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Original article

Antenatal corticosteroid treatment and infectious diseases in children and adolescents aged 5–16 years

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ABSTRACT

Objectives: Although maternal antenatal corticosteroid treatment (ACT) improves outcomes of infants born preterm, it is associated with an increased risk of infectious diseases during infancy and early childhood. We studied whether the risk of infectious diseases related to ACT persists into adolescence and whether it differs according to gestational age at birth.

Methods: We conducted a nationwide register-based cohort study of all singleton live births in Finland between 2006 and 2017, with follow-up from age 5 to 16 years (2011–2022). Children were classified as being born either very-to-moderately preterm (<34 weeks), late preterm (34–36 weeks), or term (≥37 weeks). Exposure was receipt or not of maternal ACT. The primary outcomes were differences in the annual number of hospitalizations, inpatient treatment days, and specialized care outpatient visits for any infectious disease. We used generalized linear models to assess associations between ACT exposure and the outcomes and reported mean differences from the generalized linear models with 95% confidence intervals (CIs). A subgroup analysis restricted the analysis to late preterm-born and term-born sibling pairs who received discordant (yes or no) ACT treatment.

Results: The cohort included 669 474 children (all children had outcome data for ages 5–10 years; a subsample of 345 591 children had outcome data for ages 6–11 years). Among 6519 children born very-to-moderately preterm, 22 024 late preterm, and 640 931 term, there were 4329 (66.4%), 3786 (17.2%), and 6716 (1.1%) treated with ACT. Of these, there were 353 and 3322 sibling pairs born late preterm or term analysed in the subgroup analysis for discordant receipt of ACT. Compared with nonexposed children, late preterm and term treatment-exposed children had a higher annual number of hospitalizations (adjusted mean difference [aMD], 0.02; 95% CI, 0.00–0.04; p <0.025; and aMD, 0.01; 95% CI, 0.00–0.02; p <0.009, respectively) and specialized care outpatient visits (aMD, 0.11; 95% CI, 0.04–0.17; p <0.001; and aMD, 0.10; 95% CI, 0.07–0.14; p <0.001, respectively) for any infectious disease, between the ages of 5 and 10 years. Late preterm treatment-exposed children also had a higher annual number of inpatient treatment days (aMD, 0.06; 95% CI, 0.01–0.10; p <0.017). This was not the case for children born very-to-moderately preterm (for hospitalizations: aMD, −0.05; −0.09 to −0.01; p <0.024; for inpatient treatment days: aMD, −0.23; 95% CI, −0.44 to −0.02; p <0.035; for specialized care outpatient visits: aMD, −0.13; 95% CI, −0.25 to −0.00; p <0.050). In the subgroup analysis of discordant sibling pairs, an increased risk for infectious diseases was only observed in the late preterm group. None of the observed risks persisted between ages 11 and 16 years.

Discussion: Our results support caution when considering ACT beyond 34 gestational weeks.

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Introduction

There is wide consensus that maternal antenatal corticosteroid treatment (ACT) improves outcomes of babies born very (<32 weeks) or moderately (33–34 weeks) preterm [1]. ACT reduces the rates of perinatal and neonatal deaths and respiratory distress syndrome (RDS) [1]. Consequently, guidelines are consistent in recommending ACT up to 34 weeks [2–6]. ACT may also reduce the risk of neonatal respiratory problems at 34–36 weeks [7]. However, two recent randomized controlled trials have challenged these benefits [8,9]. Respiratory benefits have also been reported at 37–38 weeks in cases of elective caesarean section [10]. These findings have led to significant treatment expansions [11].

Although the early benefits of ACT in preterm babies are well established, concerns about the potential long-term harms remain. Synthetic glucocorticoids are poorly metabolized by the placental glucocorticoid barrier, exposing the foetus to glucocorticoid excess. Given their well-documented anti-inflammatory and immunosuppressive effects, foetal exposure to ACT may adversely affect foetal immune system development and increase the risk of infectious diseases later in life [12,13]. Two recent nationwide register-based cohort studies have shown a link between ACT exposure and a higher risk of infectious diseases during the first 12 months of life in children born preterm and term [14] and the first 4 years of life in children born late preterm and term [15]. However, whether ACT exposure affects infection risk beyond early childhood remains unclear, which is a critical gap given that immune system development begins *in utero* and peaks between ages 5 and 14 years [16].

We examined whether ACT exposure was associated with the risk of infectious diseases in a nationwide register-based cohort of children followed from the age of 5–16 years. As approximately half of the babies exposed to ACT are born at term [14,15,17,18] and given that the effects of ACT may vary by gestational age at birth [15,17], we report the outcomes in groups stratified by gestational age at birth. Additionally, as the differences between ACT-exposed and nonexposed children may reflect unmeasured familial confounding [15,17], we performed a subgroup analysis restricted to sibling comparisons.

Methods

Study population

We linked data from national registers at the Finnish Institute for Health and Welfare using unique personal identification numbers assigned to all Finnish residents. This nationwide register-based cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

All live-born singletons (≥22 weeks of gestation or ≥500 g birth weight) in Finland (January 2006 to December 2017) with data on gestational age and identification numbers were included from the Finnish Medical Birth Register (MBR). We also identified consecutive maternal cosibling pairs born late preterm or term, including those with differing ACT exposure. The small number of sibling pairs born very-to-moderately preterm did not allow meaningful comparisons. Follow-up occurred from ages 5 to 16 years (January 2011 to December 2022).

