrists in private practice. These patients are not recorded in the Danish Psychiatric Registry or the DNPR. Therefore, to ensure completeness, we defined ADHD as either a diagnosis of ADHD or redemption of a prescription for ADHD medication. Information on prescription rede mption was obtained from the Danish National Prescription Registry.

Covariates

We obtained information on several risk factors for ADHD in offspring. This included information from the Danish Psychiatric Registry on maternal and paternal psychiatric diagnoses any time before pregnancy, information from the DNPR and the Danish National Prescription Registry on maternal diabetes and infectious diseases during pregnancy, and information from the Danish Medical Birth Registry on maternal age at birth, sex of the child and maternal smoking during pregnancy. As maternal body mass index was available only from 2004 on, and marital status was incompletely registered after 2006, body mass index and marital status were included as covariates only in separate subanalyses. Since the prevalence of both GC use and ADHD increased between 1996 and 2014, we also adjusted for calendar year of birth. We also obtained information from the Danish Medical Birth Registry on the following characteristics of newborns: gestational age at birth, birth weight, mode of delivery, birth order and 5 min Apgar score. The characteristics of the newborn were investigated as possible intermediators in the pathway from prenatal GC exposure to ADHD development and therefore only investigated for descriptive purposes and not included in the regression analyses.

Statistical analyses

All statistical analyses were performed using SAS (V.9.4). The study was approved by the Danish Data Protection Agency (record no 2011-41-6465). Codes used to define study variables are provided in the online supplementary appendices 1 and 2.

Children were followed from date of birth until the date of an ADHD diagnosis, redemption of a prescription for an ADHD medication, emigration, death or the end of follow-up on 31 December 2014, whichever came first.

General population comparison cohort

We computed cumulative incidences of ADHD at 10 years of age in children exposed prenatally to GCs, in children of maternal former users and unexposed children of never users. Then, we compared children exposed prenatally to GCs and children of maternal former users with the unexposed children of never users. Using Cox proportional-hazards regression, we computed crude and adjusted HRs (aHRs) with 95% CIs as measures of relative risk. The assumption of proportional hazards was graphically verified.

We performed subanalyses: first, we disaggregated GCs as local/inhaled or systemic. Second, we disaggregated systemic exposure as one redeemed prescription or two or more redeemed prescriptions.

Table 2 Characteristics of 875 996 singleton births in Denmark in 1996–2009, according to maternal use of glucocorticoids during pregnancy

	Prenatally exposed, n (%)	Prenatally unexposed and born to maternal never users, n (%)	Prenatally unexposed and born to maternal former users, n (%)
All	42 099	656 732	177 165
Birth year			
1996–2000	13 416 (31.8)	273 713 (41.7)	34 256 (19.3)
2001–2005	14 647 (34.8)	223 783 (34.0)	69 991 (39.5)
2006–2009	14 036 (33.3)	159 236 (24.2)	72 918 (41.1)
Sex			
Boy	21 875 (52.0)	336 827 (51.3)	90 955 (51.3)
Girl	20 224 (48.0)	319 905 (48.7)	86 210 (48.7)
Birth order			
1	16 326 (38.8)	297 280 (45.3)	62 592 (35.3)
2	16 464 (39.1)	239 674 (36.5)	70 810 (40.0)
≥3	9309 (22.1)	119 778 (18.2)	43 763 (24.7)
Birth weight			
<2000 g	282 (0.7)	4692 (0.7)	1222 (0.7)
2000–2499 g	960 (2.3)	14.405 (2.2)	3848 (2, 2)
2500–2999 g	4132 (9.8)	67 642 (10.3)	17 425 (9.8)
3000–5500 g	36 244 (86.1)	560 481 (85.3)	152 627 (86.2)
Missing, very low or very high	481 (1.1)	9512 (1.5)	2043 (1.2)
Apgar score			
≤7	539 (1.3)	8391 (1.3)	2179 (1.2)
>7	41 158 (97.8)	640 191 (97.5)	173 423 (97.9)
Missing	402 (1.0)	8150 (1.2)	1563 (0.9)
Gestational age			
<30 weeks	127 (0.3)	2225 (0.3)	648 (0.4)
30–36 weeks	1846 (4.4)	28 964 (4.4)	8462 (4.8)
37–41 weeks	36 690 (87.2)	569 898 (86.8)	155 774 (87.9)
>41 weeks	3223 (7.7)	50 699 (7.7)	11 550 (6.5)
Very low or missing	213 (0.5)	4946 (0.8)	731 (0.4)
Mode of delivery			
Vaginal	33 180 (78.8)	547 163 (83.3)	140 626 (79.4)
Caesarean	8919 (21.2)	109 569 (16.7)	36 539 (20.6)

