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Associations Between Maternal Antenatal Corticosteroid Treatment and Mental and Behavioral Disorders in Children

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Supplemental content

IMPORTANCE Maternal antenatal corticosteroid treatment is standard care to accelerate fetal maturation when birth before 34 weeks is imminent. Recently, expansion of the indications beyond 34 gestational weeks has been debated. However, data about long-term outcomes remain limited, especially among infants who after treatment exposure are born at term.

OBJECTIVE To study if antenatal corticosteroid treatment is associated with mental and behavioral disorders in children born at term (≥37 weeks 0 days' gestation) and preterm (<37 weeks 0 days' gestation) and if unmeasured familial confounding explains these associations.

DESIGN, SETTING, AND PARTICIPANTS Population-based retrospective cohort study using nationwide registries of all singleton live births in Finland surviving until 1 year and a within-sibpair comparison among term siblings. Children were born between January 1, 2006, and December 31, 2017, and followed up until December 31, 2017.

EXPOSURES Maternal antenatal corticosteroid treatment.

MAIN OUTCOMES AND MEASURES Primary outcome was any childhood mental and behavioral disorder diagnosed in public specialized medical care settings.

RESULTS Of the 674 877 singleton children born in Finland during the study period, 670 097 were eligible for analysis. The median length of follow-up was 5.8 (interquartile-range, 3.1-8.7) years. Of the 14 868 (2.22%; 46.1% female) corticosteroid treatment–exposed children, 6730 (45.27%) were born at term and 8138 (54.74%) were born preterm; of the 655 229 (97.78%; 48.9% female) nonexposed children, 634 757 (96.88%) were born at term and 20 472 (3.12%) were born preterm. Among the 241 621 eligible term-born maternal sibpairs nested within this population, 4128 (1.71%) pairs were discordant for treatment exposure. Treatment exposure, compared with nonexposure, was significantly associated with higher risk of any mental and behavioral disorder in the entire cohort of children (12.01% vs 6.45%; absolute difference, 5.56% [95% CI, 5.04%-6.19%]; adjusted hazard ratio [HR], 1.33 [95% CI, 1.26-1.41]), in term-born children (8.89% vs 6.31%; absolute difference, 2.58% [95% CI, 1.92%-3.29%]; HR, 1.47 [95% CI, 1.36-1.69]), and when sibpairs discordant for treatment exposure were compared with sibpairs concordant for nonexposure (6.56% vs 4.17% for within-sibpair differences; absolute difference, 2.40% [95% CI, 1.67%-3.21%]; HR, 1.38 [95% CI, 1.21-1.58]). In preterm-born children, the cumulative incidence rate of any mental and behavioral disorder was also significantly higher for the treatment-exposed compared with the nonexposed children, but the HR was not significant (14.59% vs 10.71%; absolute difference, 3.38% [95% CI, 2.95%-4.87%]; HR, 1.00 [95% CI, 0.92-1.09]).

CONCLUSIONS AND RELEVANCE In this population-based cohort study, exposure to maternal antenatal corticosteroid treatment was significantly associated with mental and behavioral disorders in children. These findings may help inform decisions about maternal antenatal corticosteroid treatment.

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Maternal antenatal corticosteroid treatment to accelerate fetal maturation is standard care before 34 weeks 0 days' gestation when there is a risk of delivery within 7 days.[1-3] In infants born before 34 weeks 0 days, this treatment reduces risks of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, need for mechanical ventilation, systemic infections, and death.[1-4] Because treatment also reduces neonatal morbidity when administered beyond 34 weeks,[5-8] updates to US guidelines in 2016 recommended treatment for pregnant women between 34 weeks 0 days to 36 weeks 6 days who are at risk for preterm delivery within 7 days and who have not received a previous course of antenatal corticosteroids.[1] This recommendation may lead to an increase in the number of treatment-exposed children: in the US, 2.76% of all infants are born before 34 weeks 0 days, while 7.17% are born between 34 weeks 0 days and 36 weeks 6 days.[9]

While the short-term benefits for infant morbidity and mortality are known, the long-term outcomes of treatment exposure remain uncertain. The effects on child neurodevelopment are of particular concern, as corticosteroids cross the placenta and the blood-brain barrier and may harm fetal brain development.[10-13] Moreover, as the prediction of timing of birth is difficult, a large number of treatment-exposed children are not delivered within 7 days and go on to be born at term (≥37 weeks 0 days).[5,14] However, data on neurodevelopmental outcomes of treatment-exposed term-born children remain limited. In addition, to our knowledge, no population-based studies testing associations between treatment exposure and child neurodevelopment or studies testing if unmeasured familial confounding would explain any associations have been performed.

To address these knowledge gaps, this population-based study examined whether treatment exposure was associated with a risk of childhood mental and behavioral disorders, and whether this risk was similar in infants born at term and preterm.

Methods

Study Population

Unique personal identification numbers assigned to all Finnish citizens and permanent residents were used to merge information from different registers kept at the Finnish Institute for Health and Welfare, the statutory statistical authority for social and health care data in Finland, with permission from the registries. The data analysis was conducted as an internal procedure of the Finnish Institute for Health and Welfare, and registered individuals were not contacted. According to Finnish legislation, neither institutional review board approval nor informed consent is required in such studies.

All singleton pregnancies ending in a live birth in Finland between January 1, 2006, and December 31, 2017, were identified from the Medical Birth Register.[15] This register includes information since 1987 on all live births and stillbirths in Finland with gestational age of 22 weeks or more or birth weight 500 g or greater. Infants who had valid maternal and child personal identification codes for register data linkage,

had data on gestational age, and survived until the end of the first year of life were eligible for data analyses. From this population, we also identified all consecutive maternal sibpairs born at term, including sibpairs discordant for maternal antenatal corticosteroid treatment exposure and concordant for treatment exposure and for nonexposure.