The study was approved by the Finnish Institute for Health and Welfare (THL/5640/6.02.00/2023). Per Finnish law, ethics committee review and individual consent were not required as no direct contact with registered individuals occurred.

Exposure to maternal ACT

The MBR includes data on whether the mother has received ACT (yes/no) [19]. Data are not available on the number of treatments, timing, or the specific corticosteroid used. The Finnish national guidelines [20,21] recommended intramuscular betamethasone 12 mg administered twice, 24 hours apart, throughout the study period. Until 2009, treatment was recommended until $34^{0/7}$ weeks ($32^{0/7}$ weeks in case of premature rupture of membranes) [20]. After 2009, treatment was recommended until $34^{6/7}$ weeks and, in select cases, later [21]. Specific conditions mentioned were foetal hydrops and maternal disorder warranting caesarean section [21]. Repeated treatments were not recommended before 2009 [20]. After 2009, one repeat course could be considered when the risk of respiratory distress was high [21]. There is a high concordance (97%) between the MBR and hospital patient records in identifying whether or not ACT was received [17].

Infectious diseases in children and adolescents

We obtained infectious disease diagnoses from the Care Register for Health Care (HILMO), covering all inpatient hospitalizations (since 1969) and specialized care outpatient treatments (since 1998). We defined infectious diseases using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) and the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures codes, listed in Table S1. The accuracy of diagnoses and the quality of data in these registers have been reported to be good [22].

Primary outcomes included the annual number of hospitalizations, inpatient treatment days, and outpatient visits in specialized infectious disease care for any infectious diseases identified using ICD-10 and NOMESCO Classification of Surgical Procedures codes at ages 5–10 and 11–16 years. These same outcomes with respiratory, gastrointestinal, urinary tract, and severe infections were studied as secondary outcomes.

Covariates

We identified covariates linked to ACT, preterm birth, and infectious diseases [14,15] from the MBR or HILMO (Table 1). Mother-related covariates included age, parity, delivery mode, smoking, reported body mass index (control measured at 7–10 weeks), premature rupture of membranes, gestational diabetes, chronic hypertension, gestational hypertension, preeclampsia, eclampsia, chorioamnionitis, lifetime asthma, and mental disorders. Child-related covariates included birth year, sex, Apgar scores, neonatal intensive care unit admission, birth weight, and gestational age. Race and ethnicity were not recorded in Finnish registers.

Statistical analysis

The main analysis

We used generalized linear models (GLMs) to assess associations between ACT exposure and annual number of hospitalizations, inpatient treatment days, and specialized care outpatient visits for any infectious disease at ages 5–10 and 11–16 years, analysing very-to-moderately preterm, late preterm, and term groups separately.

The benchmarking analysis

To address potential confounding by indication, we performed a benchmarking analysis [15,18] and studied the effect of ACT on the outcomes of neonatal RDS (ICD-10 code: P22.0) and transient tachypnea of the newborn (ICD-10 code: P22.1) using logistic regression.

The subgroup analysis

The subgroup analysis examined infectious diseases according to the sites of infection. Moreover, to address unmeasured familial confounding, we conducted sibling comparisons (Fig. S1) using a GLM with sibling pairs as separate strata. We first compared differences in the primary outcome within one exposure-discordant cosibling pair (younger or older treatment-exposed vs. younger or older nonexposed). Because of secular trends in seeking health care [15,17,18], and because younger siblings have a higher risk of infectious diseases [23], we also compared younger siblings of two cosibling pairs (in one pair, the younger sibling

Table 1
Characteristics of the children born very-to-moderately preterm (<34 gestational weeks), late preterm (34–36 gestational weeks), and term (≥37 gestational weeks) according to maternal antenatal corticosteroid treatment-exposure.

