Antenatal corticosteroid treatment and infectious diseases in children: a nationwide observational study

Katri Räikkönen,[a,b,*] Mika Gissler,[c,d,e] Eero Kajantie,[f,g,h,i] and Terhi Tapiainen[f,j]

[a]Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Helsinki, Finland
[b]Department of Obstetrics and Gynecology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland
[c]Department of Knowledge Brokers, THL Finnish Institute for Health and Welfare, Helsinki, Finland
[d]Research Centre for Child Psychiatry, University of Turku, Turku, Finland
[e]Department of Molecular Medicine and Surgery, Karolinska Institutet and Academic Primary Health Care Centre, Region Stockholm, Stockholm, Sweden
[f]Research Unit of Clinical Medicine, University of Oulu, Oulu, Finland
[g]Department of Public Health Solutions, THL Finnish Institute for Health and Welfare, Helsinki and Oulu, Finland
[h]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[i]Children's Hospital, Helsinki University Hospital, University of Helsinki, Helsinki, Finland
[j]Department of Pediatrics and Adolescent Medicine, Medical Research Center, Oulu University Hospital, Oulu, Finland

The Lancet Regional Health - Europe 2023;35: 100750

Published Online xxx https://doi.org/10.1016/j.lanepe.2023.100750

Summary

Background Antenatal Corticosteroid Treatment (ACT) improves the outcome of preterm infants, but may influence immune system development and risk of immune-related diseases. We investigated whether ACT is associated with infectious diseases in children born at term (≥37 gestational weeks), and very-to-moderate (<34 gestational weeks), and late (34–36 completed gestational weeks) preterm.

Methods All singleton live births in Finland between 01/01/2006 and 31/12/2021, were followed-up until 31/12/2021. Exposure was maternal ACT. Primary outcomes were numbers of inpatient treatment days, episodes, and specialized care outpatient visits with any infectious disease diagnoses between ages 0 and 4 years. We considered mother- and child-related covariates, and conducted term-born co-sibling comparisons.

Findings Data comprised 855,234 children. Of the 20,858 (2.4%) treatment-exposed children, 5981 (28.2%) were very-to-moderate preterm-born, 5809 (27.9%) late preterm-born, and 9069 (43.5%) term-born. Of the 271,767 term-born co-sibling pairs, 5010 (1.8%) were treatment-exposure-discordant, and 266,522 (98.1%) nonexposure-concordant. Among the term- and late preterm-born, treatment-exposed children had more inpatient treatment days than nonexposed children (term: 0.87 vs. 0.56 day/y, adjusted mean difference [aMD] 0.19, 95% CI 0.17–0.28; late preterm: 1.35 vs. 1.00 days/y, aMD 0.31,0.13–0.31), more inpatient treatment episodes (term: 0.43 vs. 0.33 episodes/y, aMD 0.06, 0.06–0.11; late preterm: 0.55 vs. 0.48 episodes/y, aMD 0.12, 0.06–0.18), and specialized care treatment visits (term: 1.46 vs. 0.95 visits/y, aMD 0.38; 0.34–0.43; late preterm: 1.63 vs. 1.28 visits/y, aMD 0.22, 0.12–0.32). Treatment-exposed and nonexposed very-to-moderate preterm-born children were similar in these outcomes, though they had less inpatient treatment days and episodes at 3–4 years. Differences remained in term-born co-sibling comparisons.

Interpretation These findings reinforce previous suggestions for careful consideration of risks and benefits of ACT.

Funding Academy of Finland, HiLIFE Fellows-Programme.

Keywords: Corticosteroid; Antenatal; Infectious diseases; Children; Follow-up; Sibling; Population-based

Introduction

Globally 13 million newborn infants are born preterm (<37 completed weeks of gestation) each year.[1] While survival has improved, preterm birth still causes one in three neonatal deaths,[1] and may result in lifelong health problems.[2–5] Antenatal Corticosteroid Treatment (ACT)

*Corresponding author. Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Helsinki, Finland.
E-mail address: katri.raikkonen@helsinki.fi (K. Räikkönen).

Research in context

Evidence before this study

We searched PubMed for peer-reviewed papers published from database inception to 05/15/2023, with the language restricted to English. We used the terms "human" and "betamethasone", "dexamethasone", "glucocorticoid*", "corticosteroid*", "steroid*" and "antenatal", "neonatal", "prenatal", "fetal", "foet*", "fetus", "pregnancy" and "infecti*", "immun*". We also searched the Cochrane Database for systematic reviews and meta-analyses published from database inception to 05/15/2023, using the terms "corticosteroid*", "glucocorticoid*", "steroid*" and ""antenatal", "prenatal", "fetal", "foet*", "fetus", "pregnancy". Additional relevant references on infectious diseases as outcomes after exposure to maternal Antenatal Corticosteroid Treatment (ACT) were found by checking the citations from the identified papers. Our search resulted in two studies that had examined the long-lasting effects of ACT on infectious diseases in children. One of these studies was an observational cohort study, which followed up 304 very low birth weight (<1500 g) children from birth until the end of the first 2 years of life. It reported that treatment-exposed compared with nonexposed children did not differ from each other in occurrence of lower respiratory tract infections as indicated by confirmed hospital admissions or medical treatments. The other study on the long-lasting effects was a randomized, double-blind, placebo-controlled trial which followed-up 84 children from birth until 10–12 years of age. That study reported that exposure to betamethasone, in comparison to saline placebo, increased the risk of parent-reported hospital admissions for any infectious disease in the children during the first 8–10 years of life. External validity of these findings is, however, limited because of small sample sizes, non-representative samples, and follow-up data attrition, which may have been selective. Moreover, the studied children were born in 1974–1982. Internal validity of the findings remains limited as well, as the studies did not account for mother-, child-, or family-related related covariates, or did not conduct stratified subgroup or sensitivity analyses according to the child's gestational age at birth.

Added value of this study

To our knowledge, this is the first large-scale population-based cohort study to examine whether treatment-exposed and nonexposed children differ in infectious diseases morbidity in infancy and early childhood, whether any potential benefits and harms of ACT may differ depending on whether the treatment-exposed child was born very-to-moderate (<34 gestational weeks) or late preterm (34–36 gestational weeks) or at term (≥37 gestational weeks), and whether any differences persist in term-born co-sibling comparisons. We found that among the entire cohort, and among the 43.5% who after treatment-exposure ended up being born at term, as well as among the 27.9% who after treatment-exposure ended up being born late preterm, treatment-exposed children had more inpatient treatment days, episodes, and specialized care treatment visits with any infectious disease diagnoses between 0 and 4 years, compared with the nonexposed children. Furthermore, while very-to-moderate preterm-born treatment-exposed children did not differ in these outcomes, they had less inpatient treatment days and episodes with any infectious disease diagnoses at age 3–4 years. These differences were not explained by mother- and child-related covariates, which we showed that at least in the late preterm- and term-born children may have adequately, though not entirely, accounted for confounding by indication. These differences also persisted in term-born co-sibling comparisons, suggesting that unmeasured familial confounding, secular trends in seeking medical care, or the higher load for infectious diseases that the younger sibling carries, did not account for the differences.