Maternal Antenatal Corticosteroid Treatment

Maternal antenatal corticosteroid treatment during pregnancy was recorded in the Medical Birth Register as treatment received or not. This register does not include information on the number or timing of treatments. The treatment recommended by Finnish national guidelines consisted of betamethasone (12 mg) administered twice, 24 hours apart throughout the study period. Until 2009, treatment was recommended up to 34 weeks 0 days (32 weeks 0 days in case of premature rupture of membranes); after 2009, treatment was recommended up to 34 weeks 6 days and, in select cases, later (eg, fetal hydrops; maternal disorder warranting cesarean delivery). Repeated treatments were not recommended before 2009; after 2009, 1 repeat course could be considered when the risk of respiratory distress was high.[16]

The treatment recorded in the Medical Birth Register showed high agreement with treatment recorded in patient case reports in 2 samples nested within our study population: in 1041 and 771 women giving birth to a singleton child in 2006-2010 and 2012-2017 in Finland, the crude agreements were 97.3% and 98.8%, respectively (eTable 1 in the Supplement).

Childhood Mental and Behavioral Disorders

Disorder diagnoses, as primary or secondary diagnoses, came from the Finnish Care Register for Health Care using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) codes on all hospital inpatient (since 1969) and outpatient (since 1998) treatments by physicians in specialized medical care. Validation studies have indicated that the Finnish Care Register for Health Care has high validity for psychiatric diagnoses.[17,18]

Any childhood mental and behavioral disorder was studied as the primary outcome. Secondary outcomes included 10 specific mental and behavioral disorders grouped as described,[19] based on symptomatic similarities (eTable 2 in the Supplement).

Key Points

Question Is maternal antenatal corticosteroid treatment associated with mental and behavioral disorders in children?

Findings In this population-based retrospective cohort study that included 670 097 children, exposure to maternal antenatal corticosteroid treatment, compared with nonexposure, was significantly associated with mental and behavioral disorders in children (hazard ratio, 1.33).

Meaning These findings may help inform decisions about maternal antenatal corticosteroid treatment.

Covariates

Based on previous literature, we identified covariates that were associated with either antenatal corticosteroids, preterm birth, and/or childhood mental and behavioral disorders.[1-4,14,20,21] Of these, the Medical Birth Register provided data on child birth year, sex, 1-minute and 5-minute Apgar score, admission to a neonatal intensive care unit, weight and gestational age at birth, and maternal age at delivery, parity, mode of delivery, smoking during pregnancy, prepregnancy body mass index (calculated from weight and height verified by measurement in the first antenatal clinic visit between 7-10 gestational weeks), premature rupture of membranes (*ICD-10* code O42), gestational diabetes (*ICD-10* code O24), and hypertension in pregnancy (*ICD-10* codes O10, O13-O15). Data on maternal any lifetime mental disorder diagnosis, including disorders due to psychoactive substance use, came from the Finnish Care Register for Health Care (*International Classification of Diseases, Ninth Revision* codes 290-319 in 1987-1995 and *ICD-10* codes F00-F99 in 1996-2017). Race or ethnicity are not recorded in Finnish registers, including the Medical Birth Register, because of European Union legislation (General Data Protection Regulation).

Statistical Analysis

Cox proportional hazards modeling estimated the associations between maternal antenatal corticosteroid treatment exposure and mental and behavioral disorders in the entire cohort, and in term-born and preterm-born children. Kaplan-Meier curves estimated the length of time from birth to the primary outcome, the first diagnosis of any mental and behavioral disorder, and the cumulative probability to remain diagnosis-free at the end of the follow-up. Length of time from birth to the primary outcome was also quantified as the median age (interquartile range) at the first diagnosis. These analyses were repeated for the 10 secondary outcomes. Because of the potential for type I error due to multiple comparisons, findings for the secondary outcomes should be interpreted as exploratory.

We performed sensitivity analyses on the primary outcome by excluding postterm births (≥42 weeks 0 days) from the analyses, as they may increase the risk for mental and behavioral disorders.[22]

In all within-sibpair analyses of term-born maternal siblings, within-sibpair differences of treatment exposure-discordant sibpairs were compared with within-sibpair differences of nonexposure-concordant sibpairs for the primary outcome.[23] The first within-sibpair comparison included all maternal treatment exposure-discordant and nonexposure-concordant sibpairs in consecutive order. To account for reverse temporality, we then compared within-sibpair differences of treatment exposure-discordant sibpairs of which the younger was treatment exposed and the older was nonexposed with within-sibpair differences of nonexposure-concordant sibpairs of which both the younger and the older were nonexposed. To account for the dependence of sibling observations in our analyses, we compared within-sibpair differences of the first treatment exposure-discordant sibpairs with those of the first nonexposure-concordant sibpairs for each mother.

We present the associations in the entire cohort and term-born and preterm-born children as unadjusted and adjusted for all covariates. For within-sibpair comparisons, maternal age, parity, interpregnancy interval, any lifetime mental disorder diagnosis, child gestational age, sex, and any mental or behavioral disorder of the sibling who was not exposed to treatment were used as covariates.