Characteristics	Preterm					
	Very-to-moderately (*n* = 6519)		Late (*n* = 22 024)		Term (*n* = 640 931)	
	Treatment-exposed (*n* = 4329)[a]	Nonexposed (*n* = 2190)[a]	Treatment-exposed (*n* = 3786)[a]	Nonexposed (*n* = 18 238)[a]	Treatment-exposed (*n* = 6717)[a]	Nonexposed (*n* = 634 214)[a]
Children						
Sex, n (%)						
Boy	2397 (55.4)	1232 (56.3)	2083 (55.9)	10 285 (56.3)	3505 (52.3)	322 714 (50.9)
Girl	1932 (44.6)	957 (43.7)	1703 (45.0)	7953 (43.6)	3212 (47.8)	311 500 (49.1)
Gestational age at birth (wk), mean (SD)	30.8 (2.6)	31.7 (2.7)	35.2 (0.9)	36.0 (0.7)	39.3 (1.3)	40.1 (1.2)
Birth weight (g), mean (SD)	1556.7 (561.7)	1771.2 (542.7)	2580.9 (585.3)	2767.4 (515.0)	3409.5 (509.7)	3577.0 (464.8)
Small-for-gestational-age at birth, n (%)[b]	695 (16.1)	257 (11.7)	512 (13.5)	1546 (8.5)	390 (5.8)	17 818 (2.8)
Apgar score (maximum of 1 and 5 min)[c]						
0–3	156 (3.6)	86 (3.9)	22 (0.6)	97 (0.5)	12 (0.2)	979 (0.2)
4–6	775 (17.9)	372 (17.0)	169 (4.5)	601 (3.3)	103 (1.5)	7497 (1.2)
7–10	3346 (77.3)	1706 (77.9)	3548 (93.7)	17 473 (95.8)	6587 (98.1)	624 993 (98.5)
Unknown	52 (1.2)	26 (1.2)	47 (1.2)	67 (0.4)	15 (0.2)	745 (0.1)
Admission to neonatal intensive care unit, n (%)						
No	238 (5.5)	139 (6.3)	1234 (32.6)	10 239 (56.1)	5876 (87.5)	583 515 (92.0)
Yes	4091 (94.5)	2051 (93.7)	2552 (67.4)	7999 (43.9)	841 (12.5)	50 699 (8.0)
Neonatal sepsis, n (%)[d]						
No	4081 (94.3)	2042 (93.2)	3667 (96.9)	17 697 (97.0)	6600 (98.3)	623 305 (98.3)
Yes	248 (5.7)	148 (6.8)	119 (3.1)	541 (3.0)	117 (1.7)	10 909 (1.7)
Major congenital anomaly, n (%)						
No	3749 (86.6)	2532 (86.5)	3352 (88.5)	16 798 (92.1)	6297 (93.7)	607 142 (95.7)
Yes	580 (13.4)	253 (11.6)	434 (11.5)	1440 (7.9)	420 (6.3)	27 072 (4.3)
Mothers						
Age at delivery (y), mean (SD)	31.0 (5.8)	30.4 (5.9)	31.0 (5.6)	30.4 (5.6)	30.1 (5.7)	30.3 (5.3)
Parity, n (%)						
0	2248 (51.9)	1063 (48.5)	1732 (45.7)	9080 (49.8)	2755 (41.0)	261 477 (41.2)
1	1099 (25.4)	598 (27.3)	1067 (28.2)	5037 (27.6)	2278 (33.9)	216 803 (34.2)
2	530 (12.2)	284 (13.0)	544 (14.4)	2232 (12.2)	1003 (14.9)	93 401 (14.7)
3	211 (4.9)	132 (6.0)	214 (5.7)	952 (5.2)	369 (5.5)	31 957 (5.0)
≥4	241 (5.6)	113 (5.2)	229 (6.0)	934 (5.1)	312 (4.6)	30 474 (4.8)
Unknown	0	0	0	3 (0.0)	0	102 (0.0)
Delivery mode, n (%)						
Vaginal	1723 (39.8)	943 (43.1)	1913 (50.5)	12 014 (65.9)	4878 (72.6)	483 179 (76.2)
Instrumental	62 (1.4)	38 (1.7)	147 (3.9)	1160 (6.4)	584 (8.7)	56 676 (8.9)
Caesarean	2544 (58.8)	1209 (55.2)	1726 (45.6)	5064 (27.8)	1255 (18.7)	94 358 (14.9)
Prepregnancy body mass index (kg/m^2), mean (SD)	25.1 (5.7)	24.8 (5.3)	24.6 (5.74)	24.6 (5.2)	24.1 (5.3)	24.4 (4.9)
Unknown	78 (1.8)	139 (6.3)	31 (0.8)	503 (2.8)	51 (0.8)	12 386 (2.0)
Premature rupture of membranes, n (%)[d]						
No	3038 (70.2)	1786 (81.6)	2862 (75.6)	15 222 (83.5)	6489 (96.6)	620 291 (97.8)
Yes	1291 (29.8)	404 (18.4)	942 (24.4)	3016 (16.5)	228 (3.4)	13 923 (2.2)
Gestational diabetes, n (%)[d]						
No	3891 (89.9)	1991 (90.9)	3285 (86.8)	15 975 (87.6)	5773 (85.9)	566 816 (89.4)
Yes	482 (10.1)	199 (9.1)	501 (13.2)	2263 (12.4)	944 (14.1)	67 398 (10.6)
Chronic hypertension, n (%)[d]						
No	4170 (96.3)	2014 (96.1)	3664 (96.8)	17 910 (98.2)	6607 (98.4)	634 214 (99.2)
Yes	159 (3.9.1)	86 (3.9)	122 (3.2)	328 (1.8)	10 (1.6)	4892 (0.1)
Gestational hypertension n (%)[d]						
No	4107 (94.8)	2098 (95.8)	3561 (94.1)	17 362 (95.1)	6440 (95.9)	616 378 (97.2)
Yes	222 (5.1)	92 (4.2)	225 (5.9)	676 (4.8)	277 (4.1)	17 836 (2.8)
Preeclampsia or eclampsia n (%)[d]						
No	3379 (78.1)	1845 (84.3)	3304 (87.3)	16 610 (91.1)	6535 (97.3)	624 647 (98.5)
Yes	859 (22.0)	345 (15.8)	482 (12.7)	1628 (8.9)	182 (2.7)	9567 (1.5)
Chorioamnionitis, n (%)[d]						
No	3965 (91.6)	2102 (96.0)	3720 (98.3)	18 079 (99.1)	6657 (99.1)	628 658 (99.1)
Yes	364 (8.2)	88 (4.0)	66 (1.7)	159 (0.9)	60 (0.9)	5556 (0.9)
Asthma, n (%)[d]						
No	4001 (92.4)	2015 (92.0)	3448 (91.1)	6940 (92.9)	6149 (91.5)	594 518 (93.7)
Yes	328 (7.6)	175 (8.0)	338 (8.9)	1298 (7.1)	568 (8.5)	39 696 (6.3)
Any mental or behavioural disorder, n (%)[d]						
No	3089 (71.4)	1599 (73.0)	2644 (69.8)	13 526 (74.2)	4569 (68.0)	633 868 (78.4)
Yes	1240 (28.6)	591 (27.0)	1142 (30.2)	4712 (25.8)	2148 (32.3)	136 649 (21.5)
Smoking during pregnancy, n (%)						
No	3346 (77.3)	1583 (72.3)	3018 (79.7)	14 455 (79.3)	5289 (78.7)	525 767 (82.9)
Yes	795 (18.4)	432 (19.7)	685 (18.1)	3134 (17.2)	1315 (19.6)	92 967 (14.7)
Unknown	188 (4.3)	175 (8.0)	83 (2.2)	649 (3.6)	113 (1.7)	15 480 (2.4)

