Population Improvement Bias Observed in Estimates of the Impact of Antenatal Steroids to Outcomes in Preterm Birth

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Objective To examine the hypothesis that increasing rates and differential uptake of antenatal steroids would bias estimation of impact of antenatal steroids on neonatal death and severe (grade III-IV) intraventricular hemorrhage (IVH).

Study design The study population included infants born between 24 and 28 weeks of gestational age in the California Perinatal Quality Care Collaborative. Outcomes were in-hospital mortality and severe IVH. Mixed multivariable logistic regression models estimated the effect of antenatal steroid exposure, one model accounting for individual risk factors as fixed effects, and a second model incorporating a predicted probability factor estimating overall risk status for each time period.

Results The study cohort included 28 252 infants. Antenatal steroid exposure increased from 80.1% in 2005 to 90.3% in 2016, severe IVH decreased from 14.5% to 9.0%, and mortality decreased from 12.8% to 9.1%. When stratified by group, 3-year observed outcomes improved significantly in infants exposed to antenatal steroids (12.5%-8.6% for IVH, 11.5%-8.8% for death) but not in those not exposed (20.7%-19.1% and 16.6%-15.5%, respectively). Women not receiving antenatal steroids had greater risk profile (such as no prenatal care) and greater predicted probability for severe IVH and mortality. Both outcomes exhibited little change ($P > .05$) over time for the group without antenatal steroids. In contrast, in women receiving antenatal steroids, observed and adjusted rates for both outcomes decreased ($P < .0001$).

Conclusions As the population's proportion of antenatal steroid use increased, the observed positive effect of antenatal steroids also increased. This apparent increase may be designated as the "population improvement bias." *(J Pediatr 2021;232:17-22)*.

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Multiple studies have reported that the administration of antenatal steroids to women threatening preterm delivery is associated with both crude and risk-adjusted reductions in the rates of death and severe intraventricular hemorrhage (IVH).[1-5] A typical strategy to assess this association has been to compare the rates of outcomes in the births exposed to antenatal steroids with the rates seen in the infants not exposed to antenatal steroids, after accounting for site of care as a random effect and identified risk factors as fixed effects in risk adjustment.[2] This strategy has a potential limitation in that there may be unidentified risk factors and mediators that also may influence both the administration of antenatal steroids and the outcomes and could therefore, unknowingly bias the estimates of associated risk.

A hypothetical case may involve an intervention, such as antenatal steroids, that gradually increases in uptake over time through quality-improvement activities.[6,7] The risk profile of those who receive and those who do not receive the intervention will initially be similar with respect to both identified and unidentified risk factors, yielding a relative risk of X for the intervention. As the overall population level of a potentially effective intervention increases, the risk profile of those who do not receive the intervention may change in the direction of an increasingly adverse profile. The increasing risk disparity created by selective adoption of the intervention will then inflate the estimate of its potential impact, yielding a relative risk greater than X. This risk disparity would potentially be composed of 2 components: an increase in identified risk factors that can be adjusted for in the estimation models; and an increase in unidentified risk factors and unidentified mediators. In this scenario, we hypothesize that "population-improvement bias" will be generated by an increase in unidentified risk factors or mediators in those patients who do not receive the intervention.

The neonatal intensive care units (NICUs) of the California Perinatal Quality Care Collaborative (CPQCC) care for more than 90% of all infants of very low

CPQCC	California Perinatal Quality Care Collaborative
IUGR	Intrauterine growth restriction
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
ROP	Retinopathy of prematurity

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birth weight born in California. During the period 2005-2016 across 132 member NICUs, antenatal steroid use increased from 80.1% to 90.3%. The purpose of this study was to examine the hypothesis that this improvement in the use of antenatal steroids would bias the most recent estimation of its potential impact on the rates of neonatal death and severe IVH. Specifically, we hypothesize that for infants not exposed to antenatal steroids compared with those exposed to antenatal steroids, both the observed and the risk-adjusted relative risk of death and severe IVH estimated in years after increased antenatal steroid use would appear to be significantly improved than the estimates obtained in earlier years.

Methods

The study population was derived from the CPQCC database from 2005 to 2016. CPQCC has standardized data collection across its member hospitals, aligning with definitions developed by the Vermont Oxford Network.[8,9] The number of infants between $24^{0/7}$ weeks and $28^{6/7}$ during the study period was 30 253. We excluded infants who died in the delivery room (n = 673), who were previously discharged home (n = 30), and those whose antenatal steroid administration status and/or outcomes was unknown (n = 1298). The resulting cohort consists of 28 252 eligible infants.