Absolute risk differences of cumulative incidence rates and hazard ratios (HRs) with 95% CIs indicated effect sizes, and *P* < .05 (2-sided) was regarded as statistically significant. Proportional hazards assumptions were assessed on the plots of log(time) vs log (−log[survival]) and Schoenfeld tests and were verified as acceptable. Deviance and Martingale residuals were plotted, and these did not detect any outliers or nonlinearity. We conducted complete case analyses, as missing data in our study population were minimal. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).
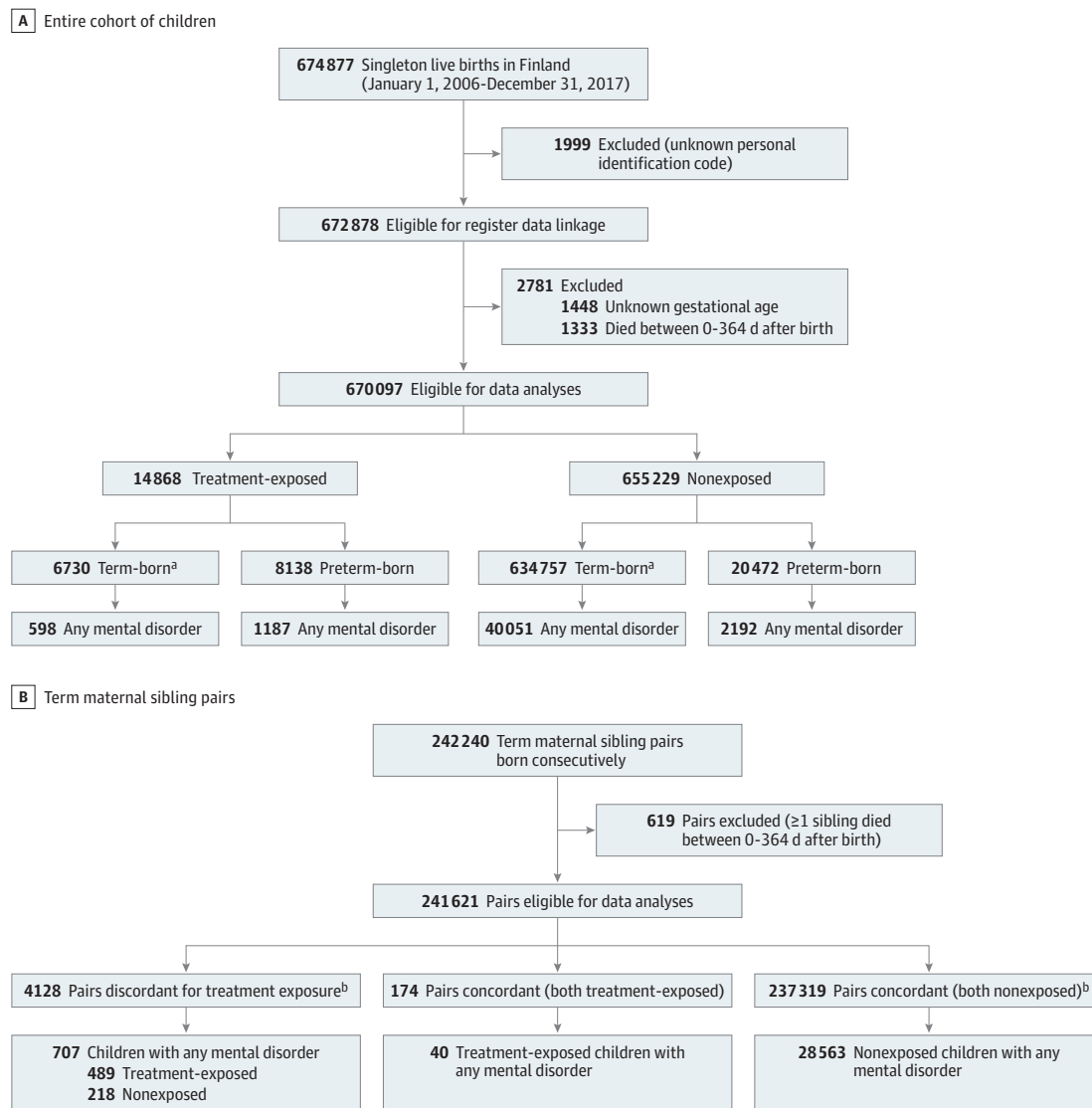
Results

Of 674 877 singleton infants born in Finland in the study period, 670 097 were eligible for analysis (**Figure 1**). Descriptive characteristics of the eligible study population of treatment-exposed and nonexposed children, followed up for a median of 5.8 (interquartile range, 3.1-8.7) years, are reported in the **Table**. Data on these characteristics were missing in 0.1% to 2.0% of the study population (Table). Of the 14 868 (2.22%; 46.1% female) treatment-exposed children, 6730 (45.27%) were born at term and 8138 (54.74%) born preterm; of the 655 229 (97.78%; 48.9% female) nonexposed children, 634 757 (96.88%) were born at term and 20 472 (3.12%) born preterm. Descriptive characteristics of term-born and preterm-born treatment-exposed and nonexposed children are reported in eTable 3 in the Supplement.

Mental and Behavioral Disorders in Treatment-Exposed and Nonexposed Children

The unadjusted cumulative incidence rates and adjusted HRs from multivariable models (**Figure 2**; eTable 4 in the Supplement) for any mental and behavioral disorder were statistically significantly higher for the treatment-exposed compared with the nonexposed children in the entire cohort (12.01% vs 6.45%; absolute difference, 5.56% [95% CI, 5.04%-6.19%]; *P* < .001; HR, 1.33 [95% CI, 1.26-1.41]; *P* < .001) and in term-born children (8.89% vs 6.31%; absolute difference, 2.58% [95% CI, 1.92%-3.29%]; *P* < .001; HR, 1.47 [95% CI, 1.36-1.69]; *P* < .001). In preterm-born children, the cumulative incidence rate of any mental and behavioral disorder was also significantly higher for the treatment-exposed compared with the nonexposed children, but the HR was not significant (14.59% vs 10.71%; absolute difference, 3.38% [95% CI, 2.95%-4.87%]; *P* < .001; HR, 1.00 [95% CI, 0.92-1.09]; *P* = .97) (Figure 2). Treatment-exposed children were 1.4 years younger in median age at any first diagnosis than their nonexposed peers (eTable 5 in the Supplement). At the end of follow-up, the probability to remain diagnosis-free for treatment-exposed children was 92.74% in the entire cohort, 95.71% in

Figure 1. Participant Flow of the Population-Based Sample

A | Entire cohort of children

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                    674877  Singleton live births in Finland
                            (January 1, 2006-December 31, 2017)

                                    1999  Excluded (unknown personal
                                          identification code)

                    672878  Eligible for register data linkage

                                    2781  Excluded
                                    1448  Unknown gestational age
                                    1333  Died between 0-364 d after birth

                    670097  Eligible for data analyses

        14868  Treatment-exposed                      655229  Nonexposed

  6730  Term-borna    8138  Preterm-born     634757  Term-borna    20472  Preterm-born

  598  Any mental     1187  Any mental       40051  Any mental     2192  Any mental
       disorder             disorder                disorder             disorder
```

B | Term maternal sibling pairs