[a] Percentages may not total up to 100% due to rounding.
[b] Small-for-gestational-age at birth is defined as birth weight for gestational age and sex ≤ −2 standard deviations according to Finnish growth charts.
[c] The Apgar score is calculated at 1 and 5 minutes after birth uses skin colour, pulse rate, reflexes, muscle tone, and respiratory effort to determine medical attention: scores 0–3 suggest a need for resuscitation, whereas scores of ≥7 are considered normal.
[d] International Statistical Classification of Diseases and Related Health Problems, Tenth revision codes: Neonatal sepsis P36; Premature rupture of membranes O42; Gestational diabetes O24.4; Chronic hypertension O10; Gestational hypertension O13; Preeclampsia O14; Eclampsia O15; Chorioamnionitis O41.1, O85, and O86; Asthma J45-J4; Any mental or behavioural disorder F00–F99.

was treatment-exposed and older nonexposed, and in the other pair, both the younger and older were nonexposed). Analyses used first siblings per mother to control for dependence.

We report mean differences from the GLMs and ORs from the logistic regression with 95% confidence intervals (CIs). Two-sided p values <0.05 were considered significant. Complete case analyses were performed as missing data were minimal, except for smoking (missing, 1.7–8.0%), where missing values were treated as a separate category. Analyses were conducted using SAS 9.4 (SAS Institute, Inc).

Results

The cohort comprised 669 474 singleton children born alive, of whom 14 814 (2.2%) were treatment-exposed (Table 1). Of the 6519 (0.9%) born very-to-moderately preterm, 4329 (66.4%) were treatment-exposed, and of the 22 024 (3.3%) born late preterm, 3786 (17.2%) were treatment-exposed. Among the 640 931 (95.7%) born at term, this number was 6716 (1.1%). Of all the 14 814 treatment-exposed children, 4329 (29.2%) were born very-to-moderately preterm, 3786 (25.6%) late preterm, and 6717 (45.3%) at term. During the study period between January 2006 to December 2017 and December 2022, all children in the cohort had outcome data for ages 5–10 years. For ages 11–16 years, these data were available for children born from January 2006 to December 2011 ($n = 345\,591$). Cumulative incidence rates of the annual number of hospitalizations and specialized care outpatient visits for infectious diseases at ages 5–10 and 11–16 years, across very-to-moderate-, late-, and term-born treatment-exposed and nonexposed groups are shown in Tables S2 and S3.

The main analysis

Compared with nonexposed children, very-to-moderately preterm treatment-exposed children had a lower annual number of hospitalizations (adjusted mean difference [aMD], −0.05; 95% CI, −0.09 to −0.01; p <0.024), inpatient treatment days (aMD, −0.23; 95% CI, −0.44 to −0.02; p <0.035), and specialized care outpatient visits (aMD, −0.13; 95% CI, −0.25 to −0.00; p <0.050) for any infectious disease between the ages of 5 and 10 years (Fig. 1(a)–(c)). Compared with nonexposed children, late preterm and term treatment-exposed children had a higher annual number of hospitalization (aMD, 0.02; 95% CI, 0.00–0.04; p <0.025; and aMD, 0.01; 95% CI, 0.00–0.02; p <0.009, respectively) and specialized care outpatient visits (aMD, 0.11; 95% CI, 0.04–0.17; p <0.001; and aMD, 0.10; 95% CI, 0.07–0.14; p <0.001, respectively) for any infectious disease between the ages of 5 and 10 years (Fig. 1(a) and (c)). Late preterm treatment-exposed children also had a higher annual number of inpatient treatment days for any infectious disease during this age period (aMD, 0.06; 95% CI, 0.01–0.10; p <0.017) (Fig. 1(b)). None of the observed risks persisted between ages 11 and 16 years (Figs. 1(a)–(c)). Figures 2–4 display these associations in annual age groups from 5 to 10 years and in a combined group for ages 11–16 years.

