



<http://sciencenordic.com/surprisingly-many-women-drug-use-during-pregnancy>

USE OF GLUCOCORTICOIDS DURING PREGNANCY AND RISK OF ADHD IN OFFSPRING

Kristina Laugesen, Anna Byrjalsen, Trine Frøslev, Morten Olsen, Henrik Toft Sørensen

Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Department of Clinical Genetics, Rigshospitalet, Copenhagen, Denmark

No disclosures

Why investigate this association?

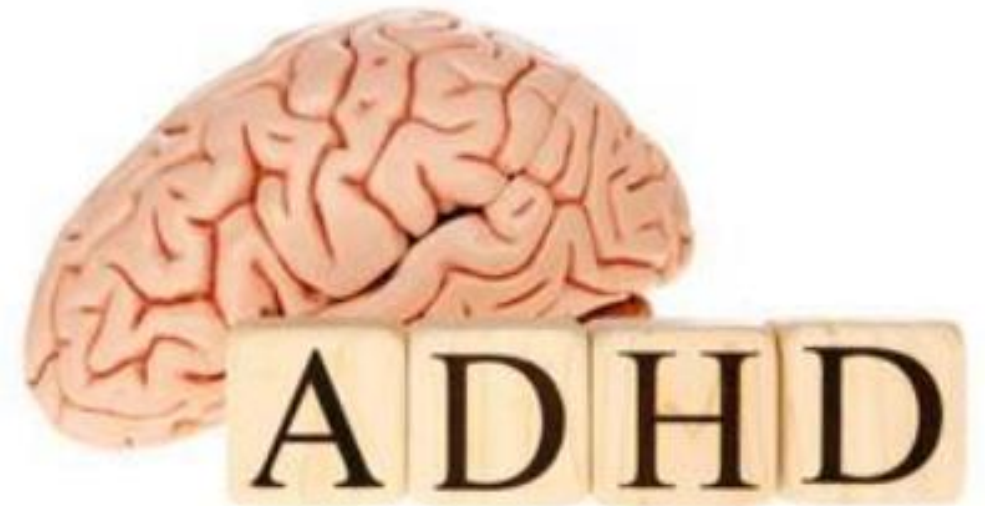


Photo:www.istockphoto.com/dk/photos/fetus?excludenudity=false&sort=mostpopular&mediatype=photography&phrase=fetus

Photo<https://articles.mercola.com/sites/articles/archive/2017/03/02/people-with-adhd-have-altered-brains.aspx>:

ADHD

(Attention/deficit-hyperactivity disorder)

- Inattention, hyperactivity, impulsivity
- Reduced size of subcortical structures in the brain and alteration in neurotransmitter systems



Hoogman M, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. *Lancet Psychiatry*. 2017
Photo: <https://www.kenhub.com/en/start/c/subcortical-structures>

Early life programming

- **Alter development of brain and impact behaviour in animals, including hyperactivity and attention**