Sibling comparison cohort

To control for family-related factors such as genetics and socioeconomic status, we conducted a sibling-matched analysis.[28] We used stratified Cox regression with a separate stratum for each family identified by the mother's personal registration number. In this analysis, each family has its own baseline rate function reflecting the family's shared genetic and social factors. The stratified Cox regression model is an extension of the paired binomial model, taking into account the differences in follow-up time. Hence, only siblings discordant for exposure and ADHD contributed with information to the estimates. We adjusted for calendar year of birth, sex of the child, birth order, maternal smoking status and maternal infectious diseases during pregnancy.

In the general population analyses as well as in the sibling design, we accounted for clustering of observations in computation of CIs, as some children were born by the same mother.

RESULTS

We identified 875 996 singletons born alive between 1996 and 2009, of whom 42 099 (4.8%) were exposed to GCs prenatally, 177 165 (20.2%) were born to maternal former users of GCs and 656 732 (75.0%) were born to maternal never users. Table 1 presents the distribution of exposure according to trimester and form of GC administration.

In the sibling analysis, we identified 608 643 children born by 269 987 mothers. Of these, 44 660 were discordant for exposure (20 162 prenatally exposed). Only 2246 children contributed informative to the estimates.

Birth outcomes

The sex distribution was the same for prenatally exposed and unexposed children. Children exposed prenatally to GCs and unexposed children born to never users had the same prevalence of low birth weight (3.0% vs 2.9%), low 5 min Apgar score (1.3% vs 1.3%) and the same prevalence of premature birth (4.7% vs 4.8%). Caesarean section was performed more often in mothers of prenatally exposed children compared with unexposed children born to never users (21.2% vs 16.7%) (table 2).

Maternal and paternal characteristics

Age at delivery was higher among maternal users of GCs than among never users. Compared with maternal never users, maternal users of GCs were more likely to have a prior diagnosis of psychiatric illness (9.4% vs 6.6%), inflammatory bowel disease (2.7% vs 0.3%), asthma (15.9% vs 0.7%), other autoimmune disease (4.5% vs 1.4%) and type 1 and 2 diabetes (1.7% vs 1.0%). There was no difference in prior psychiatric illness in fathers (table 3).

Risk estimates

Cumulative incidences of ADHD at 10 years of age were 2.65% (CI 2.56% to 2.74%) in prenatally exposed children, 2.65% (95% CI 2.56% to 2.74%) in children of former users and 2.03% (95% CI 2.00% to 2.07%) in unexposed children of never users. When we compared prenatally exposed children to unexposed children born to never users, we observed an elevated risk of ADHD in exposed children (aHR=1.43 (95% CI 1.24 to 1.65) for systemic GCs and aHR=1.23 (95% CI 1.15 to 1.31) for local/inhaled GCs.) We did not observe a substantial variation of the HRs according to dose or timing of exposure. Unexposed children born to former GC users had an elevated risk of ADHD (aHR=1.25 (95% CI 1.20 to 1.29)) (table 4). When including BMI and marital status in sub analyses the estimates did not change substantially. The aHR in the sibling analysis was 1.03 (95% CI 0.87 to 1.20) (table 5).

DISCUSSION

Our analyses based on a general population comparison cohort showed an association between prenatal exposure to GCs and ADHD. However, the sibling design did not support a causal association. This observation strongly indicates the presence of unmeasured confounding in the comparison with the general population cohort. Further, this is underlined in the general population comparison cohort by unexposed children born to former GC users had an elevated risk of ADHD.

Previous studies examining the association between stress during pregnancy and the development of ADHD in offspring suggested that endogenous GC plays a role in ADHD development, and some studies reported an association between prenatal exposure to GCs and the development of ADHD.[18 19] However, the children were burdened by a number of comorbidities associated with preterm birth and thus are not comparable with our cohort.