The benchmarking analysis

In the analysis adjusted for covariates, compared with nonexposed children, very-to-moderately and late preterm treatment-exposed children had a lower risk of RDS, whereas the risk of transient tachypnea of the newborn was higher in the children born very-to-moderately preterm (Table S4).

The subgroup analysis

Because ACT was associated with the risk of any infectious disease only at ages 5–10 years, we present the subgroup analysis for this age group. Associations with sites of infection are shown in Table S5. Compared with nonexposed children, very-to-moderately preterm treatment-exposed children had a lower annual number of inpatient treatment days and specialized care outpatient visit for respiratory infections and a lower annual number of hospitalizations and specialized care outpatient visits for severe infections. Compared with nonexposed children, late preterm and term treatment-exposed children had a higher annual number of specialized care outpatient visits for respiratory, gastrointestinal, and urinary tract infections. Late preterm treatment-exposed children also had a higher annual number of hospitalizations and inpatient treatment days for gastrointestinal infections.

In the analysis of sibling pairs who received discordant ACT treatment, the late preterm treatment-exposed sibling had a higher annual number of hospitalizations, inpatient treatment days, and specialized care outpatient visits for any infectious disease compared with nonexposed cosibling (Fig. S1, Table S6). Annual inpatient treatment days were also higher for younger late preterm siblings discordant for treatment-exposure compared with younger late preterm siblings concordant for nonexposure, and annual specialized care outpatient visits were higher for younger term siblings discordant for treatment-exposure compared with younger term siblings concordant for nonexposure (Fig. S1, Table S6).

Discussion

This nationwide cohort study of 669 474 children found that among those born late preterm or term, ACT exposure was associated with a significantly higher risk of infectious diseases at ages 5–10 years compared with nonexposed children of the same gestational age. Conversely, among the children born very-to-moderately preterm, ACT exposure was associated with a significantly lower risk of infectious diseases at ages 5–10 years compared with nonexposed children of the same gestational age. As expected, the overall risk of infectious diseases was highest among those born very-to-moderately preterm [24]. However, across all treatment-exposed children, significant differences in infectious disease risk did not persist between ages 11 and 16 years. The significant associations remained consistent in models adjusted for covariates, and the findings in the late preterm-born children were also confirmed in sibling comparisons.

The higher risk for infectious diseases at ages 5–10 years associated with ACT exposure in late preterm and term children was reflected in a higher annual number of hospitalizations and/or longer hospital stays and more annual specialized care outpatient visits, mainly for respiratory, gastrointestinal, and urinary tract infections. However, in terms of effect size, these differences were small. Treatment-exposed very-to-moderately preterm-born children had a lower annual number of hospitalizations and specialized care outpatient visits, and shorter hospital stays, primarily for respiratory and severe infections.

Our findings in term-born treatment-exposed children align with previous studies from Taiwan and Finland, which showed increased risks of respiratory, gastrointestinal, urinary tract, and severe infections up to age 4 years in ACT-exposed children [14,15]. Our findings in the late preterm-born treatment-exposed children are also in agreement with the previous Finnish study [15].

Our findings in very-to-moderately preterm-born treatment-exposed children differ from the Taiwanese study, which reported increased severe infection risk in those born preterm but did not separate preterm births into subgroups, of which more than 70% were late preterm [14]. Our findings partially align with the Finnish study, which found no overall difference up to 4 years of age but noted a lower infection risk at ages 3–4 years in this group [15]. This suggests that the benefits of ACT in reducing RDS may translate to fewer respiratory and severe infections in later childhood.

The effects of ACT were not limited to specific sites of infection, consistent with the pleiotropic effects of ACT shown in early childhood [15]. Synthetic glucocorticoids have a high affinity, 25 times greater than endogenous cortisol, for glucocorticoid receptors [25,26], which are ubiquitously expressed in human tissues and organs. They therefore