Implications of all the available evidence

Consistent evidence from RCTs and observational studies shows that ACT carries multiple short-term benefits for infants born preterm, including decreasing the occurrence of neonatal infections. These benefits must, however, be balanced with possible longer-lasting harms, in particular in relatively low-risk situations, such as after 34 gestational weeks. As shown here, possible harms include the higher risk of infectious diseases morbidity throughout infancy and early childhood in children who after treatment-exposure ended up being born late preterm or at term. These findings inform clinical decision-making when balancing the short-term benefits with the potential longer-lasting harms of ACT, and inform guidelines about decisions to expand treatment beyond 34 gestational weeks.

is one of the most cost-effective treatments to improve the outcome of infants born preterm. ACT is effective in preventing perinatal and neonatal deaths and respiratory distress syndrome in high and low resource settings.[6] While there is uncertainty in the optimal dosing regimen and possible contraindications, guidelines are consistent in recommending ACT up to 34 weeks of gestation[7–11] at least in settings where gestational age can be accurately assessed and adequate childbirth and neonatal care are available.[10]

Corticosteroids are potent drugs, and it is essential to balance risks and benefits of ACT. Two points make this timely. First, even if the treatment is given earlier during pregnancy, all infants will not be born preterm. For example, one recent Finnish whole-population register study, during an era when treatment was recommended

up to $34^{6/7}$ weeks, reported that 45% of treatment-exposed fetuses ended up being born at term.[12] Second, considerable expansions of treatment indications have been proposed as ACT has been shown effective in preventing neonatal respiratory problems also when administered late preterm, 34–36 weeks of gestation,[13,14] or 37–38 gestational weeks with elective caesarean section.[15] This would lead to substantial increases in treatment-exposed children, as late preterm birth alone is 2.5-fold more common than birth below 34 weeks.

While follow-up studies of ACT trials[6] have largely been reassuring, the potential long-lasting harms of ACT exposure on the fetal immune system development remains a matter of contention.[16,17] Synthetic glucocorticoids readily cross the placenta bypassing the feto-placental glucocorticoid barrier causing a peak in the supraphysiological bioactivity of glucocorticoids in the fetus. Glucocorticoids have well-established anti-inflammatory and immunosuppressive effects and potential to carry programming effects on fetal immune system development. Accordingly, exposure to ACT could increase the risk of infectious diseases in later life,[16,17] but direct evidence is limited. One observational study of 304 children born with very low birth weight (<1500 g) followed-up until 2 years of age reported that ACT was not associated with occurrence of lower respiratory tract infections as indicated by confirmed hospital admissions or medical treatments.[18] One randomized clinical trial of 84 children reported that treatment-exposed children compared with children exposed to saline placebo increased the risk of parent-reported hospital admissions for any infectious diseases in the first 8–10 years of life.[19]

We set out to investigate whether ACT was associated with the risk of infectious diseases in the offspring in a large population-based cohort study. As the benefits and harms of ACT on the risk of mental and behavioral, and neurosensory disorders have been shown to differ depending on whether the exposed child ended up being born preterm or at term (≥37 gestational weeks),[12,20] we report the outcomes separately for children born preterm, and at term. We divided the preterm-born children into very-to-moderate (<$34^{0/7}$) and late ($34^{0/7}$–$36^{6/7}$) preterm, as most guidelines recommend ACT up to 34 gestational weeks,[7–11] and as recent RCTs have focused on ACT administration during the late preterm period.[6,14] We also investigated whether any possible differences in infectious diseases persisted in term-born co-sibling comparisons.

Methods

Study design and study population

We linked information from different national registers at the Finnish Institute for Health and Welfare by using unique personal identification numbers assigned to all Finnish citizens and permanent residents. This cohort study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

From the Medical Birth Register, we included all singleton pregnancies in Finland between 01/01/2006 and 31/12/2021. The Medical Birth Register includes all live births and stillbirths in Finland with gestational age of ≥22 weeks or birth weight ≥500 g. Infants eligible for the data analyses were born alive, had data on gestational age, and valid maternal and child personal identification codes for register data linkage. From this population, we also identified all consecutive maternal sibling pairs born at term, including sibling pairs whom the other one was exposed to ACT and the other one was not, and whom neither one was exposed to ACT. The children we followed-up from birth until 31/12/2021.

The study was conducted with permission from the register holder, Finnish Institute for Health and Welfare (THL). According to Finnish legislation, studies using register data only do not require Ethics Committee review or individual consent.

Exposure to maternal antenatal corticosteroid treatment

The Medical Birth Register includes data on whether the mother has received ACT (yes/no). Data are not available on the number of treatments, their timing or the specific corticosteroid used. The Finnish national guidelines[21–23] recommended betamethasone 12 mg administered twice, 24 h 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)[21] after 2009, treatment was recommended until $34^{6/7}$ weeks and, in select cases, later (in the 2009 version,[22] specific conditions mentioned were fetal hydrops and maternal disorder warranting Caesarean section; in the 2018 update,[23] these were high risk of newborn respiratory distress or need of intensive care, and elective Caesarean section). Repeated treatments were not recommended before 2009; after 2009 one repeat course could be considered when the risk of respiratory distress was high,[22] and after 2018 when preterm delivery is likely within 1–8 days.[23] We have previously shown that the ACT recorded in the Medical Birth Register shows high agreement (>97%) with ACT recorded in medical records in two clinical cohorts nested within our study population.[12]

Infectious diseases in the children

We obtained diagnoses of infectious diseases in the children from the Care Register for Health Care comprising all inpatient hospitalizations (since 1969) and all outpatient treatments (since 1998) by physicians in specialized medical care.[24] Diagnoses are coded using the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10) and procedures with NOMESCO Classification of

Surgical Procedures (NCSP). The validity of the register has been reported as good.[24]

As primary outcomes we assessed treatments for any infectious diseases: number of inpatient treatment days, number of inpatient treatment episodes, and number of specialty care outpatient visits with infectious disease diagnoses between ages 0–4 completed years, and at age stages categorized into 0, 1, 2, and 3–4 years. As secondary outcomes we studied these same outcomes at ages 0–4 years with specific groups of infectious diseases: respiratory, gastrointestinal, urinary tract and severe infections. The specific ICD-10 and NCPS codes are shown in Supplementary Table S1.

Covariates

We identified covariates that have been previously shown to be associated with ACT, preterm birth and infectious diseases, or their risk factors. We identified the following covariates from the Medical Birth Register: maternal age at delivery (years), parity (primiparous vs. multiparous), mode of delivery (vaginal vs. Caesarean section), smoking during pregnancy (yes vs. no), pre-pregnancy body mass index (kg/m^2 calculated from weight and height verified by measurement in the first antenatal clinic visit between 7 and 10 gestational weeks), premature rupture of membranes (ICD-10 code O42), gestational diabetes (O24.4), hypertension in pregnancy (O10, O13–O15), chorioamnionitis (O41.1, O85, O86), child's birth year, sex, Apgar score (maximum of 1 and 5 min), admission to neonatal intensive care unit (NICU; yes. vs. no), weight (g) and gestational age (weeks) at birth. We obtained additional maternal covariates from the Care Register for Health Care, including lifetime asthma diagnosis (J45-J46) and mental disorder diagnosis (F00–F99) recorded between 01/01/1996 and 31/12/2021. Race or ethnicity are not recorded in Finnish registers.

To assess how the above set of covariates address confounding by indication,[14] we studied neonatal respiratory distress syndrome (RDS; 1CD-10: P22.0) and transient tachypnea of the newborn (TTN ICD-10: P22.1) as additional outcomes. The rationale was to see whether our observational study was able to replicate the protective effects of ACT on respiratory morbidity as shown in the previous RCTs.[6,13] It has been suggested that if the short-term benefits were replicated, this would increase confidence that an observational study has adequately addressed confounding, and increase confidence when studying the other long-lasting outcomes.[14]

Statistical analysis

We used generalized linear models (GLM) to estimate the associations between ACT exposure and the number of inpatient treatment days and episodes, and specialized care outpatient treatment visits for any infectious diseases in children between the ages of 0–4 years, and at ages 0, 1, 2, and 3–4 years as the primary outcomes. We conducted the analyses in the entire cohort and in term-born and very-to-moderate and late preterm-born groups. We repeated the analyses with the number of inpatient treatment days and episodes, and specialized care outpatient treatment visits for respiratory, gastrointestinal, urinary tract, and severe infections between the ages 0 and 4 years as the secondary outcomes.