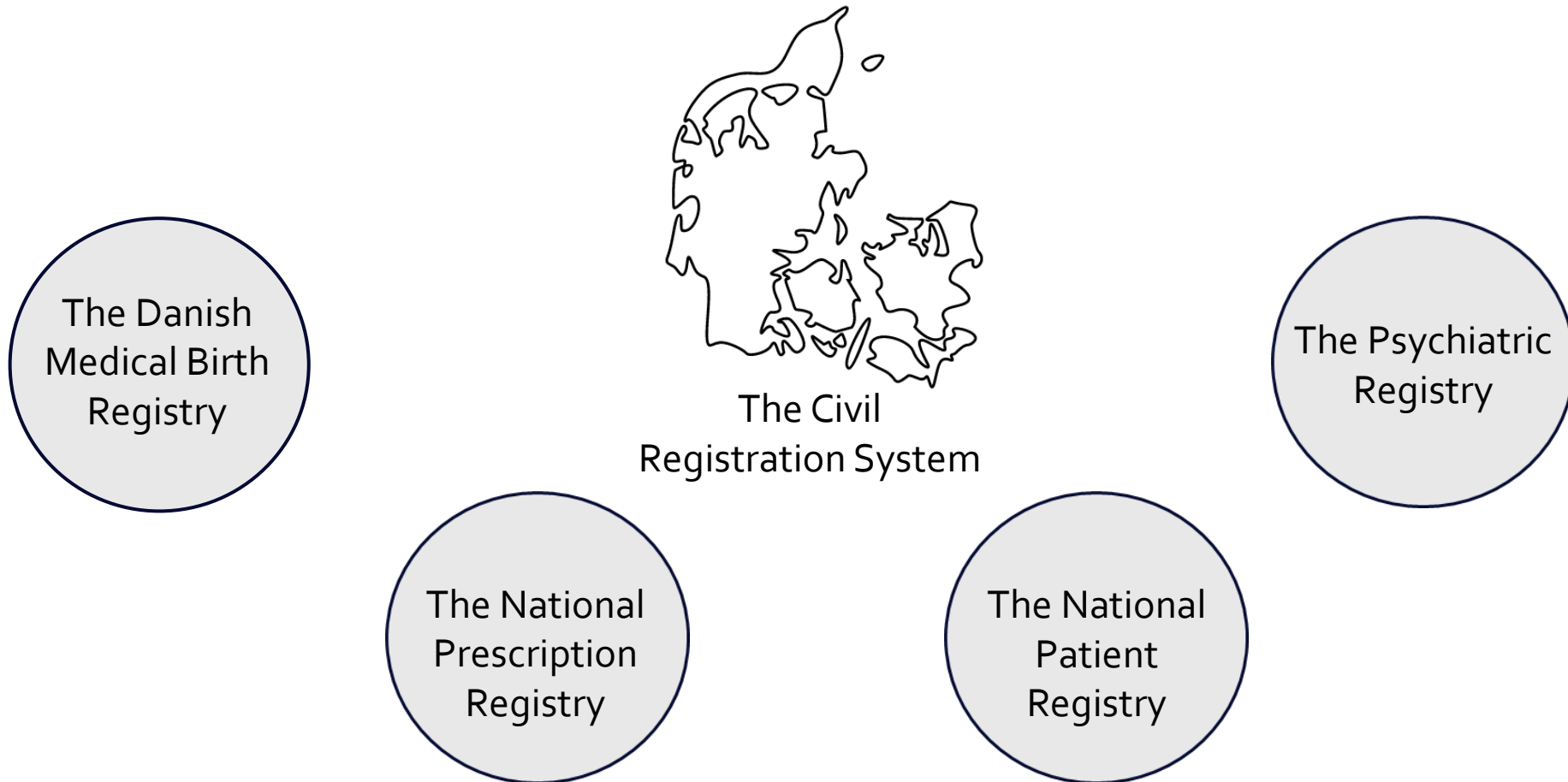
(Welberg L, et al. Prenatal glucocorticoid programming of brain corticosteroid receptors. Neuroscience 2001)