Any infectious disease at age	Treatment-exposed M (SD)	Non-exposed M (SD)	Unadjusted Mean difference	Unadjusted 95% CI	Unadjusted P	Adjusted Mean differen	Adjusted 95% CI	Adjusted P
A. Annual number of hospitalizations								
Very-to-moderately preterm								
5-10 years	0.124 (0.642)	0.180 (0.975)	-0.056	-0.096, -0.017	.006	-0.050	-0.093, -0.006	.024
11-16 years	0.015 (0.133)	0.031 (0.272)	-0.016	-0.030, -0.003	.021	-0.011	-0.026, 0.004	.143
Late preterm								
5-10 years	0.104 (0.555)	0.094 (0.460)	0.010	-0.007, 0.027	.237	0.020	0.003, 0.038	.025
11-16 years	0.022 (0.174)	0.021 (0.213)	0.001	-0.011, 0.013	.888	0.006	-0.006, 0.019	.332
Term								
5-10 years	0.078 (0.412)	0.070 (0.379)	0.008	-0.001, 0.018	.069	0.012	0.003, 0.021	.009
11-16 years	0.012 (0.122)	0.015 (0.178)	-0.003	-0.009, 0.004	.379	-0.002	-0.008, 0.005	.639
B. Annual number of inpatient treatment days								
Very-to-moderately preterm								
5-10 years	0.237 (2.383)	0.458 (5.516)	-0.221	-0.413, -0.029	.024	-0.228	-0.440, -0.016	.035
11-16 years	0.033 (0.496)	0.075 (0.768)	-0.041	-0.085, 0.002	<.001	-0.023	-0.069, 0.024	.342
Late preterm								
5-10 years	0.203 (1.477)	0.149 (1.171)	0.055	0.012, 0.098	.013	0.057	0.010, 0.103	.017
11-16 years	0.045 (0.454)	0.059 (1.030)	0.014	-0.069, 0.042	.632	0.004	-0.056, 0.064	.906
Term								
5-10 years	0.116 (0.795)	0.115 (1.202)	0.001	-1.028, 0.030	<.001	0.004	-0.026, 0.033	.808
11-16 years	0.049 (0.933)	0.046 (1.050)	0.004	-0.035, 0.042	<.001	0.006	-0.033, 0.045	.763
C. Annual number of specialized care outpatient visits								
Very-to-moderately preterm								
5-10 years	0.660 (1.939)	0.750 (2.741)	-0.091	-0.206, 0.024	.123	-0.125	-0.250, 0.000	.050
11-16 years	0.187 (0.861)	0.271(1.068)	-0.085	-0.151, -0.018	.013	-0.041	-0.114, 0.031	.262
Late preterm								
5-10 years	0.631 (2.183)	0.522 (1.536)	0.108	0.050, 0.167	<.001	0.106	0.042, 0.171	<.001
11-16 years	0.254 (0.994)	0.248 (1.214)	0.006	-0.062, 0.074	.861	0.061	-0.005, 0.127	.071
Term								
5-10 years	0.553 (1.655)	0.426 (1.476)	0.127	0.091, 0.162	<.001	0.102	0.067, 0.138	<.001
11-16 years	0.211 (1.149)	0.198 (1.117)	0.013	-0.028, 0.054	.530	0.030	-0.011, 0.071	.153

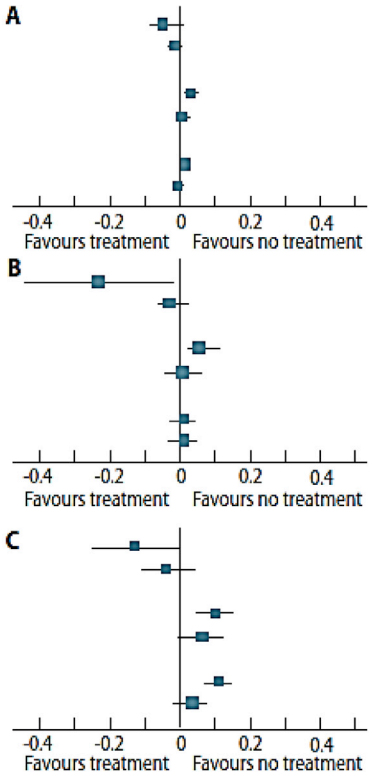

Fig. 1. Associations between maternal antenatal corticosteroid treatment-exposure and treatment for any infectious disease in children and adolescents. The panels present unadjusted means, as well as unadjusted and adjusted mean differences, between treatment-exposed and nonexposed children and adolescents in terms of the annual number of hospitalizations (a), inpatient treatment days (b), and specialized care outpatient visits (c) for any infectious disease, across groups born very-to-moderately preterm (<34 gestational weeks), late preterm (34–36 gestational weeks), and term (≥37 gestational weeks). The forest plot displays adjusted mean differences (squares) and 95% confidence intervals (CIs; error bars). Covariates in the adjusted models included maternal age at delivery, parity, mode of delivery, maternal smoking during pregnancy, prepregnancy body mass index, premature rupture of membranes (O42), gestational diabetes (O24), hypertension in pregnancy (O10 and O13–O15), chorioamnionitis (O41.1, O85, and O86), lifetime asthma diagnosis (J45–J46), lifetime mental disorder diagnosis (F00–F99), child's birth year, sex, Apgar score (maximum of 1 and 5 min), admission to neonatal intensive care unit, weight, and gestational age at birth (O- and F-codes in parenthesis refer to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes). M, mean.