The strengths of our study include its large study population with long and virtually complete (≈95%) follow-up and use of population-based registries. Thus, selection biases were virtually eliminated. As well, the sibling design allowed us to adjust for shared confounders among the siblings. These could be family-related factors, such as genetic and socioeconomic factors, as siblings are thought to grow up in the same environment and share their genetic background. Genetic factors could be a potentially strong confounder in the general population comparison cohort as associations between autoimmune disorders and psychiatric disorders do exist.[29] However, the sibling design also has limitations. First, the analysis reduces the size of the study population, since only sibling pairs discordant for both exposure and outcome are informative and contribute to the effect estimate. These births may represent a selected part of the population. Moreover, the analysis has lower statistical power than the conventional cohort study design. Second, in regards to non-shared confounders, the exposure-discordant sibling pairs are likely to differ more from each other than two randomly selected persons from the same population

Table 3 Maternal and paternal baseline characteristics of 875 996 singleton births in Denmark in 1996–2009, according to maternal use of glucocorticoids (GCs) during pregnancy

	Maternal users of GCs, n (%)	Maternal never users of GCs, n (%)	Maternal former users of GCs, n (%)
All	42 099	656 732	177 165
Age at delivery (years)			
<25	3376 (8.0)	101 264 (15.4)	16 709 (9.4)
25–29	12 690 (30.1)	235 419 (35.9)	56 297 (31.8)
30–34	16 672 (39.6)	223 127 (34.0)	68 364 (38.6)
35–39	7947 (18.9)	83 615 (12.7)	30 505 (17.2)
>40	1414 (3.4)	13 307 (2.0)	5290 (3.0)
Smoking during pregnancy			
No	33 515 (79.6)	502 326 (76.5)	141 429 (79.8)
1–10 cigarettes/day	5223 (12.4)	97 302 (14.8)	21 647 (12.2)
11–20 cigarettes/day	1593 (3.8)	27 333 (4.2)	7393 (4.2)
>20 cigarettes/day	248 (0.6)	3791 (0.6)	1088 (0.6)
Missing	1520 (3.6)	25 980 (4.0)	5608 (3.2)
Maternal psychiatric illness (ADHD not included)	3950 (9.4)	43 284 (6.6)	17 930 (10.1)
Maternal ADHD	39 (0.09)	292 (0.04)	163 (0.09)
Paternal psychiatric illness (ADHD not included)	2370 (5.6)	36 492 (5.6)	11 515 (6.5)
Paternal ADHD	51 (0.12)	588 (0.09)	253 (0.14)
Maternal diseases			
Diabetes	702 (1.7)	6555 (1.0)	3013 (1.7)
Asthma	6674 (15.9)	4820 (0.7)	10 093 (5.7)
COPD	405 (1.0)	986 (0.2)	800 (0.5)
IBD	1128 (2.7)	1993 (0.3)	3073 (1.7)
Other autoimmune diseases	1707 (4.1)	8998 (1.4)	5265 (3.0)
Infections during pregnancy	19 026 (45.2)	210 747 (32.1)	67 977 (38.4)
Maternal BMI			
Low	730 (1.7)	12 374 (1.9)	4244 (2.4)
Normal	11 466 (27.2)	143 008 (21.8)	58 237 (32.9)
Overweight	4174 (9.9)	45 727 (7.0)	21 515 (12.1)
Obese and severely obese	2496 (6.0)	24 588 (3.7)	12 795 (7.2)
No BMI (before 2004)	21 840 (51.9)	411 956 (62.7)	72 933 (41.2)
Missing or very low	1393 (3.3)	19 079 (2.9)	7441 (4.2)
Maternal marital status			
Married	17 941 (42.6)	290 268 (44.2)	69 011 (39)
Not married	13 422 (31.9)	248 501 (37.8)	52 581 (30)
Missing/not registered from 2007 and onwards*	10 736 (25.5)	117 963 (18)	55 573 (31.4)

Low BMI: 15–18.4 kg/m^2; normal BMI: 18.5–24.9 kg/m^2; overweight: 25–29.9 kg/m^2; obese and severely obese: ≥30 kg/m^2. Data on BMI only available starting in 2004.

* N = 129 with missing information before 2007. This number is not further outlined in the table due to legislations.

ADHD, Attention-deficit/hyperactivity disorder; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease.