```
                    242240  Term maternal sibling pairs
                            born consecutively

                                    619  Pairs excluded (≥1 sibling died
                                         between 0-364 d after birth)

                    241621  Pairs eligible for data analyses

  4128  Pairs discordant for         174  Pairs concordant (both       237319  Pairs concordant (both
        treatment exposureb               treatment-exposed)                   nonexposed)b

  707  Children with any mental      40  Treatment-exposed children   28563  Nonexposed children with any
       disorder                          with any mental disorder            mental disorder
  489  Treatment-exposed
  218  Nonexposed
```

A, Entire cohort of children, including term (≥37 weeks 0 days' gestation) and preterm-born (<37 weeks 0 days' gestation) children. B, Cohort of term-born consecutive maternal sibling pairs.

[a] Term group included children born postterm at 42 weeks 0 days or more.

[b] In within-sibpair comparisons all maternal treatment exposure–discordant and nonexposure-concordant siblings are analyzed in consecutive order.

term-born children, and 90.28% in preterm-born children; corresponding values for nonexposed children were 97.46%, 97.55%, and 94.89% (**Figure 3**).

When we excluded children born post-term (n = 30 958, 4.6%) from the analyses, the differences between treatment-exposed and nonexposed children for any disorder were significant in the entire cohort (11.96% vs 6.41%; absolute difference, 5.55% [95% CI, 5.03%-6.10%]; *P* < .001; HR, 1.29 [95% CI, 1.22-1.37]; *P* < .001) and in term-born children (8.72% vs 6.27%; absolute difference, 2.46% [95% CI, 1.80%-3.17%]; *P* < .001; HR, 1.44 [95% CI, 1.33-1.57]; *P* < .001).

The unadjusted cumulative incidence rates and HRs from multivariable models testing associations between

maternal antenatal corticosteroid treatment and the secondary outcomes (the 10 specific mental and behavioral disorders) are shown in Figure 2. In the entire cohort and term-born children, treatment exposure, compared with nonexposure, was significantly associated with psychological development disorders; attention-deficit/hyperactivity or conduct disorders; mixed disorders of conduct and emotions, emotional disorders, disorders of social functioning or tic disorders; other behavioral or emotional disorders; and sleep disorders. In preterm-born treatment-exposed children, compared with nonexposed children, the unadjusted cumulative incidence of mild/moderate/unspecified intellectual disability and sleep disorders were

Table. Characteristics of the Study Population According to Maternal Antenatal Corticosteroid Treatment Exposure

| | No. (%)[a] | | |
	Entire cohort (N = 670 097)	Treatment-exposed (n = 14 868)	Nonexposed (n = 655 229)
Children			
Sex			
Boys	342 562 (51.1)	8010 (53.9)	334 552 (51.1)
Girls	327 535 (48.9)	6858 (46.1)	320 677 (48.9)
Timing of birth			
Preterm (<37 wk 0 d)	28 610 (4.3)	8138 (54.7)	20 472 (3.1)
Term (≥37 wk 0 d)	641 487 (95.7)	6730 (45.3)	634 757 (96.9)
Birth weight, mean (SD), g	3529 (527)	2659 (950)	3548 (496)
Apgar score (maximum at 1 and 5 min)[b]			
0-3	1364 (0.2)	192 (1.3)	1172 (0.2)
4-6	9551 (1.4)	1056 (7.1)	8495 (1.3)
7-10	658 226 (98.2)	13 504 (90.8)	644 722 (98.4)
Unknown	956 (0.1)	116 (0.8)	840 (0.1)
Admission to NICU			
No	601 723 (89.8)	7360 (49.5)	594 363 (90.7)
Yes	60 866 (10.2)	7508 (50.5)	60 866 (9.3)
Mothers			
Age at delivery, mean (SD), y	30.4 (5.3)	30.6 (5.8)	30.3 (5.3)
Parity			
0	278 639 (41.6)	6750 (45.4)	271 889 (41.5)
1	227 064 (33.9)	4458 (30.0)	222 606 (34.0)
2	98 070 (14.6)	2081 (14.0)	95 989 (14.6)
3	33 874 (5.1)	796 (5.4)	33 078 (5.0)
≥4	32 344 (4.8)	783 (5.3)	31 561 (4.8)
Unknown	106 (0.02)	0	106 (0.02)
Delivery mode			
Vaginal	563 805 (84.1)	9324 (62.7)	554 481 (84.6)
Cesarean	106 292 (15.9)	5544 (37.3)	100 748 (15.4)
Prepregnancy BMI, mean (SD)[c]	24.4 (4.9)	24.5 (5.4)	24.4 (4.9)
Unknown	13 237 (2.0)	161 (1.1)	13 076 (2.0)
Premature rupture of membranes[d]			
No	650 286 (97.4)	12 689 (83.3)	640 200 (97.3)
Yes	19 811 (3.0)	2538 (16.7)	17 451 (2.7)
Gestational diabetes[d]			
No	593 877 (88.6)	1234 (83.2)	581 503 (88.7)
Yes	76 220 (11.4)	2494 (16.8)	73 726 (11.3)
Hypertension[d]			
No	642 365 (95.9)	13 335 (89.7)	629 030 (96.0)
Yes	27 732 (4.1)	1533 (10.3)	26 199 (4.0)
Any lifetime mental disorder[d]			
No	545 435 (81.6)	10 895 (73.3)	534 540 (81.6)
Yes	124 662 (18.4)	3973 (26.7)	120 689 (18.4)