To compare term-born siblings discordant for ACT exposure (younger treatment-exposed–older nonexposed, younger nonexposed–older treatment-exposed), we used GLM with each set of siblings representing separate strata. For these analyses we used the number of inpatient treatment days and visits and specialized care outpatient treatment visits for any infectious diseases in children between the ages of 0 and 4 years as outcomes, because of lack of sufficient statistical power to reliably estimate the differences in specific infectious diseases. Because of secular trends in seeking health care,[12,20] and because younger siblings have a higher risk of infectious diseases,[25] we also compared co-sibling pairs whom the younger was treatment-exposed and the older was nonexposed with a sibpair whom both the younger and the older were nonexposed. To account for the dependence of sibling-observations in our analyses, we compared the first set of siblings for each mother.

We present the associations as unadjusted and adjusted for all covariates. In sibling comparisons, adjustments were made for maternal age at delivery, parity, interpregnancy interval, smoking during pregnancy, child's birth year, sex, and gestational age.

Associations between ACT and neonatal RDS and TTN were studied with logistic regression analyses unadjusted and adjusted for all covariates.

As effect sizes, we report unadjusted and adjusted mean differences from the GLMs, and odds ratios (ORs) from logistic regression analyses with 95% confidence intervals (CI). We regard 2-sided P values < 0.05 as statistically significant. We conducted complete case analyses, as missing data in our study population were minimal (Table 1), except for smoking (2.4–11.0%) for which missing values were treated as a separate category. We performed all statistical analyses using SAS 9.4 (SAS Institute, Inc).

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the entire cohort of 857,583 singleton children, 2349 (0.3%) were stillborn. Supplementary Table S2 shows the incidence rates, and unadjusted and adjusted ORs for stillbirths comparing the treatment-exposed with the nonexposed children in the entire cohort, and in the groups born at term, and very-to-moderate and late preterm.

Characteristics	Term N = 817,936		Preterm			
			Very-to-moderate N = 8907		Late N = 28,391	
	Treatment-exposed N = 9069[a]	Nonexposed N = 808,867[a]	Treatment-exposed N = 5981[a]	Nonexposed N = 2926[a]	Treatment-exposed N = 5808[a]	Nonexposed N = 22,583[a]
Children:						
Sex. no. (%)						
Boy	4746 (52.3)	411,734 (50.9)	3335 (55.8)	1644 (56.2)	3206 (55.2)	12,740
Girl	4323 (47.7)	397,133 (49.1)	2646 (44.2)	1282 (43.8)	2602 (44.8)	9843 (43.6)
Gestational age at birth, mean (SD), weeks	38.8 (1.3)	39.6 (1.2)	30.6 (2.8)	31.2 (2.9)	35.5 (0.8)	36.0 (0.7)
Birth weight, mean (SD), g	3405.3 (519.5)	3578.0 (464.0)	1545.3 (581.9)	1695.2 (601.3)	2617.9 (626.2)	2772.0 (517.1)
Small-for-gestational-age at birth, no. (%)[b]	533 (5.9)	22,562 (2.8)	211 (3.5)	123 (4.2)	630 (10.8)	2217 (9.8)
Apgar score (maximum of 1 and 5 min)[c]						
0–3	25 (0.3)	1465 (0.2)	337 (5.6)	289 (9.9)	47 (0.8)	170 (0.8)
4–6	155 (1.7)	10,367 (1.3)	1229 (20.5)	537 (18.4)	308 (5.3)	871 (3.9)
7–10	8862 (97.7)	795,904 (98.4)	4347 (72.7)	2048 (70.0)	5386 (92.7)	21,440 (94.9)
Unknown	27 (0.3)	1131 (0.1)	68 (1.1)	52 (1.8)	67 (1.2)	102 (0.5)
Admission to neonatal intensive care unit, no. (%)						
No	7789 (85.9)	741,259 (91.6)	336 (6.1)	293 (10.0)	1886 (32.5)	12,782 (56.6)
Yes	1280 (14.1)	67,608 (8.4)	5615 (93.9)	2633 (90.0)	3922 (67.5)	9801 (43.4)
Neonatal sepsis, no. (%)[d]						
No	160 (1.8)	13,965 (1.7)	321 (5.4)	170 (5.8)	161 (2.8)	621 (2.7)
Yes	8909 (98.2)	794,902 (98.3)	5660 (94.6)	2756 (94.2)	5647 (97.2)	22,232 (97.3)
Major congenital anomaly, no. (%)						
No	8446 (93.1)	773,869 (95.7)	5053 (84.5)	2532 (86.5)	5088 (87.6)	20,672 (91.5)
Yes	623 (6.9)	34,998 (4.3)	928 (15.5)	394 (13.5)	720 (12.4)	1911 (8.5)
Mothers:						
Age at delivery, mean (SD), years	30.2 (5.8)	30.5 (5.3)	31.3 (5.8)	30.8 (5.9)	31.2 (5.7)	30.6 (5.7)
Parity, no. (%)						
0	3717 (41.0)	334,459 (41.3)	3108 (52.0)	1404 (48.0)	2616 (45.0)	11,143 (49.3)
1	3045 (33.6)	276,486 (34.2)	1510 (25.2)	789 (27.0)	1674 (28.8)	6272 (27.8)
2	1349 (14.9)	117,737 (14.6)	737 (12.3)	385 (13.2)	823 (14.2)	2754 (12.2)
3	516 (5.7)	40,677 (5.0)	290 (4.8)	182 (6.2)	330 (5.7)	1190 (5.3)
≥4	442 (4.9)	39,362 (4.9)	336 (5.6)	166 (5.7)	365 (6.3)	1217 (5.4)
Unknown	0	146 (0.0)	0	0	0	7 (0.0)
Delivery mode, no. (%)						
Vaginal	7143 (78.8)	685,576 (84.8)	2462 (41.2)	1345 (46.0)	3027 (52.1)	16,311 (72.2)
Caesarean	1925 (21.2)	123,245 (15.2)	3519 (58.2)	1581 (54.0)	2778 (47.8)	6270 (27.8)
Pre-pregnancy body mass index, mean (SD), kg/m^2	24.8 (5.5)	24.6 (5.0)	25.4 (5.8)	25.1 (5.4)	25.3 (5.7)	24.8 (5.3)
Unknown	119 (1.3)	19,756 (2.4)	142 (2.4)	280 (9.6)	64 (1.1)	791 (3.5)
Premature rupture of membranes, no. (%)[d]						
No	8717 (96.1)	787,652 (97.4)	4123 (68.9)	2341 (80.0)	4358 (75.0)	18,318 (81.1)
Yes	352 (3.9)	21,215 (2.6)	1858 (31.1)	585 (20.0)	1450 (25.0)	4265 (18.9)
Gestational diabetes, no. (%)[d]						
No	7565 (83.4)	707,129 (87.4)	5265 (88.0)	2640 (90.2)	4850 (83.5)	19,575 (85.9)
Yes	1504 (16.6)	101,738 (12.6)	716 (12.0)	286 (9.8)	958 (16.5)	3187 (14.1)
Hypertension, no. (%)[d]						
No	8405 (92.7)	771,022 (95.3)	4446 (74.3)	2382 (81.4)	4850 (81.3)	19,575 (86.7)
Yes	664 (7.3)	37,845 (4.7)	1535 (25.7)	544 (18.6)	958 (16.5)	3008 (13.3)
Chorioamnionitis, no. (%)[d]						
No	8982 (99.0)	800,565 (99.0)	5493 (91.8)	2798 (95.6)	5714 (98.4)	23,390 (99.1)
Yes	87 (1.0)	8302 (1.0)	488 (8.2)	238 (4.4)	94 (1.6)	193 (0.9)