Table 4 Crude and adjusted HRs (aHRs) and 95% CIs for attention-deficit/hyperactivity disorder (ADHD), comparing prenatally exposed children and unexposed children born to maternal former users, to unexposed children born to maternal never users

	Children classified with ADHD, n	Children not classified with ADHD, n	Crude HR (95% CI)	aHR* (95% CI)
Unexposed	22 936	810 961	1.00 (reference)	1.00 (reference)
Exposed to systemic, inhaled or topical GCs	1263	40 836	1.23 (1.16 to 1.30)	1.26 (1.18 to 1.33)
According to administration and dose				
Exposed systemic GCs	194	5125	1.53 (1.33 to 1.76)	1.43 (1.24 to 1.65)
Exposed systemic GCs low dose (1 prescription)	136	3661	1.47 (1.24 to 1.73)	1.37 (1.15 to 1.62)
Exposed systemic GCs high dose (≥2 prescriptions)	58	1464	1.68 (1.29 to 2.19)	1.60 (1.23 to 2.08)
Exposed local or inhaled GCs	1069	35 711	1.18 (1.11 to 1.26)	1.23 (1.15 to 1.31)
According to trimester of exposure				
First trimester	469	14 146	1.30 (1.17 to 1.44)	1.32 (1.19 to 1.47)
Second or third trimester	794	26 690	1.19 (1.11 to 1.28)	1.23 (1.14 to 1.32)
Former users (unexposed during pregnancy)	4574	172 591	1.27 (1.23 to 1.31)	1.25 (1.20 to 1.29)

*Adjusted for sex of the child, calendar year of birth, birth order, maternal age at birth, maternal smoking status, maternal psychiatric diagnoses, paternal psychiatric diagnoses and maternal diabetes or infectious disease during pregnancy.
GCs, glucocorticoids.

having the same exposure levels. This can potentially increase the effect of the non-shared confounders. Third, misclassification will lead to attenuation of the estimates.[30] Nevertheless, our findings of no association in the sibling design is supported by the results from our former user analysis based on the general population comparison cohort. In addition, we found a slightly higher HR for systemic high dose GC than systemic low dose GC exposure when we compared prenatally exposed children to unexposed children born to never users in our general population comparison cohort. The higher HR found in the high dose category could be explained by confounding by severity of underlying disease, thus, supporting our conclusion.

We were limited by our lack of data on actual maternal use of GCs, as we used prescription redemption as a proxy for this information. This could have led to misclassification of exposure status. For children classified as prenatally exposed, we cannot be sure that women who redeemed a prescription 30 days before or during pregnancy actually used the GCs during pregnancy. Also, GCs redeemed prior to pregnancy could have been stored and later used during pregnancy. Furthermore, the Danish National Prescription Registry has only recorded information since 1994 and some women categorised as never users may have used GCs before that year. Misclassification of exposure would bias our results towards no association.[31]

While the majority of children with ADHD are diagnosed in outpatient clinics at public hospitals, some are diagnosed by private psychiatrists and thus not included in the DNPR. However, use of prescription data allowed us to include most ADHD cases not diagnosed in public outpatient clinics. Still, patients with ADHD diagnosed by private psychiatrists but not prescribed medication would be misclassified. It also must be noted that the primary medication used to treat ADHD is methylphenidate, which only has one other rare indication (narcolepsy). Misclassification of ADHD therefore would be non-differential and bias our results towards no association.

In conclusion, the cause of ADHD is multifaceted and may involve risk factors common to ADHD and indications for GC treatment, as well as environmental and genetic factors. Based on our sibling design, prenatal exposure to GCs does not appear to be a risk factor for developing ADHD.

Table 5 Crude and adjusted HRs (aHRs) and 95% CIs for attention-deficit/hyperactivity disorder (ADHD) in children prenatally exposed to glucocorticoids compared with their unexposed siblings

	Children classified with ADHD, n	Children not classified with ADHD, n	Crude HR (95% CI)	aHR* (95% CI)
Unexposed children	573	705	1.00 (Reference)	1.00 (Reference)
Exposed children	438	530	1.04 (0.90 to 1.19)	1.03 (0.87 to 1.20)

*Adjusted for birth year (1996–2000, 2001–2005, 2006–2009), sex of the child, birth order, maternal smoking status and maternal infectious diseases during pregnancy.

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Contributors AB, KL, HTS and MSO made primary contributions to writing the manuscript. All authors contributed to the study conception and study design. TF performed data collection, statistical analyses and commented on the manuscript. TF had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. All authors contributed to the interpretation of the results, HTS revised the manuscript critically and all approved the final manuscript. HTS is the guarantor for this study.

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Competing interests None declared.

Ethics approval Registry studies do not require ethics approval in Denmark. The study was approved by the Danish Data Protection Agency (Record no 2011-41-6465).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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