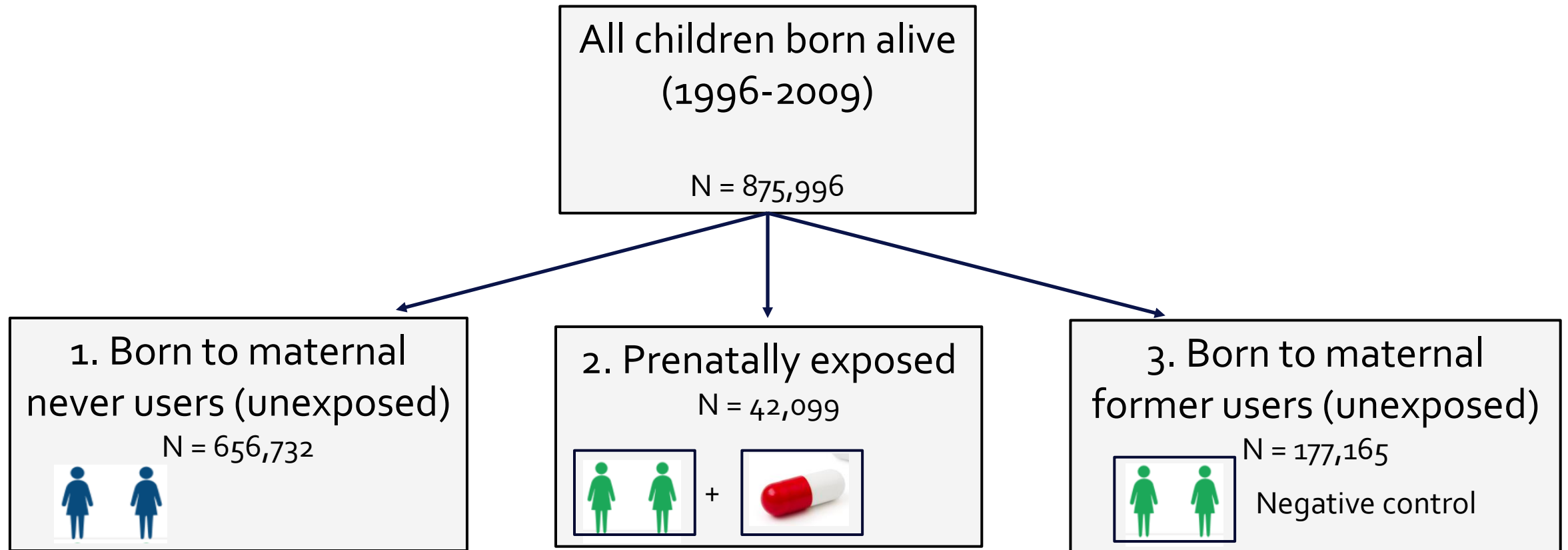
Photo: www.istockphoto.com/dk/photos/fetus?excludenudity=false&sort=mostpopular&mediatype=photography&phrase=fetus