Smoking during pregnancy			
No	571 447 (85.3)	12 101 (81.4)	559 346 (85.4)
Yes	98 650 (14.7)	2767 (18.6)	95 883 (14.6)

Abbreviations: BMI, body mass index; NICU, neonatal intensive care unit.

[a] Percentages may not total 100% because of rounding.

[b] The Apgar score is calculated at 1 and 5 minutes after birth, uses skin color, pulse rate, reflexes, muscle tone, and respiratory effort to determine medical attention. Scores from 0 to 3 suggest a need for resuscitation, while scores of 7 or more are considered normal.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes: premature rupture of membranes, O42; gestational diabetes, O24; hypertension, O10, O13-O15; any lifetime mental disorder, including organic mental disorders, disorders due to psychoactive substance use, schizophrenia, schizotypal and delusional disorders, mood disorders, neurotic, stress-related and somatoform disorders, behavioral syndromes associated with physiological disturbances and physical factors, disorders of adult personality and behavior, intellectual disabilities, disorders of psychological development, behavioral and emotional disorders with onset usually occurring in childhood and adolescence, F00-F99.
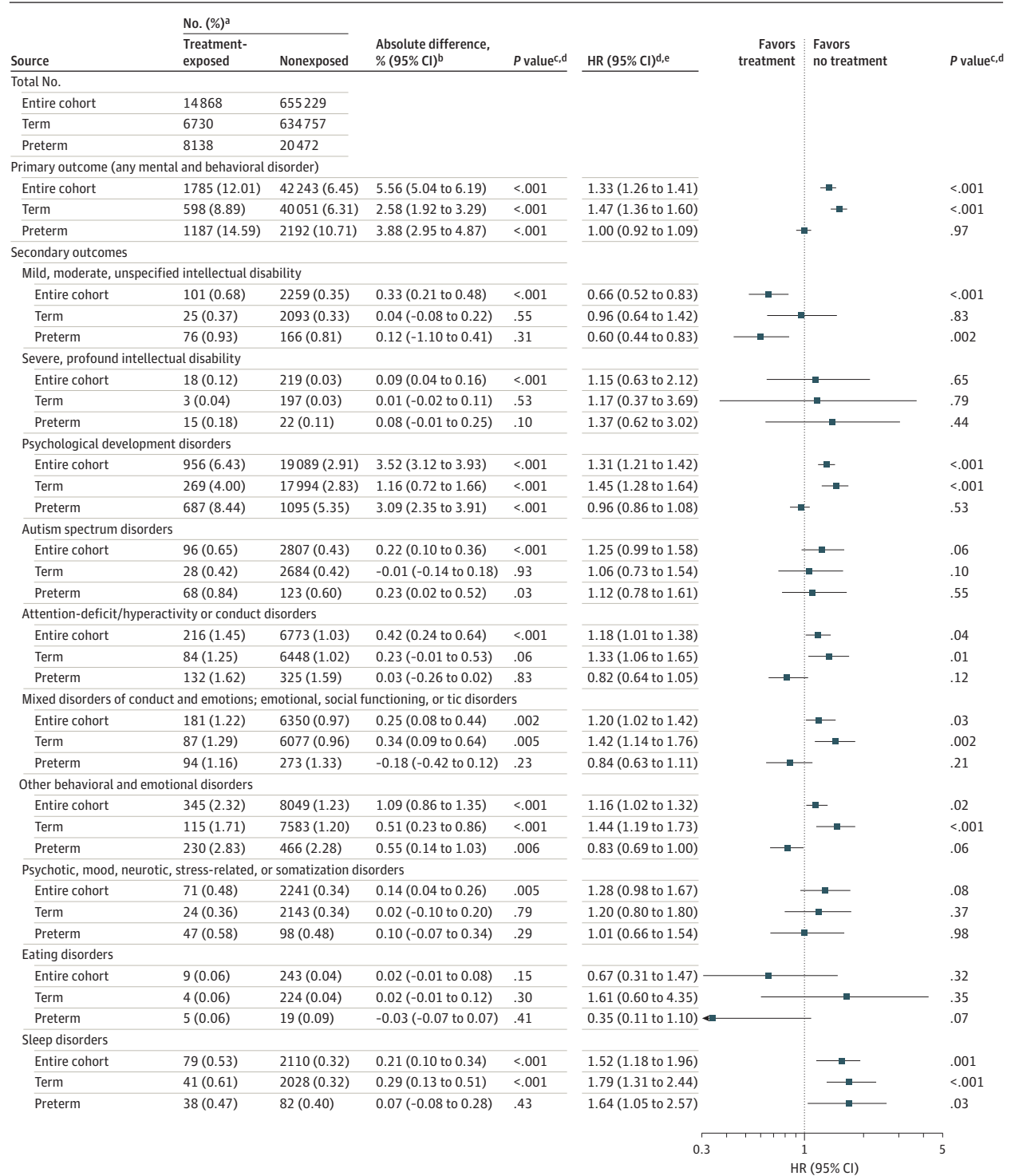
not statistically significantly different, but the adjusted hazard was significantly lower for intellectual disability and higher for sleep disorders.

Within-Sibpair Comparisons

Of 242 240 consecutive sibpairs born at term, 241 621 were eligible for analysis (Figure 1). When within-sibpair

Figure 2. Associations Between Maternal Antenatal Corticosteroid Treatment Exposure and Mental and Behavioral Disorders in Children

Source	No. (%)[a] Treatment-exposed	Nonexposed	Absolute difference, % (95% CI)[b]	P value[c,d]	HR (95% CI)[d,e]	Favors treatment / Favors no treatment	P value[c,d]
Total No.							
Entire cohort	14 868	655 229					
Term	6730	634 757					
Preterm	8138	20 472					
Primary outcome (any mental and behavioral disorder)							
Entire cohort	1785 (12.01)	42 243 (6.45)	5.56 (5.04 to 6.19)	<.001	1.33 (1.26 to 1.41)		<.001
Term	598 (8.89)	40 051 (6.31)	2.58 (1.92 to 3.29)	<.001	1.47 (1.36 to 1.60)		<.001
Preterm	1187 (14.59)	2192 (10.71)	3.88 (2.95 to 4.87)	<.001	1.00 (0.92 to 1.09)		.97
Secondary outcomes							
Mild, moderate, unspecified intellectual disability							
Entire cohort	101 (0.68)	2259 (0.35)	0.33 (0.21 to 0.48)	<.001	0.66 (0.52 to 0.83)		<.001
Term	25 (0.37)	2093 (0.33)	0.04 (−0.08 to 0.22)	.55	0.96 (0.64 to 1.42)		.83
Preterm	76 (0.93)	166 (0.81)	0.12 (−1.10 to 0.41)	.31	0.60 (0.44 to 0.83)		.002
Severe, profound intellectual disability							
Entire cohort	18 (0.12)	219 (0.03)	0.09 (0.04 to 0.16)	<.001	1.15 (0.63 to 2.12)		.65
Term	3 (0.04)	197 (0.03)	0.01 (−0.02 to 0.11)	.53	1.17 (0.37 to 3.69)		.79
Preterm	15 (0.18)	22 (0.11)	0.08 (−0.01 to 0.25)	.10	1.37 (0.62 to 3.02)		.44
Psychological development disorders							
Entire cohort	956 (6.43)	19 089 (2.91)	3.52 (3.12 to 3.93)	<.001	1.31 (1.21 to 1.42)		<.001
Term	269 (4.00)	17 994 (2.83)	1.16 (0.72 to 1.66)	<.001	1.45 (1.28 to 1.64)		<.001
Preterm	687 (8.44)	1095 (5.35)	3.09 (2.35 to 3.91)	<.001	0.96 (0.86 to 1.08)		.53
Autism spectrum disorders							
Entire cohort	96 (0.65)	2807 (0.43)	0.22 (0.10 to 0.36)	<.001	1.25 (0.99 to 1.58)		.06
Term	28 (0.42)	2684 (0.42)	−0.01 (−0.14 to 0.18)	.93	1.06 (0.73 to 1.54)		.10
Preterm	68 (0.84)	123 (0.60)	0.23 (0.02 to 0.52)	.03	1.12 (0.78 to 1.61)		.55
Attention-deficit/hyperactivity or conduct disorders							
Entire cohort	216 (1.45)	6773 (1.03)	0.42 (0.24 to 0.64)	<.001	1.18 (1.01 to 1.38)		.04
Term	84 (1.25)	6448 (1.02)	0.23 (−0.01 to 0.53)	.06	1.33 (1.06 to 1.65)		.01
Preterm	132 (1.62)	325 (1.59)	0.03 (−0.26 to 0.02)	.83	0.82 (0.64 to 1.05)		.12
Mixed disorders of conduct and emotions; emotional, social functioning, or tic disorders							
Entire cohort	181 (1.22)	6350 (0.97)	0.25 (0.08 to 0.44)	.002	1.20 (1.02 to 1.42)		.03
Term	87 (1.29)	6077 (0.96)	0.34 (0.09 to 0.64)	.005	1.42 (1.14 to 1.76)		.002
Preterm	94 (1.16)	273 (1.33)	−0.18 (−0.42 to 0.12)	.23	0.84 (0.63 to 1.11)		.21
Other behavioral and emotional disorders							
Entire cohort	345 (2.32)	8049 (1.23)	1.09 (0.86 to 1.35)	<.001	1.16 (1.02 to 1.32)		.02
Term	115 (1.71)	7583 (1.20)	0.51 (0.23 to 0.86)	<.001	1.44 (1.19 to 1.73)		<.001
Preterm	230 (2.83)	466 (2.28)	0.55 (0.14 to 1.03)	.006	0.83 (0.69 to 1.00)		.06
Psychotic, mood, neurotic, stress-related, or somatization disorders							