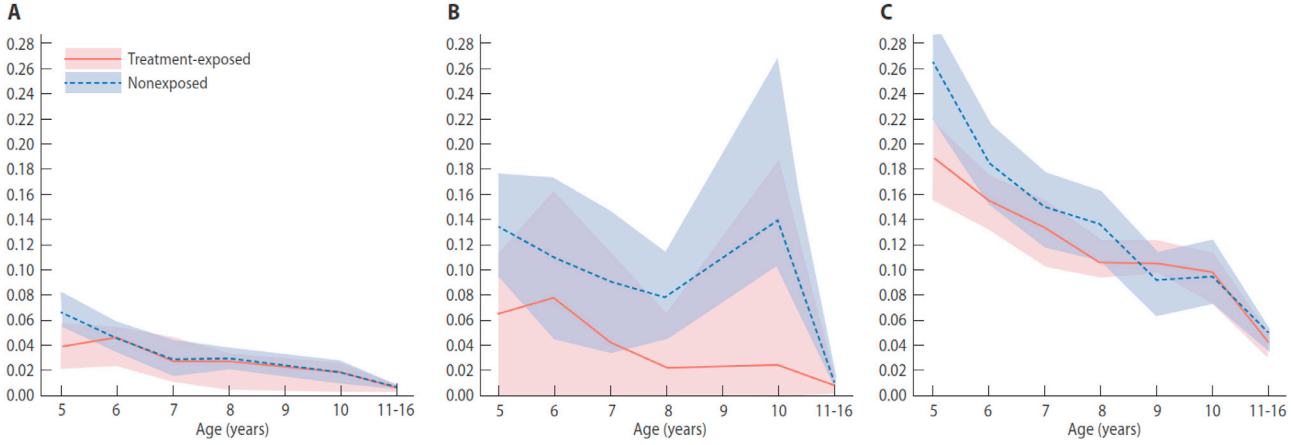

Fig. 2. Associations between maternal antenatal corticosteroid treatment-exposure and treatment for any infectious disease in children and adolescents born very-to-moderately preterm (<34 gestational weeks) in annual age groups from 5 to 10 years and in a combined group for ages 11–16 years. Panels show adjusted means for the annual number of hospitalizations (a), inpatient treatment days (b), and specialized care outpatient visits (c). Solid lines refer to treatment-exposed children and adolescents, and dashed lines refer to nonexposed ones. Shaded areas indicate 95% confidence intervals. Covariates in the adjusted models included maternal age at delivery, parity, mode of delivery, maternal smoking during pregnancy, prepregnancy body mass index, premature rupture of membranes (O42), gestational diabetes (O24), hypertension in pregnancy (O10 and O13–O15), chorioamnionitis (O41.1, O85, and O86), lifetime asthma diagnosis (J45–J46), lifetime mental disorder diagnosis (F00–F99), child's birth year, sex, Apgar score (maximum of 1 and 5 min), admission to neonatal intensive care unit, weight, and gestational age at birth (O- and F-codes in parenthesis refer to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes).

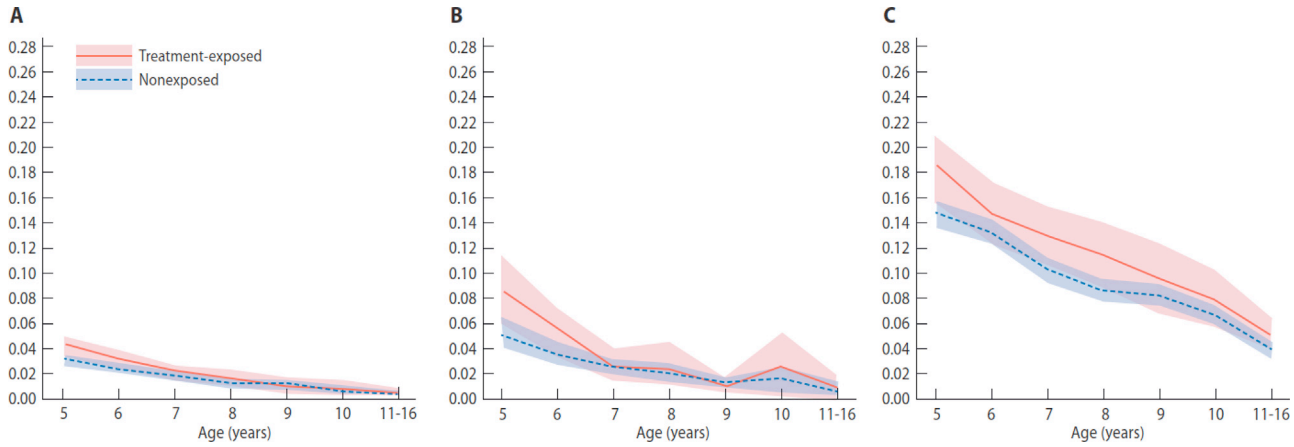

Fig. 3. Associations between maternal antenatal corticosteroid treatment-exposure and treatment for any infectious disease in children and adolescents born late preterm (34–36 gestational weeks) in annual age groups from 5 to 10 years and in a combined group for ages 11–16 years. Panels show adjusted means for the annual number of hospitalizations (a), inpatient treatment days (b), and specialized care outpatient visits (c). Solid lines refer to treatment-exposed children and adolescents, and dashed lines refer to nonexposed ones. Shaded areas indicate 95% confidence intervals. Covariates in the adjusted models included maternal age at delivery, parity, mode of delivery, maternal smoking during pregnancy, prepregnancy body mass index, premature rupture of membranes (O42), gestational diabetes (O24), hypertension in pregnancy (O10 and O13–O15), chorioamnionitis (O41.1, O85, and O86), lifetime asthma diagnosis (J45-J46), lifetime mental disorder diagnosis (F00–F99), child's birth year, sex, Apgar score (maximum of 1 and 5 min), admission to neonatal intensive care unit, weight, and gestational age at birth (O- and F-codes in parenthesis refer to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes).