(Table 1 continues on next page)

Characteristics	Term N = 817,936		Preterm			
			Very-to-moderate N = 8907		Late N = 28,391	
	Treatment-exposed N = 9069[a]	Nonexposed N = 808,867[a]	Treatment-exposed N = 5981[a]	Nonexposed N = 2926[a]	Treatment-exposed N = 5808[a]	Nonexposed N = 22,583[a]
(Continued from previous page)						
Asthma, no. (%)[d]						
No	8313 (91.7)	757,925 (93.7)	5549 (92.8)	2704 (92.4)	5316 (91.5)	20,971 (92.9)
Yes	756 (8.3)	50,942 (6.3)	432 (7.2)	222 (7.6)	492 (8.5)	1612 (7.1)
Any mental or behavioral disorder, no. (%)[d]						
No	6139 (67.7)	633,868 (78.4)	4210 (70.4)	2109 (72.1)	4028 (69.4)	16,691 (73.9)
Yes	2930 (32.3)	174,999 (21.6)	1771 (29.6)	817 (29.6)	1780 (30.6)	5892 (26.1)
Smoking during pregnancy, no. (%)						
No	7199 (79.4)	679,693 (83.3)	4633 (77.5)	2088 (71.3)	4652 (80.1)	17,962 (79.5)
Yes	1648 (18.2)	108,570 (13.4)	1015 (17.0)	515 (17.6)	939 (16.2)	3067 (16.0)
Unknown	222 (2.4)	26,604 (3.3)	333 (5.6)	323 (11.0)	217 (3.7)	1014 (4.5)

[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 min after birth uses skin color, pulse rate, reflexes, muscle tone, and respiratory effort to determine medical attention: Scores 0–3 suggest a need for resuscitation. while scores of 7 or more 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; Hypertension O10, O13–O15; Chorioamnionitis O41.1, O85. O86; Asthma J45-J4; Any mental or behavioral disorder F00–F99.

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

The analytic sample, thus, comprised 855,234 singletons born alive, of whom 20,858 (2.4%) were treatment-exposed. Of the 8907 (1.0%) born very-to-moderate preterm, 5981 (67.2%) were treatment-exposed, and of the 28,391 (3.3%) born late preterm 5808 (20.1%) were treatment-exposed, whereas among the 817,936 (95.6%) born at term, this number was 9069 (2.3%). Of all the 20,858 treatment-exposed children, 28.2% were born very-to-moderate preterm, 27.9% late preterm, and 43.5% at term. The children were followed-up between ages 0 and 4 years (Median = 4.99 years, Interquartile Range 4.61–4.99 years). Characteristics of the children born very-to-moderate and late preterm, and at term are shown in Table 1, and of the entire cohort in Supplementary Table S3. Table 2 shows the cumulative incidence rates of inpatient treatment episodes and specialized care outpatient treatment visits for any and the specific infectious diseases between the ages 0 and 4 years in the entire cohort of children and in the term-born and very-to-moderate, and late preterm-born groups according to treatment-exposure.

Nested within this study population were 271,767 term-born sibling pairs. Of these sibling pairs. there were 5010 pairs whom the other one (younger or older) was treatment-exposed and the other one (younger or older) was nonexposed, 266,522 pairs whom both were nonexposed, and 235 pairs whom both were treatment-exposed.

Associations between ACT and treatment of any infectious diseases

We first assessed associations with inpatient treatment days and episodes, and specialized care outpatient treatment visits for any infectious diseases between ages 0 and 4 years. Treatment-exposed compared with nonexposed children in the entire cohort, and in the term-born and late preterm-born groups had significantly more inpatient treatment days and episodes, and specialized care outpatient treatment visits in both unadjusted and adjusted analyses (Fig. 1). In the very-to-moderate preterm-born group, treatment-exposed compared with nonexposed children, had significantly more specialized care outpatient visits in unadjusted analyses, but in the adjusted analyses this association was rendered non-significant (Fig. 1).

We then assessed the same outcomes for any infectious diseases at annual age groups. Treatment-exposed compared with nonexposed children in the entire cohort, and in the term-born, and late preterm-born groups had significantly more inpatient treatment days and episodes, in the entire cohort at ages 0, 1, and 2 years, in the term-born group at all ages, and in the late preterm-born group at ages 0 and 1 years for both of these outcomes, and for inpatient episodes also at the age of 2 years (Fig. 1). Treatment-exposed compared with nonexposed children in these groups had also significantly more specialized care outpatient treatment visits in the entire cohort and in the term-born group at all ages, and in the late preterm-born group at ages 0, 1, and 3–4 years (Fig. 1). In the very-to-moderate preterm-born group, treatment-exposed compared with nonexposed children had significantly less inpatient treatment days and visits at the age of 3–4 years (Fig. 1).

Associations between ACT and treatment of specific infectious diseases

Treatment-exposed compared with the nonexposed children in the entire cohort, and in the term-born, and

Inpatient treatment episodes and specialized care outpatient visits for infectious diseases at age 0–4 y, no. (%)	Entire cohort N = 855,234		Term N = 817,936		Preterm			
					Very-to-moderate N = 8907		Late N = 28,391	
	Treatment-exposed N = 20,858	Nonexposed N = 834,376	Treatment-exposed N = 9069	Nonexposed N = 808,867	Treatment-exposed N = 5981	Nonexposed N = 2926	Treatment-exposed N = 5808	Nonexposed N = 22,583
Any infections								
Inpatient treatment episodes	5527 (26.5)	154,120 (18.5)	2014 (22.2)	147,752 (18.3)	2145 (35.9)	1024 (35.0)	1386 (23.6)	5344 (23.7)
Specialized care outpatient visits	10,508 (50.4)	324,996 (39.0)	4290 (47.3)	313,417 (38.7)	3307 (56.8)	1507 (51.5)	2821 (48.6)	10,072 (44.6)
Respiratory infections								
Inpatient treatment episodes	4274 (20.5)	110,794 (13.3)	1461 (16.1)	105,970 (13.1)	1755 (29.3)	811 (27.7)	1058 (18.2)	4013 (17.8)
Specialized care outpatient visits	9078 (43.5)	265,521 (31.8)	3605 (39.8)	255,697 (31.6)	3057 (51.1)	1332 (45.5)	2416 (41.6)	8492 (37.6)
Gastrointestinal infections								
Inpatient treatment episodes	611 (2.9)	16,164 (1.9)	238 (2.6)	15,406 (1.9)	211 (3.7)	140 (4.8)	152 (2.6)	618 (2.7)
Specialized care outpatient visits	1787 (8.0)	47,017 (5.6)	693 (7.6)	45,230 (5.6)	516 (8.6)	227 (7.8)	463 (8.0)	1560 (6.9)
Urinary tract infections								
Inpatient treatment episodes	289 (1.4)	8612 (1.0)	145 (1.6)	8334 (1.0)	64 (1.1)	43 (1.5)	80 (1.4)	245 (1.1)
Specialized care outpatient visits	467 (2.2)	14,871 (1.8)	226 (2.5)	14,422 (1.8)	109 (1.8)	57 (1.9)	132 (2.3)	392 (1.7)
Severe infections								
Inpatient treatment episodes	164 (0.8)	3944 (0.5)	50 (0.6)	3759 (0.5)	72 (1.2)	41 (1.4)	42 (0.7)	144 (0.6)
Specialized care outpatient visits	153 (0.7)	4071 (0.5)	53 (0.6)	3921 (0.5)	54 (0.9)	22 (0.8)	46 (0.8)	128 (0.6)

Table 2: **Cumulative incidence rates of inpatient treatment episodes and specialized care outpatient visits for any and specific infectious diseases in the entire cohort of children and the children born at term (≥37 gestational weeks) and very-to-moderate (<34 gestational weeks) and late preterm (34–36 gestational weeks) according to maternal antenatal corticosteroid treatment-exposure.**

late preterm-born groups had significantly more inpatient treatment days, episodes, and/or specialized care outpatient visits for respiratory, gastrointestinal, and urinary tract infections (Supplementary Table S4). The term-born treatment-exposed compared with nonexposed children had also significantly more inpatient treatment days and episodes for severe infections (Supplementary Table S4). In the very-to-moderate preterm-born group, treatment-exposed compared with nonexposed children did not differ in any of these specific infectious diseases outcomes (Supplementary Table S4).