Methods

- Cohort study using national registries-

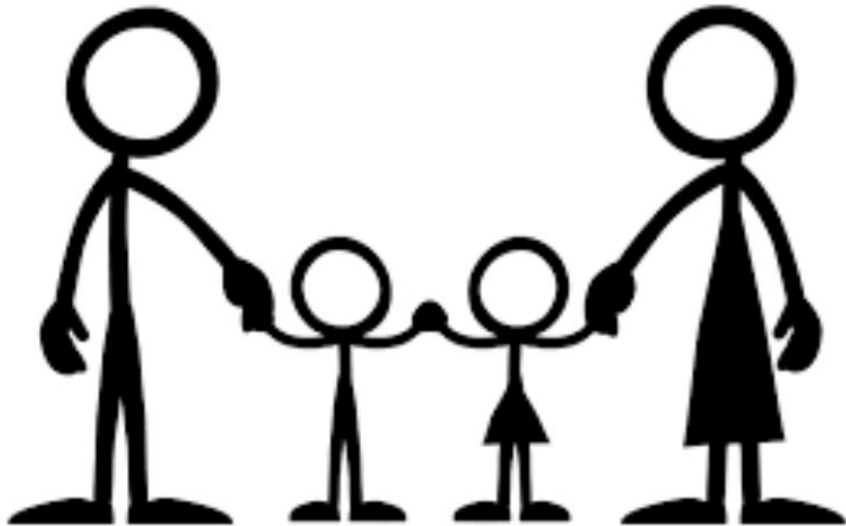


General population cohort



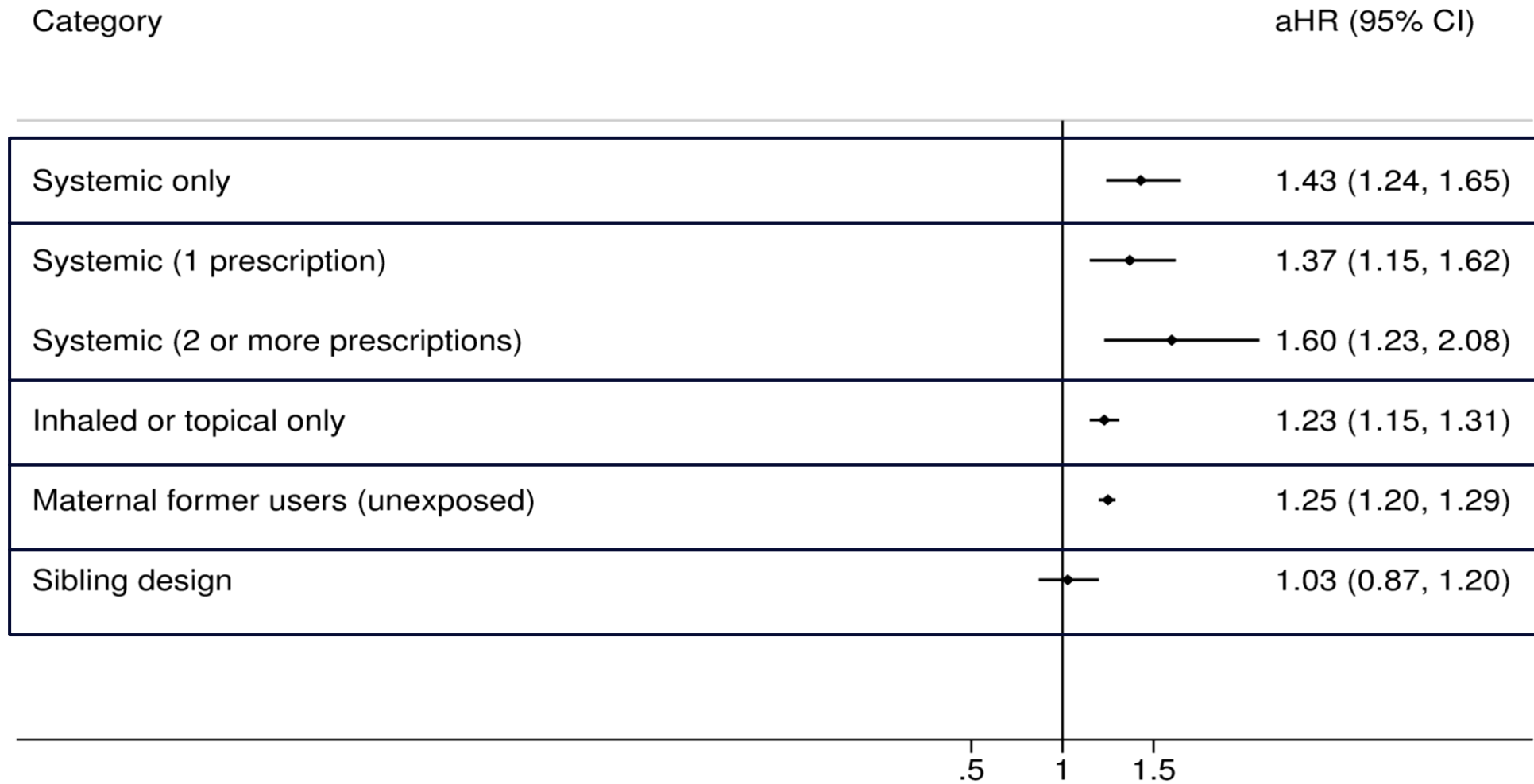
Adjusted for: Birth order, maternal age, smoking status, maternal and paternal psychiatric morbidity, maternal infections during pregnancy and diabetes, calendar year, sex