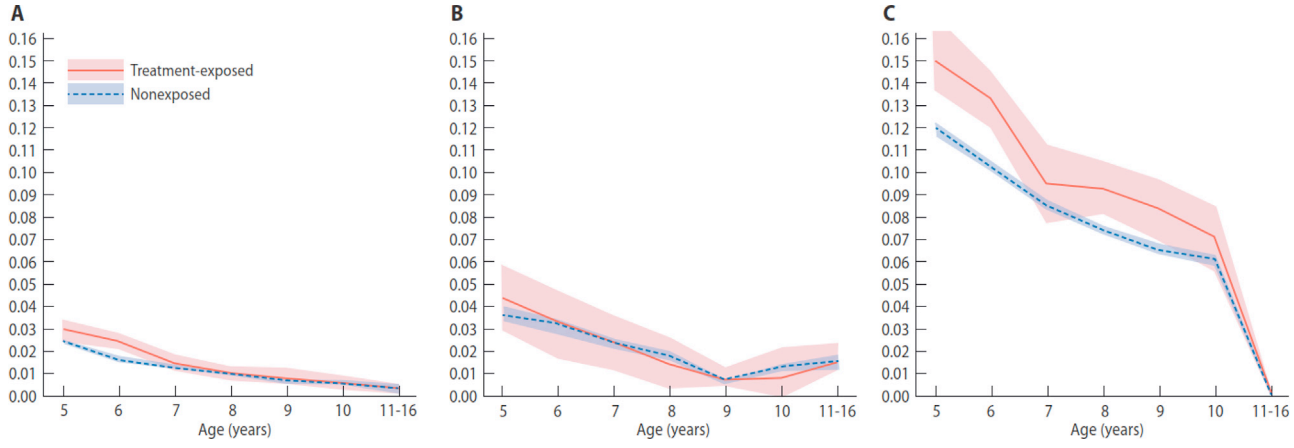

Fig. 4. Associations between maternal antenatal corticosteroid treatment-exposure and treatment of any infectious disease in children and adolescents born at term (≥37 gestational weeks) in annual age groups from 5 to 10 years and in a combined group for ages 11–16 years. Panels show adjusted means for the annual number of hospitalizations (a), inpatient treatment days (b), and specialized care outpatient visits (c). Solid lines refer to treatment-exposed children and adolescents, and dashed lines refer to nonexposed ones. Shaded areas indicate 95% confidence intervals. Covariates in the adjusted models included maternal age at delivery, parity, mode of delivery, maternal smoking during pregnancy, prepregnancy body mass index, premature rupture of membranes (O42), gestational diabetes (O24), hypertension in pregnancy (O10 and O13–O15), chorioamnionitis (O41.1, O85, and O86), lifetime asthma diagnosis (J45–J46), lifetime mental disorder diagnosis (F00–F99), child's birth year, sex, Apgar score (maximum of 1 and 5 min), admission to neonatal intensive care unit, weight, and gestational age at birth (O- and F-codes in parenthesis refer to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes).

have widespread effects on the development of foetal organs and physiological systems [12,13,25].

Cosibling comparisons showed an increased risk for infectious diseases in late preterm-born treatment-exposed siblings but no differences among term-born siblings. The late preterm-born treatment-exposed siblings had a higher annual number of hospitalizations, inpatient treatment days, and specialized care outpatient visits than the nonexposed siblings of the same gestational age. This suggests that the findings were unlikely to be explained by unmeasured familial factors, birth order, or secular trends in healthcare-seeking behaviours.

At ages 11–16 years, the risks and benefits of ACT appeared to have levelled off. This may be attributable to acquired immunity or developmental changes related to sexual maturation. Alternatively, it might be due to limitations in the sample size and the number of cases with infectious disease diagnoses available for the analyses.

Our study's strengths included the large nationwide sample, long follow-up, and minimal data attrition. This addressed a common limitation of randomized controlled trials, which were often not designed to study longer-term outcomes, and suffered from significant and selective data attrition, compromising random allocation and statistical power [27,28]. Limitations related to the inability to draw causal inferences, exclude residual confounding, and generalize findings to populations differing from ours. Neither were we able to assess the number of treatments or timing of ACT. Lastly, we were not able to examine the complex maternal or foetoplacental mechanisms behind these associations.

Overall, our findings suggest that receipt of ACT among late preterm and term children was associated with an increased risk of infection that persisted to age 10 years but lower risk in very-to-moderately preterm children. These findings support caution when considering ACT beyond 34 gestational weeks.

Transparency declaration

Financial report

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Katri Räikkönen: Writing – original draft, Conceptualization, Methodology. **Mika Gissler:** Data curation, Conceptualization, Methodology, Writing – review & editing. **Eero Kajantie:** Conceptualization, Methodology, Writing – review & editing. **Terhi Ruuska-Loewald:** Conceptualization, Methodology, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmicom.2025.105118.

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