Term-born co-sibling comparisons

Table 3 shows that in the term-born co-sibling analyses, the treatment-exposed sibling had significantly more inpatient treatment days and episodes, and specialized care outpatient visits than the non-exposed co-sibling. These differences were significant also in the analyses comparing co-sibling pairs whom the other one was treatment-exposed and the other was nonexposed with the pairs whom both siblings were nonexposed (Table 3).

Associations between ACT and neonatal RDS and TTN

The incidence rates and unadjusted ORs of RDS were significantly lower for the treatment-exposed compared with the nonexposed children born very-to-moderate preterm, whereas in the other groups these numbers implicated significantly higher risk (Supplementary Table S5). However, in the analyses adjusted for all covariates, the risk of RDS was significantly lower for the treatment-exposed compared with non-exposed children in the entire cohort, and in the very-to-moderate and late preterm groups, whereas in the term group the association was no longer statistically significant (Supplementary Table S5). With regards to TTN, the incidence rates and unadjusted ORs were significantly higher for the treatment-exposed compared with the nonexposed children in the entire cohort, and in the late preterm and term group, whereas in the very-to-moderate preterm group the difference was not statistically significant (Supplementary Table S5). When adjusted for all covariates, the risk of TTN was significantly lower in treatment-exposed children in the term group, significantly higher in the very-to-moderate preterm group, whereas in the entire cohort and in the late preterm group the associations with treatment-exposure were no longer statistically significant (Supplementary Table S5).

Discussion

In this large population-based cohort study, exposure to ACT was associated with an increased risk of infectious diseases in infants and young children during the first four years of life. In the entire cohort and in the group born at term, treatment-exposed children had more inpatient treatment days, inpatient treatment episodes and specialized care treatment visits with infectious

Any infectious diseases at age	Treatment-exposed M (SD)	Non-exposed M (SD)	Unadjusted Mean difference	Unadjusted 95% CI	Unadjusted P	Adjusted Mean difference	Adjusted 95% CI	Adjusted P
A Inpatient treatment days								
Entire cohort								
0-4 years	1·78 (8·83)	0·58 (2·85)	1·21	1·16, 1·25	<·001	0·42	0·37, 0·46	<·001
0 years	1·10 (6·78)	0·24 (1·68)	0·85	0·83, 0·88	<·001	0·32	0·30, 0·36	<·001
1 years	0·35 (2·67)	0·16 (1·16)	0·19	0·18, 0·21	<·001	0·06	0·04, 0·07	<·001
2 years	0·18 (1·83)	0·09 (0·84)	0·09	0·08, 0·10	<·001	0·02	0·01, 0·04	·008
3-4 years	0·16 (1·47)	0·09 (0·96)	0·07	0·05, 0·08	<·001	0·01	-0·01, 0·02	·399
Term								
0-4 years	0·87 (6·30)	0·56 (2·65)	0·31	0·26, 0·37	<·001	0·19	0·17, 0·28	<·001
0 years	0·43 (4·64)	0·23 (1·53)	0·20	0·16, 0·23	<·001	0·13	0·10, 0·17	<·001
1 years	0·21 (1·79)	0·16 (1·12)	0·05	0·03, 0·07	<·001	0·02	0·01, 0·06	·006
2 years	0·13 (1·10)	0·08 (0·82)	0·04	0·03, 0·06	<·001	0·03	0·02, 0·05	<·001
3-4 years	0·12 (1·07)	0·09 (0·90)	0·03	0·01, 0·05	·004	0·01	0·00, 0·04	·03
Very-to-moderate preterm								
0-4 years	3·60 (12·33)	3·52 (13·50)	0·08	-0·48, 0·64	·78	-0·32	-0·91, 0·27	·29
0 years	2·44 (10·08)	2·19 (9·15)	0·25	-0·18, 0·68	·26	-0·15	-0·60, 0·30	·52
1 years	0·63 (3·37)	0·60 (3·86)	0·04	-0·12, 0·19	·65	0·05	-0·11, 0·21	·54
2 years	0·20 (2·96)	0·31 (2·17)	-0·01	-0·13, 0·11	·85	-0·02	-0·15, 0·12	·80
3-4 years	0·23 (1·86)	0·42 (4·37)	-0·19	-0·32, -0·06	·004	-0·21	-0·35, -0·06	·006
Late preterm								
0-4 years	1·35 (7·53)	1·00 (5·02)	0·34	0·18, 0·51	<·001	0·31	0·13, 0·49	<·001
0 years	0·76 (4·90)	0·49 (3·04)	0·27	0·17, 0·37	<·001	0·18	0·07, 0·29	·002
1 years	0·30 (2·96)	0·25 (1·63)	0·05	-0·00, 0·11	·07	0·08	0·02, 0·15	·01
2 years	0·13 (1·01)	0·13 (1·28)	0·00	-0·03, 0·04	·89	0·02	-0·02, 0·06	·31
3-4 years	0·15 (1·54)	0·14 (1·50)	0·02	-0·03, 0·06	·43	0·03	-0·02, 0·08	·18
B Inpatient treatment episodes								
Entire cohort								
0-4 years	0·60 (2·07)	0·34 (1·14)	0·26	0·25, 0·28	<·001	0·08	0·06, 0·09	<·001
0 years	0·20 (0·68)	0·10 (0·39)	0·11	0·10, 0·11	<·001	0·03	0·03, 0·04	<·001
1 years	0·18 (1·06)	0·10 (0·43)	0·07	0·06, 0·07	<·001	0·02	0·02, 0·03	<·001
2 years	0·09 (0·41)	0·06 (0·30)	0·04	0·03, 0·04	<·001	0·01	0·01, 0·02	<·001
3-4 years	0·13 (1·00)	0·08 (0·74)	0·05	0·04, 0·06	<·001	0·00	-0·01, 0·02	·29
Term								
0-4 years	0·43 (1·27)	0·33 (1·10)	0·10	0·08, 0·13	<·001	0·08	0·06, 0·11	<·001
0 years	0·14 (0·50)	0·09 (0·38)	0·05	0·04, 0·05	<·001	0·03	0·02, 0·04	<·001
1 years	0·13 (0·49)	0·10 (0·42)	0·02	0·01, 0·03	<·001	0·01	0·01, 0·03	<·001
2 years	0·07 (0·37)	0·06 (0·30)	0·02	0·01, 0·03	<·001	0·02	0·01, 0·02	<·001
3-4 years	0·09 (0·71)	0·08 (0·71)	0·18	-0·09, 0,45	·15	0·01	0·00, 0·03	·04
Very-to-moderate preterm								
0-4 years	0·90 (2·16)	0·98 (3·35)	-0·09	-0·20, 0·03	·14	-0·10	-0·33, 0·04	·13
0 years	0·32 (0·87)	0·31 (0·79)	0·01	-0·02, 0·05	·44	0·00	-0·04, 0·04	·93
1 years	0·26 (0·76)	0·25 (0·75)	0·01	-0·03, 0·04	·55	0·02	-0·02, 0·05	·40
2 years	0·13 (0·50)	0·14 (0·59)	0·00	-0·02, 0·02	·95	0·00	-0·02, 0·03	·93
3-4 years	0·18 (1·13)	0·29 (2·45)	-0·11	-0·19, -0·04	·004	-0·12	-0·20, -0·03	·006
Late preterm								
0-4 years	0·55 (2·81)	0·48 (1·71)	0·07	0·01, 0·12	·02	0·12	0·06, 0·18	<·001
0 years	0·18 (0·67)	0·15 (0·53)	0·03	0·01, 0·05	<·001	0·03	0·01, 0·04	·006
1 years	0·17 (1·75)	0·14 (0·52)	0·03	0·00, 0·05	·06	0·05	0·02, 0·08	<·001
2 years	0·08 (0·39)	0·08 (0·37)	0·00	-0·01, 0·01	·51	0·02	0·00, 0·03	·01
3-4 years	0·13 (1·22)	0·11 (1·19)	0·01	-0·02, 0·05	·45	0·05	-0·01, 0·07	·14
C Specialized care outpatient visits								
Entire cohort								
0-4 years	1·73 (3·83)	0·97 (2·12)	0·76	0·73, 0·79	<·001	0·30	0·27, 0·34	<·001
0 years	0·57 (1·48)	0·29 (0·93)	0·28	0·26, 0·29	<·001	0·12	0·11, 0·14	<·001
1 years	0·51 (1·76)	0·28 (0·91)	0·23	0·22, 0·25	<·001	0·09	0·07, 0·10	<·001
2 years	0·30 (1·09)	0·18 (0·69)	0·12	0·12, 0·13	<·001	0·04	0·03, 0·05	<·001
3-4 years	0·34 (1·26)	0·21 (0·82)	0·12	0·11, 0·14	<·001	0·04	0·04, 0·06	<·001
Term								
0-4 years	1·46 (2·90)	0·95 (2·09)	0·50	0·46, 0·54	<·001	0·38	0·34, 0·43	<·001
0 years	0·48 (1·29)	0·29 (0·92)	0·19	0·18, 0·21	<·001	0·15	0·13, 0·17	<·001
1 years	0·41 (1·17)	0·28 (0·90)	0·13	0·11, 0·15	<·001	0·09	0·07, 0·11	<·001
2 years	0·26 (0·85)	0·18 (0·68)	0·08	0·07, 0·10	<·001	0·06	0·05, 0·08	<·001
3-4 years	0·31 (1·12)	0·21 (0·81)	0·10	0·08, 0·11	<·001	0·08	0·07, 0·10	<·001
Very-to-moderate preterm								
0-4 years	2·24 (4·02)	1·97 (4·06)	0·26	0·09, 0·44	·004	0·10	-0·09, 0·29	·30
0 years	0·75 (1·74)	0·64 (1·50)	0·12	0·04, 0·19	·002	0·07	-0·01, 0·15	·09
1 years	0·67 (1·71)	0·57 (1·65)	0·10	0·03, 0·18	·008	0·04	-0·05, 0·12	·39
2 years	0·40 (1·18)	0·34 (1·11)	0·06	0·00, 0·11	·03	0·03	-0·03, 0·08	·35
3-4 years	0·41 (1·26)	0·42 (1·46)	-0·01	-0·07, 0·05	·78	-0·03	-0·09, 0·03	·37
Late preterm								
0-4 years	1·63 (4·72)	1·28 (2·68)	0·35	0·25, 0·44	<·001	0·22	0·12, 0·32	<·001
0 years	0·52 (1·47)	0·40 (1·10)	0·13	0·09, 0·16	<·001	0·08	0·04, 0·11	<·001
1 years	0·52 (2·44)	0·37 (1·12)	0·15	0·10, 0·19	<·001	0·10	0·05, 0·14	<·001
2 years	0·27 (1·30)	0·24 (0·91)	0·04	0·01, 0·07	·01	0·00	-0·03, 0·04	·77
3-4 years	0·31 (1·46)	0·28 (0·96)	0·03	0·00, 0·07	·04	0·04	0·01, 0·08	·02