Sibling design



- **Genetics and socioeconomic status are potentially strong confounders**
- **To control for family-related factors, we compared exposed to unexposed siblings**

Results



Adjusted for: Calendar year, sex, birth order, maternal age, smoking status, maternal and paternal psychiatric morbidity, maternal infections during pregnancy and diabetes

Conclusion

This study does not support a causal association between prenatal exposure to glucocorticoids and ADHD development

THANK YOU

Confounding

- Adjusted for maternal age, birth order, maternal smoking status, maternal and paternal psychiatric disease, maternal diabetes, maternal infection during pregnancy.
- Confounding by indication was partly explored in our former user analysis. However, confounding by disease severity could still be a problem
- Confounding from family-related factors (socioeconomic status and genetics) was assessed in our sibling design

Misclassification

Exposure

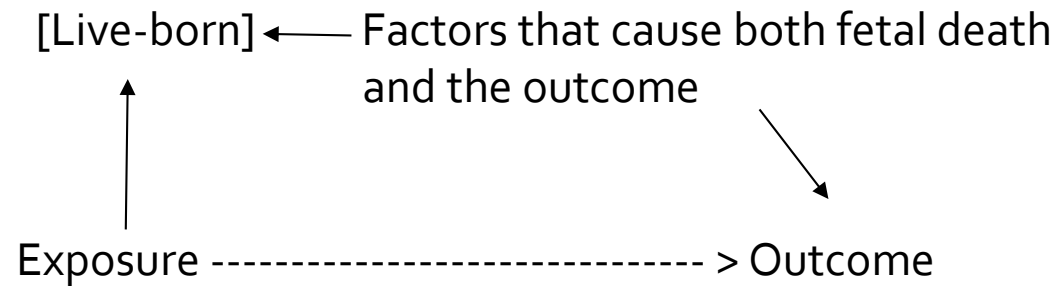
- Used prescription redemption as a proxy for use
- Lack of information on in-hospital medication use

Outcome

- ADHD defined as a diagnosis in the National Patient Registry or Danish Psychiatric Registry or a prescription redemption of medication to treat ADHD

Selection bias

- **General population cohort and virtually complete follow up minimize selection bias**
- **Potential collider bias as we condition on live-births**



Limitations in the sibling design

- Siblings discordant for exposure and ADHD contributed to the estimates (N = 2,246)
- Reduces the size of the study population
- May represent a selected part of the population
- 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 having the same exposure levels
- Misclassification of exposure status more likely? -> Could potentially explain our null association in the sibling design

Exposure distribution

	n (%)
All	42, 099
All systemic treatment	5319 (13)
Systemic, low dose (1 prescription)	3797 (9.0)
Systemic, high dose (≥ 2 prescriptions)	1522 (3.6)
Local	36,780 (87)
First-trimester	11,702 (28)
Second- and third- trimester	27,484 (65)
≤ 30 days prior to pregnancy	2913 (6.7)

Birth characteristics

	Exposed	Unexposed (born to maternal never users)	Unexposed (born to maternal former users)
All	42,099	656,732	177,165
Birth year			
1996-2000	13,416 (32)	273,713 (42)	34,256 (19)
2001-2005	14,647 (35)	223,783 (34)	69,991 (40)
2006-2009	14,036 (33)	159,236 (24)	72,918 (41)
Sex			
Boy	21,875 (52)	336,827 (51)	90,955 (51)
Girl	20,224 (48)	319,905 (49)	86,210 (49)
Birth order			
1	16,326 (39)	297,280 (45)	62,592 (35)
2	16,464 (39)	239,674 (37)	70,810 (40)
≥ 3	9309 (22)	119,778 (18)	43,763 (25)