Entire cohort	71 (0.48)	2241 (0.34)	0.14 (0.04 to 0.26)	.005	1.28 (0.98 to 1.67)		.08
Term	24 (0.36)	2143 (0.34)	0.02 (−0.10 to 0.20)	.79	1.20 (0.80 to 1.80)		.37
Preterm	47 (0.58)	98 (0.48)	0.10 (−0.07 to 0.34)	.29	1.01 (0.66 to 1.54)		.98
Eating disorders							
Entire cohort	9 (0.06)	243 (0.04)	0.02 (−0.01 to 0.08)	.15	0.67 (0.31 to 1.47)		.32
Term	4 (0.06)	224 (0.04)	0.02 (−0.01 to 0.12)	.30	1.61 (0.60 to 4.35)		.35
Preterm	5 (0.06)	19 (0.09)	−0.03 (−0.07 to 0.07)	.41	0.35 (0.11 to 1.10)		.07
Sleep disorders							
Entire cohort	79 (0.53)	2110 (0.32)	0.21 (0.10 to 0.34)	<.001	1.52 (1.18 to 1.96)		.001
Term	41 (0.61)	2028 (0.32)	0.29 (0.13 to 0.51)	<.001	1.79 (1.31 to 2.44)		<.001
Preterm	38 (0.47)	82 (0.40)	0.07 (−0.08 to 0.28)	.43	1.64 (1.05 to 2.57)		.03

0.3   1   5
HR (95% CI)

[a] Number of cases with diagnosis of mental and behavioral disorders and cumulative incidences during follow-up of the entire cohort of children (N = 670 097) and term-born (n = 641 487) and preterm-born (n = 28 610) children eligible for data analyses. See Figure 1 for eligibility criteria for data analyses and definitions of term and preterm births. See eTable 2 in the Supplement for definitions of mental and behavioral disorders. [b] Absolute differences may differ from the arithmetic difference of group totals because of rounding. [c] From χ^2 statistics. [d] Hazard ratios (HRs), 95% CIs, and P values are from multivariable Cox proportional hazard models adjusting for maternal age at delivery, parity, mode of delivery, maternal smoking during pregnancy, prepregnancy body mass index, premature rupture of membranes (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code O42), gestational diabetes (O24), hypertension in pregnancy (O10, O13-O15), and any lifetime mental disorder diagnosis (F00-F99), child sex, Apgar score (maximum of 1 and 5 minutes), admission to neonatal intensive care unit, weight, and gestational age at birth. [e] Hazard ratios for entire cohort may fall outside the boundaries of HRs for term-born and preterm-born children as a result of differences in the proportion of treatment-exposed and nonexposed children between those born at term and preterm.

Figure 3. Maternal Antenatal Corticosteroid Treatment Exposure and Probability of Any Mental and Behavioral
Disorder in Children

A Entire cohort

HR, 1.33 (95% CI, 1.26-1.41)
Inverse log-normal rank *P* < .001
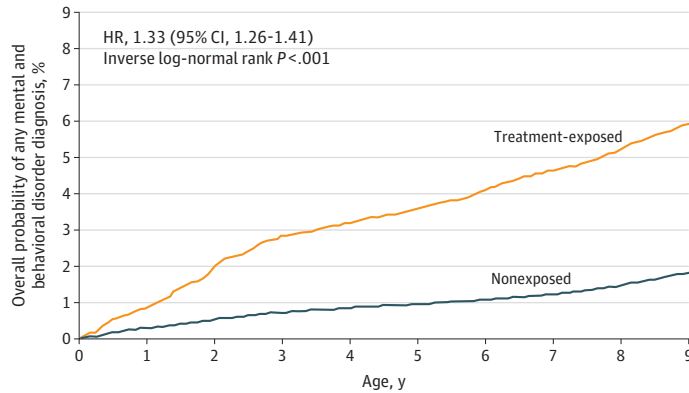
No. at risk										
Treatment-exposed	14 868	14 740	14 576	14 448	14 394	14 336	14 264	14 180	14 095	13 988
Nonexposed	655 299	653 217	651 658	650 355	649 575	648 914	648 115	647 094	645 505	643 216

B Term

HR, 1.47 (95% CI, 1.36-1.60)
Inverse log-normal rank *P* < .001
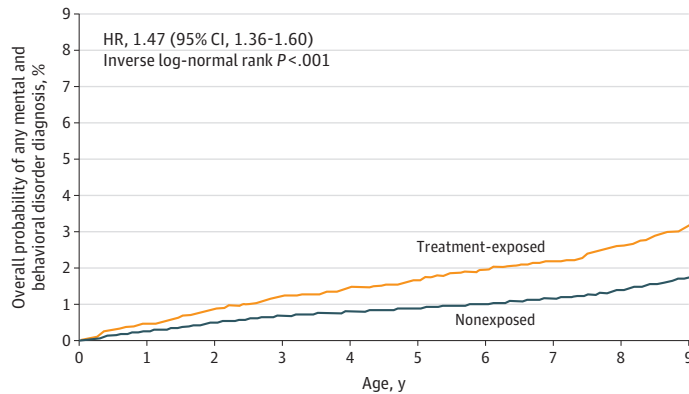
No. at risk										
Treatment-exposed	6730	6698	6670	6646	6631	6616	6598	6583	6553	6516
Nonexposed	634 757	632 907	631 463	630 250	629 525	628 912	628 170	627 232	625 738	623 567

C Preterm

HR, 1.00 (95% CI, 0.92-1.09)
Inverse log-normal rank *P* = .97
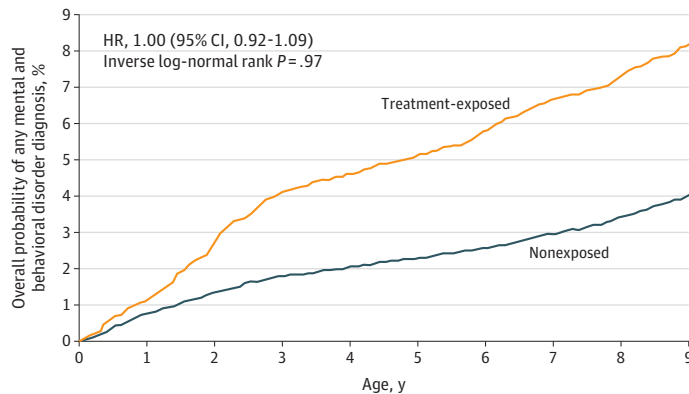
No. at risk										
Treatment-exposed	8138	8042	7906	7802	7763	7720	7666	7597	7542	7472
Nonexposed	20 472	20 310	20 195	20 105	20 050	20 002	19 945	19 862	19 767	19 649

Overall probability of any mental and behavioral disorder diagnosis of treatment-exposed and nonexposed children, from Kaplan-Meier analyses. See Figure 1 for definitions of term and preterm births. See eTable 2 in the Supplement for definition of any mental and behavioral disorder. See eTable 5 in the Supplement for the median age at first diagnosis of any mental and behavioral disorder in the entire cohort of children and in term and preterm children. Hazard ratios (HRs), 95% CIs, and *P* values are from multivariable Cox proportional hazard models adjusting for maternal age at delivery, parity, mode of delivery, maternal smoking during pregnancy, prepregnancy body mass index, premature rupture of membranes (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] code O42), gestational diabetes (O24), hypertension in pregnancy (O10, O13-O15), and any lifetime mental disorder diagnosis (F00-F99), child sex, Apgar score (maximum at 1 and 5 minutes), admission to neonatal intensive care unit, weight, and gestational age at birth. The age of the oldest child at the last date of follow-up was 11.0 years.

differences of all treatment exposure-discordant sibpairs were compared with within-sibpair differences of all