Adjusted for maternal age at delivery, parity, mode of delivery, smoking during pregnancy, pre-pregnancy body mass index, premature rupture of membranes (O42), gestational diabetes (O24·4), hypertension in pregnancy (O10, O13-O15), chorioamnionitis (O41·1, O85, 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 Health-related Problems, Tenth Revision codes)

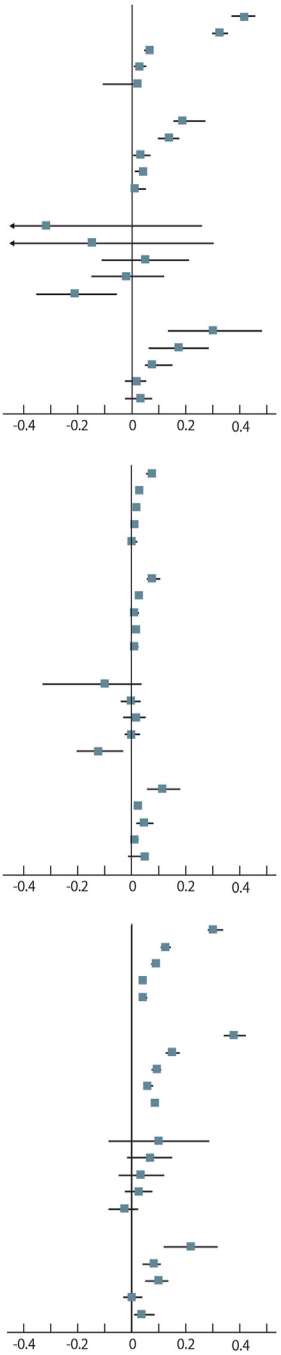

Fig. 1: **Unadjusted means, and unadjusted and adjusted mean differences of inpatient treatment days (Panel A), inpatient treatment episodes (Panel B), and specialized care outpatient visits (Panel C) per year of any infectious diseases in the entire cohort of children and the children born at term (≥37 gestational weeks), and very-to-moderate (<34 gestational weeks) and late preterm (34–36 gestational weeks) according to maternal antenatal corticosteroid treatment-exposure** The forest plots display adjusted mean differences (dots) and 95% Confidence Intervals (error bars).

Any infectious diseases at age 0–4 years:	Treatment-exposed	Non-exposed	Unadjusted			Adjusted		
	M (SD)	M (SD)	Mean difference	95% CI	P	Mean difference	95% CI	P
Difference within-sibling pair								
Younger or older treatment-exposed vs. Younger or older nonexposed (N = 5010)								
Inpatient treatment	0.88 (7.47)	0.60 (2.21)	0.28	0.06, 0.49	0.01	0.48	0.24, 0.72	<0.001
Inpatient treatment episodes	0.29 (0.60)	0.26 (0.58)	0.03	0.01, 0.05	0.02	0.11	0.09, 0.14	<0.001
Specialized care outpatient treatment visits/year	1.52 (2.99)	1.34 (2.44)	0.18	0.08, 0.29	<0.001	0.24	0.13, 0.36	<0.001
Difference of two within-sibling pairs								
Younger treatment exposed and older non-exposed (N = 2466) vs. Younger and older nonexposed (N = 266,522)								
Inpatient treatment days	0.99 (10.12)	0.53 (2.57)	0.46	0.36, 0.58	<0.001	0.41	0.30, 0.52	<0.001
Inpatient treatment episodes	0.29 (0.60)	0.21 (0.52)	0.08	0.06, 0.10	<0.001	0.06	0.05, 0.09	<0.001
Specialized care outpatient treatment visits	1.56 (2.92)	1.00 (2.16)	0.56	0.48, 0.65	<0.001	0.47	0.39, 0.56	<0.001

Adjusted for maternal age at delivery, parity, interpregnancy interval, smoking during pregnancy, child's birth year, sex, and weight and gestational age at birth.