Birth characteristics

	Exposed	Unexposed (born to maternal never users)	Unexposed (born to maternal former users)
All	42,099	656,732	177,165
Birth weight			
< 2000 g	282 (0.7)	4,692 (0.7)	1222 (0.7)
2000g-2499 g	960 (2.3)	14,405 (2.2)	3848 (2.2)
2500-2999 g	4,132 (9.8)	67,642 (10)	17,425 (9.8)
3000-5500 g	36,244 (86)	560,481 (85)	152,627 (86)
Missing, very low, very high	481 (1.1)	9512 (1.5)	20143 (1.2)
Apgar score			
≤ 7	539 (1.3)	8391 (1.3)	2179 (1.2)
> 7	41,158 (98)	640,191 (98)	173,423 (98)
Missing	402 (1.0)	8150 (1.2)	15623 (0.9)

Birth characteristics

	Exposed	Unexposed (born to maternal never users)	Unexposed (born to maternal former users)
All	42,099	656,732	177,165
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)	569,898 (87)	155,774 (88)
> 41 weeks	3223 (7.7)	50,699 (7.7)	11,550 (6.5)
Missing/ very low	213 (0.5)	4946 (0.8)	731 (0.4)
Mode of delivery			
Vaginal	33,180 (79)	547,163 (83)	140,626 (79)
Caesarean	8919 (21)	109,569 (17)	36,539 (21)

Maternal and paternal characteristics

	Maternal users	Maternal never users	Maternal former users
All	42,099	656,732	177,165
Age at delivery			
<25	3376 (8.0)	101,264 (15)	16,709 (9.4)
25-29	12,690 (30)	235,419 (36)	56,297 (32)
30-34	16,672 (40)	223,127 (34)	68,364 (39)
35-39	7947 (19)	83,615 (13)	30,505 (17)
>40	1414 (3.4)	13,307 (2.0)	5290 (3.0)
Smoking			
No	33,515 (80)	502,326 (77)	141,429 (80)
1-10	5223 (12)	97,302 (15)	21,647 (12)
11-20	1593 (3.8)	27,333 (4.2)	7393 (4.2)
>20	248 (0.6)	3791 (0.6)	1088 (0.6)
Missing	1520 (3.6)	25,980 (4.0)	5608 (3.2)

Maternal and paternal characteristics

	Maternal users	Maternal never users	Maternal former users
All	42,099	656,732	177,165
Maternal psychiatric disease	3950 (9.4)	43,284 (6.6)	17930 (10)
Maternal ADHD	39 (0.09)	22 (0.04)	163 (0.09)
Paternal psychiatric disease	2370 (5.6)	36,492 (5.6)	11,515 (6.5)
Paternal ADHD	51 (0.12)	588 (0.09)	253 (0.14)
Diabetes	702 (1.7)	6555 (1.0)	3013 (1.7)
Asthma	6674 (16)	4820 (0.7)	10,093 (5.7)
COPD	405 (1.0)	986 (0.2)	800 (0.5)
IBD	1128 (2.7)	1993 (0.3)	2073 (1.7)
Other autoimmune disease	1707 (4.1)	8998 (1.4)	5265 (3.0)
Infection during pregnancy	19,026 (45)	210,747 (32)	67,977 (38)

Maternal and paternal characteristics

	Maternal users	Maternal never users	Maternal former users
All	42,099	656,732	177,165
Maternal BMI			
Low	730 (1.7)	12,374 (1.9)	4244 (2.4)
Normal	11,466 (27)	143,008 (22)	58,237 (33)
Overweight	4174 (9.9)	45,727 (7.0)	21,515 (12)
Obese	2496 (6.0)	24,5888 (3.7)	12,795 (7.2)
No BMI (before 2004)	21,840 (52)	411,956 (63)	72,933 (41)
Missing/very low	1393 (3.3)	19,079 (2.9)	7441 (4.2)
Marital status			
Married	17,941 (43)	290,268 (44)	69,011 (39)
Not married	13,422 (32)	248,501 (38)	52,581 (30)
Missing/ not registred from 2007 or onwards	10,736 (26)	117,963 (18)	55573 (31)