nonexposure-concordant sibpairs, the adjusted HR for any mental and behavioral disorder was significantly higher for

the treatment-exposed sibling of a discordant sibpair (6.56% vs 4.17% for within-sibpair differences; absolute difference, 2.40% [95% CI, 1.67%-3.21%]; *P* < .001; HR, 1.38 [95% CI, 1.21-1.58]; *P* < .001) (eFigure in the Supplement). The HR was also significantly higher for the younger treatment-exposed sibling of a treatment exposure–discordant sibpair, compared with the younger nonexposed sibling of a nonexposure-concordant sibpair (5.74% vs 4.17% for within-sibpair differences; absolute difference, 1.58% [95% CI, 0.66%-2.66%], *P* < .001; HR, 1.53 [95% CI, 1.29-1.81]; *P* < .001) (eFigure in the Supplement). The HR was also significantly higher for the treatment-exposed sibling of the first treatment exposure–discordant sibpair for each mother, compared with the first nonexposure-concordant sibpair for each mother (6.90% vs 4.55% for within-sibpair differences; absolute difference, 2.35% [95% CI, 1.51%-3.30%]; *P* < .001; HR, 1.36 [95% CI, 1.17-1.57]; *P* < .001) (eFigure in the Supplement).

Discussion

In this population-based retrospective cohort study in which 14 868 children were exposed to maternal antenatal corticosteroid treatment, treatment-exposed children had significantly higher cumulative incidence rates and hazards for any mental and behavioral disorder in a follow-up to 11 years compared with nonexposed children. At the time of the first diagnosis, treatment-exposed children were 1.4 years younger in median age than nonexposed children. These associations were seen in children born at term, and they persisted in within-sibpair comparisons among term-born children, suggesting that unmeasured familial confounding did not explain these associations. However, when preterm-born treatment-exposed children were compared with nonexposed children, the cumulative incidence rate for any mental and behavioral disorder was significantly higher, but the HR from the multivariable model was not statistically significant.

Therefore, antenatal corticosteroid treatment may not pose a risk for mental and behavioral disorders independent of complications and illnesses related to preterm birth. Thus, these findings suggest that while maternal antenatal corticosteroid treatment reduces the risk of neonatal morbidity and mortality, this reduction in short-term risk may be counterbalanced by higher long-term risk for mental and behavioral disorders, at least in children born at term after the treatment exposure. The risk associated with treatment exposure appeared to be comparable in magnitude to the risk of key covariates, such as maternal smoking during pregnancy.

In the entire cohort and in term-born children, the higher unadjusted cumulative incidence rates and hazards were attributable to a wide range of disorders. However, these findings should be regarded as exploratory because of the possibility of type I error.

These findings, especially in term-born children, have several implications. First, while maternal antenatal corticosteroid treatment reduces morbidity and mortality in infants born preterm at less than 34 weeks 0 days,[1-4] the findings call for careful evaluation of the 2016 US guidelines update for treatment extension, namely, recommending treatment when there is a risk for imminent late preterm delivery.[1] Treatment in the late preterm window and extension of treatment to women scheduled for cesarean delivery at term before 39 weeks 0 days were recommended in European guidelines between 2016-2019.[24] These extensions were no longer included in the 2019 European guidelines update.[2] Any extension to treatment indications may lead to substantial increases in treatment-exposed children; compared with infants born before 34 weeks 0 days, the rate of late preterm birth is 2.60-fold greater and of early term birth is 9.42-fold greater.[9] Second, while antenatal corticosteroid treatment also reduces risk for respiratory problems beyond 34 weeks,[5-8] these problems are transient and treatable, and no findings, to our knowledge, show longer-term health risks of these newborn adaptation problems.[25] However, antenatal corticosteroid treatment may be accompanied by longer-term risks: treatment-exposed neonates of women at risk for late preterm delivery have been shown to have significantly higher risk of hypoglycemia,[5,7] which can be associated with a child's longer-term risk of developmental delay.[25] This study extends the longer-term risks of antenatal corticosteroid treatment to childhood mental and behavioral disorders. These disorders are not transient, they tend to track into adulthood,[26,27] and they are associated with adverse health, legal, financial, and social problems.[28]