Table 3: **Unadjusted means and unadjusted and adjusted mean differences of inpatient treatment days, inpatient treatment episodes, and specialized care outpatient visits per year of any infectious diseases according to maternal antenatal corticosteroid treatment-exposure in term-born co-sibling comparisons.**

disease diagnoses compared with the nonexposed children. The higher risk was also present in the late preterm-born treatment-exposed children who during these early life years had more inpatient treatment days and episodes, and specialized care treatment visits with infectious disease diagnoses. In the very-to-moderate preterm-born children treatment-exposure was neither associated with benefits nor harms. These differences survived adjustment for a number of mother- and child-related covariates and persisted in term-born co-sibling comparisons.

In the age-stage-specific analyses, in the entire cohort and in the group born at term, treatment-exposed compared with nonexposed children had more inpatient treatment days and episodes with infectious disease diagnoses at ages 0, 1 and 2 years, and more specialized care outpatient treatment visits with infectious disease diagnoses at all ages during the first four years of life. Late preterm-born treatment-exposed children had more inpatient treatment days at ages 0 and 1 years, more inpatient treatment episodes at ages 0, 1 and 2 years and more specialized care outpatient treatment visits with infectious disease diagnoses at ages 0, 1, and 3–4 years. However, the very-to-moderate preterm-born treatment-exposed children had less inpatient treatment days and episodes at the age of 3–4 years. The age-stage-specific findings suggest that the risks by and large appear to persist throughout infancy and early childhood years in the treatment-exposed children if they after the treatment-exposure ended up being born at term or late preterm, whereas in the very-to-moderate preterm-born children treatment-exposure may have generated benefits that manifest after infancy.

Furthermore, these risks seemed to be non-specific to any of the specific infectious disease groups studied as secondary outcomes. While the pattern of findings was not as consistent as that of our primary outcome, any infectious disease diagnoses, treatment-exposed term-born and late preterm-born children had increased risks of respiratory, gastrointestinal, and urinary tract infections, and term-born children also for severe infections as implicated by either more days spent in inpatient treatment, more inpatient treatment episodes or specialized care treatment visits. Among those born very-to-moderate preterm, treatment-exposure was not associated with treatment of the specific infectious diseases. Even though the infectious diseases we studied here have different etiologies and risk factor profiles, the non-specificity of the findings in the late preterm- and term-born groups may be expected, as the effects of glucocorticoids on the immune system development are pleiotropic.[16,17] Hence, exposure to ACT during the critical *intra uterine* window of immune organ and system development may have compromised immunity in general, and thereby modulated immune response and increased the risk of infectious diseases. ACT may have also compromise fetal hypothalamic-pituitary-adrenal axis development,[26] which plays an important role in modulating immunological defense against infections.[16,17] Given that endogenous glucocorticoids have well-established pleiotropic effects on the immune system in general, it seems plausible that synthetic glucocorticoids, which have 25-times higher affinity to glucocorticoid receptors, and hence higher genomic glucocorticoid potency than endogenous cortisol,[27] would carry such widespread programming effects when passing through to the fetal side.

The term-born co-sibling comparisons showed that shared familial factors did not explain the associations found in the term-born group, as the treatment-exposed term-born sibling had significantly higher numbers of inpatient treatment days and episodes, and specialized

care treatment visits with infectious disease diagnoses than the nonexposed term-born co-sibling. The co-sibling comparisons also showed that the associations were not either explained by a higher risk that the younger sibling may carry for infectious diseases in general,[25] or by secular trends in seeking medical care, as the associations were also significant when we compared co-sibling pairs whom the younger one was treatment-exposed and the older one was nonexposed with the pairs whom both the younger and the older were nonexposed.

These findings are in agreement with the hypothesis that exposure to ACT may carry harmful effects compromising immune system development, and increase the risk of infectious diseases later in life.[16,17] They are also in agreement with the earlier study which showed in an RCT design that treatment-exposed compared with nonexposed children had more parent-reported hospital admissions for infectious diseases in the first 8–10 years of life,[19] but in disagreement with the observational study showing no associations between ACT and lower respiratory tract infections in the first 2 years of life.[18] It is of note that, according to a Cochrane meta-analysis of RCTs, exposure to ACT decreased the risks for systemic infections within the first 48 h after birth and proven infections while at the NICU.[6] While direct comparisons of our observational study with the earlier studies are not warranted, longer-term follow-up of the existing observational studies and RCTs, and analyses stratified by the gestational age at birth, would help to either confirm or refute the longer-lasting risks or benefits of ACT.

Limitations

There are limitations to our study. Causal inferences are not warranted, and we cannot exclude residual confounding, including confounding related to regional variability. We cannot either entirely rule out confounding by indication.[14] Benchmarking findings from observational studies against those from RCTs has been proposed as a useful strategy to assess concerns related to confounding in observational studies.[14] More specifically, it has been suggested that if the protective effects of ACT on neonatal respiratory morbidity reported in RCTs[6,13] can be replicated in observational studies, this would greatly increase confidence that the observational studies have adequately addressed confounding when studying the other longer-term outcomes.[14] Our observational study, indeed, replicated the protective effects of ACT on neonatal RDS in the children who were born very-to-moderate and late preterm, and on TTN in the children who were born at term,[6] when the analyses were adjusted for covariates. However, in the very-to-moderate preterm-born children the protective effect of ACT on TTN could not be replicated,[6] as in the adjusted analyses the risk was significantly increased. Hence, while we cannot entirely rule out confounding by indication, these findings on neonatal RDS and TTN suggest that the set of covariates we used, may have adequately addressed confounding, at least in the late preterm-born and term-born children, when we have studied the other longer-term outcomes. With regard to the potential bias related to the differences in the stillbirth rates in the treatment-exposed compared with the non-exposed children in out cohort, it is of note that stillbirths represent a different clinical situation where medical attention is frequently sought only after the fetus already has died. In these situations, ACT is obviously not given. The very low ORs for stillbirths in the treatment-exposed fetuses born very-to-moderately or late preterm may, thus, represent reverse causality. During our study period, ACT was recommended mostly up to $34^{6/7}$ weeks of gestation. For infants stillborn at term, treatment-exposure is thus likely to have occurred substantially earlier; and we found no association between treatment-exposure and stillbirth at term. Moreover, even though our sample comprised over 800,000 children born in Finland between 2006 and 2021, statistical power was still limited in comparisons of treatment-exposed and nonexposed children, and preterm-born co-siblings could not be compared. As we studied only births in Finland, we cannot generalize findings to other populations. However, the rates of hospitalizations in Finnish children under the age of five years, at least for respiratory infections, have been reported to be comparable to the rates in the other EU countries and Scotland between 2006 and 2018.[28] As the timing of ACT and the number and types of treatments given are not recorded in the Medical Birth Register, we could not study timing, nor the type of steroid administered. As we focused on physician-diagnoses of infectious diseases made in hospitals and outpatient clinics in specialized medical care, our study may have captured more severe infections. However, this may have rather diminished than increased our ability to detect significant associations. Finally, we are unable to assess potential mechanisms mediating the link between ACT and infectious diseases, though such mechanisms have been thoroughly discussed.[16,17]

Conclusions

In this population-based cohort study, exposure to ACT in the late preterm-born and term-born children was significantly associated with a higher risk of infectious diseases in children during the first four years of life as implicated by inpatient treatment days, episodes, and specialized care treatment visits for infectious diseases. In contrast, in the very-to-moderate preterm-born children ACT conferred benefits as implicated by inpatient treatment days and episodes at the age of 3–4 years. These findings call for careful consideration of risks and benefits of ACT when deciding upon treatment, and in extension of treatment beyond 34 gestational weeks.