Third, during the study period, the Finnish guidelines recommended maternal corticosteroid treatment when preterm birth was imminent before 34 weeks 6 days (34 weeks 0 days in the pre-2009 guidelines). Yet 45.27% of the treatment-exposed children were born at term. This number of treatment-exposed term-born children differs from the lower numbers reported in randomized clinical trials[5,29] and may reflect that even if the clinical treatment indications do not differ, the eligibility criteria for clinical trials are not necessarily comparable with those applied in everyday clinical practice. Hence, efforts to better predict and prevent preterm delivery are needed.

Limitations

This study has several limitations. First, the observational and sibling-comparison study design limits causal inferences. Second, even though the population-based sample was well characterized, thus allowing multivariable modeling, treatment-exposed and nonexposed pregnancies may have differed in some characteristics that were not measured and residual confounding cannot be ruled out. Third, while the sample was population-based, the homogeneity of the Finnish population precludes generalizations of the findings to different populations.

Fourth, while the sample was large, it still provided limited statistical power to study the outcomes in preterm-born children and preterm-born sibpairs. Fifth, the rates of some of the secondary outcomes were lower than expected, reflecting the relatively young age of the sample and that the disorders were diagnosed in public specialized medical care settings. Sixth, the exact timing of exposure to antenatal corticosteroid treatment and the number and types of treatments given were unknown. One clinical trial has shown that

term-born, but not preterm-born, children exposed to multiple courses of antenatal corticosteroids, compared with peers exposed to a single course, displayed worse neurodevelopmental outcomes at 5 years, which included mother-reported executive function and behavior problems.[29] Another clinical trial of children born in the 1990s reported no differences in neurodevelopment between children exposed to multiple courses of antenatal corticosteroids and those exposed to a single course plus saline placebo.[30]

Seventh, while antenatal corticosteroid treatment recorded in the Medical Birth Register and patient case reports showed greater than 97% agreement, approximately 2% of the data were estimated to be incorrectly classified. However, the majority of incorrect classifications were false-negatives, which would be expected to decrease rather than increase ability to detect significant associations. Eighth, while 1333 live-born children who died in infancy were excluded, no individual-level data on deaths after infancy were available. Based on national vital statistics, 0.2 per 1000 are expected to have died after infancy during the follow-up, making the possible effect of this bias small. Ninth, as the studied disorders were diagnosed in specialized medical care settings, this study is likely to miss primary care diagnoses, and findings cannot be generalized to less severe disorders. One study has shown that treatment exposure was associated with mother-reported developmental delay and higher internalizing and externalizing problems in 2- to 5-year-old term-born and preterm-born children,[31] suggesting that antenatal corticosteroids may be associated with neurodevelopmental adversities across a range of symptom severity. However, a Cochrane meta-analysis has suggested, based on small-scale randomized clinical trials of children born in the 1970s, that treatment-exposed children had reduced rates of developmental delay but that treatment exposure was not associated with school grades, education, or social and emotional functioning.[4]

Conclusions

In this population-based cohort study, exposure to maternal antenatal corticosteroid treatment was significantly associated with mental and behavioral disorders in children. These findings may help inform decisions about maternal antenatal corticosteroid treatment.

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