Contributors

KR, MG, EK, and TT conceived the research question and designed the study. MG accessed the data in the study and verified the underlying data. KR completed the literature review. MG completed the data analyses and KR drafted the manuscript, with support from MG, EK and TT. All authors read and approved the final manuscript. All authors confirm they had full access to all the summary statistics data in the study, and MG had full access to all the individual participant level data, and all authors accept responsibility for the decision to submit for publication.

Data sharing statement

This manuscript was prepared in accordance with the STROBE statement and the STROBE checklist can be found in the appendix. Individual participant data that underlie the results are reported in this Article (after de-identification). In accordance with the Finnish data protection laws, these data cannot be made publicly available. Interested researchers who provide a methodologically sound proposal can obtain access to deidentified data with permission from the register authority. Proposals should be directed to the Finnish Social and Health Data Permit Authority Findata (findata.fi/en/). To gain access to the data, the researchers will need to attest to and sign a data-access agreement.

Declaration of interests

KR has received research grants from the Academy of Finland, and HiLife Fellows Programme, European Commission, and Norface DIAL programme. EK has received research grants from the Academy of Finland, Sigrid Juselius foundation, Foundation for pediatric research, Sigrid and Ane Gyllnberg foundation, Jalmari and Rauha Ahokas foundation, Yrjö Jahnsson foundation, Novo Nordisk foundation, Finska Läkareselsskapet, European Commission, and Norface DIAL programme. All other authors declare no competing interests.

Acknowledgements

NA.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2023.100750.

References

1 Lawn JE, Ohuma EO, Bradley E, et al. Small babies, big risks: global estimates of prevalence and mortality for vulnerable newborns to accelerate change and improve counting. *Lancet*. 2023;401:1707–1719.
2 Raju TNK, Buist S, Blaisdell CJ, Moxey-Mims M, Saigal S. Adults born preterm: a review of general health and system-specific outcomes. *Acta Paediatr*. 2017;106:1409–1437.
3 Kajantie E, Strang-Karlsson S, Evensen KAI, Haaramo P. Adult outcomes of being born late preterm or early term - what do we know? *Semin Fetal Neonatal Med*. 2019;24:66–83.
4 Eves R, Mendonca M, Baumann N, et al. Association of very preterm birth or very low birth weight with intelligence in adulthood: an individual participant data meta-analysis. *JAMA Pediatr*. 2021;175:e211058.
5 Risnes K, Bilsteen JF, Brown P, et al. Mortality among young adults born preterm and early term in 4 nordic nations. *JAMA Netw Open*. 2021;4:e2032779.
6 McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 2020;12:CD004454.
7 Dagklis T, Sen C, Tsakiridis I, et al. The use of antenatal corticosteroids for fetal maturation: clinical practice guideline by the WAPM-World Association of Perinatal Medicine and the PMF-Perinatal Medicine foundation. *J Perinat Med*. 2022;50:375–385.
8 Norman J, Shennan A, Jacobsson B, Stock SJ, Birth FWGfP. FIGO good practice recommendations on the use of prenatal corticosteroids to improve outcomes and minimize harm in babies born preterm. *Int J Gynaecol Obstet*. 2021;155:26–30.
9 Committee on Obstetric P. Committee opinion No. 713: antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2017;130:e102–e109.
10 WHO. *WHO recommendations to improve preterm birth oucomes*; 2015. https://www.who.int/publications/i/item/9789241508988.
11 Sweet DG, Carnielli VP, Greisen G, et al. European consensus guidelines on the management of respiratory distress syndrome: 2022 update. *Neonatology*. 2023;120:3–23.
12 Räikkönen K, Gissler M, Kajantie E. Associations between maternal antenatal corticosteroid treatment and mental and behavioral disorders in children. *JAMA*. 2020;323:1924–1933.
13 Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med*. 2016;374:1311–1320.
14 Hutcheon JA, Liauw J. Improving the external validity of antenatal late preterm steroids trial findings. *Paediatr Perinat Epidemiol*. 2022;37(1):1–8.
15 Sotiriadis A, Makrydimas G, Papatheodorou S, Ioannidis JP, McGoldrick E. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. *Cochrane Database Syst Rev*. 2018;8:CD006614.
16 Solano ME, Holmes MC, Mittelstadt PR, Chapman KE, Tolosa E. Antenatal endogenous and exogenous glucocorticoids and their impact on immune ontogeny and long-term immunity. *Semin Immunopathol*. 2016;38:739–763.
17 Solano ME, Arck PC. Steroids, pregnancy and fetal development. *Front Immunol*. 2019;10:3017.
18 Doyle LW, Kitchen WH, Ford GW, Rickards AL, Lissenden JV, Ryan MM. Effects of antenatal steroid therapy on mortality and morbidity in very low birth weight infants. *J Pediatr*. 1986;108:287–292.
19 Smolders-de Haas H, Neuvel J, Schmand B, Treffers PE, Koppe JG, Hoeks J. Physical development and medical history of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome: a 10- to 12-year follow-up. *Pediatrics*. 1990;86:65–70.
20 Räikkönen K, Gissler M, Tapiainen T, Kajantie E. Associations between maternal antenatal corticosteroid treatment and psychological developmental and neurosensory disorders in children. *JAMA Netw Open*. 2022;5:e2228518.
21 Suomen Perinatologinen Seura. Kortikosteroidihoito ennenaikaisen synnytyksen uhatessa. Suomen perinatologisen seuran asettama hoitosuositustyöryhmä. Corticosteroid treatment at risk of preterm delivery. Guideline committee set by finnish perinatal society. *Duodecim*. 2000;116:1334–1338.
22 Duodecim. Kortikosteroidihoito ennenaikaisen synnytyksen uhatessa. Suomalaisen Lääkäriseuran Duodecimin ja Suomen Perinatologisen Seura RY:n asettama hoitosuositustyöryhmä. [Corticosteroid treatment at risk of preterm delivery. Guideline committee set by Finnish Medical Society Duodecim and Finnish Perinatal Society]. *Duodecim*. 2009;125:1579.
23 Duodecim. *Ennenaikainen synnytys. Käypä hoito -suositus. Suomalaisen Lääkäriseuran Duodecimin ja Suomen Gynekologiyhdistyksen Seuran asettama työryhmä* [Preterm delivery. Current care guideline recommendation. Working group of Finnish Medical Society Duodecim and The Finnish Society of Obstetrics and Gynaecology]. Helsinki: Suomalainen Lääkäriseura Duodecim; 2018. Available at: www.kaypahoito.fi. Accessed December 27, 2022.
24 Sund R. Quality of the Finnish hospital discharge register: a systematic review. *Scand J Public Health*. 2012;40:505–515.
25 Miller JE, Carter KW, de Klerk N, Burgner DP. The familial risk of infection-related hospitalization in children: a population-based sibling study. *PLoS One*. 2021;16:e0250181.
26 Tegethoff M, Pryce C, Meinlschmidt G. Effects of intrauterine exposure to synthetic glucocorticoids on fetal, newborn, and infant hypothalamic-pituitary-adrenal axis function in humans: a systematic review. *Endocr Rev*. 2009;30:753–789.
27 Buttgereit F, da Silva JAP, Boers M, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis*. 2002;61:718–722.
28 Del Riccio M, Spreeuwenberg P, Osei-Yeboah R, Johannesen CK, Vazquez Fernandez L, Teirlinck AC. Burden of respiratory syncytial virus in the European union: estimation of RSV-associated hospitalizations in children under 5 years. *J Infect Dis*. 2023:jiad188.