The intervention under consideration was the administration of any dose of antenatal steroids in women before preterm delivery. The definition included betamethasone, dexamethasone, and hydrocortisone and did not distinguish complete or incomplete dosing or timing of dosing. Outcomes examined were death before discharge from the NICU (neonatal mortality) and severe (grade III-IV) IVH. We performed univariable and multivariable analyses to estimate the association of antenatal steroids on the outcomes over time. To obtain more stable estimates, we used four 3-year blocks of data (2005-2007, 2008-2010, 2011-2013, 2014-2016). For univariable analysis, we derived the outcome rates stratified by antenatal steroid status in each birth year period and estimated the relative risk. Patient characteristics were compared using the χ^2 test between women who received antenatal steroids and those who did not. For multivariable analyses, we used 2 mixed logistic regression modeling methods to examine the potential change in the effect of the intervention over the study period. In both models, location of birth or first collaborative hospital was considered as a random effect, and 13 identified risk factors as fixed effects. The first model was a risk adjustment model including maternal/infant risk factors: gestational weeks, maternal age, prenatal care, intrauterine growth restriction (IUGR), maternal diabetes, hypertension, race, cesarean delivery, male sex, multiple gestation, outborn status, 5-minute Apgar score, and a recently reported important mediator for improved severe IVH, intubation during delivery room resuscitation.[2] In addition to the 13 identified risk factors, birth year also was included as four 3-year blocks to account for temporal trends. The exposure variable of antenatal steroids and the interaction between birth year and antenatal steroid status also were added to estimate the effect of intervention over time.

In the second model, to assess the possibility that as the percent of the population receiving antenatal steroids increased, the known risks for severe IVH and for neonatal death also increased in the cohort that did not receive antenatal steroids, we used the 13-risk factor model to estimate the summarized overall risk status. We computed the predicted probability for each of the 4 periods by antenatal steroid status to compare the predicted probability for neonatal death and severe IVH in the 2 cohorts across the 4 periods.

As a sensitivity analysis to assess the potential impact of unmeasured confounders on our results, we calculated E-values based on the estimates derived from the risk adjusted models.[10] To assess if the risk factors that generate the hypothesized improvement bias for neonatal death and severe IVH in women who do not obtain antenatal steroids also may influence effects observed for other outcomes, we examined the rates of neonatal infection, necrotizing enterocolitis (NEC), and severe retinopathy of prematurity (ROP), outcomes that are not purported to be associated with antenatal steroid use, in women who received and did not receive antenatal steroids over the study period. We hypothesized that if the increased risks associated with the antenatal steroid improvement bias were specific only for neonatal death and severe IVH, then over time, the rates of infection, NEC, and ROP would be similar in the antenatal steroids and nonantenatal steroids groups.

This study was reviewed and approved by the Stanford University institutional review board. All statistical analyses were performed using SAS 9.4 (SAS Institute).

Results

In the study cohort of 28 252 infants with a gestational age of 24-28 completed weeks of gestation, the administration of antenatal steroids rose from 80.1% in 2005 to 90.3% in 2016, the overall incidence of severe IVH decreased from 14.5% to 9.0%, and death before discharge decreased from 12.8% to 9.1%. These trends grouped into 3-year time periods were markedly different in the infants of women who did and did not receive antenatal steroids (**Table I**: observed rates). Although substantial decreases were seen in infants who had been exposed to antenatal steroids, both severe IVH and death did not significantly decrease in infants who had not been exposed to antenatal steroids.

Table II shows the known characteristics of the 2 cohorts. Over the period 2005-2016, women who received antenatal steroids had a greater percentage of prenatal complications such as diabetes, hypertension, and IUGR, as well as multiple gestations and cesarean delivery. The rate of diabetes increased over time for both cohorts (trend test $P < .001$); however, hypertension and IUGR were increased for the group who had antenatal steroids (trend test $P < .001$), whereas it decreased for those without antenatal

Table I. Observed relative risks of death or severe IVH by antenatal steroid status over time

	Population		Death			Severe IVH		
Time periods	N	% Antenatal steroids	Antenatal steroids –	Antenatal steroids +	Relative risk*	Antenatal steroids –	Antenatal steroids +	Relative risk*
2005-2007	7491	79.5%	16.6%	11.5%	0.70	20.7%	12.5%	0.60
2008-2010	7223	84.4%	15.6%	10.8%	0.69	22.3%	12.0%	0.54
2011-2013	6751	86.7%	15.2%	9.1%	0.60	21.2%	10.4%	0.49
2014-2016	6787	89.2%	15.5%	8.8%	0.57	19.1%	8.6%	0.45

*Relative risks for antenatal steroids positive compared with antenatal steroids negative.

Table II. Patient characteristics by antenatal steroid status

	No antenatal steroids N = 4290		Antenatal steroids N = 23 962		
Characteristics	n	%	n/N	%	*P* value
Maternal age, y					
<20	648/4275	15.2	1898/23 937	7.9	<.0001
20-29	1948/4275	45.6	9907/23 937	41.4	–
30-39	1487/4275	34.8	10 579/23 937	44.2	–
40+	192/4275	4.5	1553/23 937	6.5	–
Prenatal care					
Yes	3687/4251	86.7	23 307/23 903	97.5	<.0001
Fetal anomaly					
Yes	51/4179	1.2	420/23 665	1.8	.01
Fetal distress	949/4178	22.7	5421/23 665	22.9	.78
IUGR	168/4179	4	2003/23 665	8.5	<.0001
Maternal diabetes	226/4180	5.4	2495/23 690	10.5	<.0001
Maternal hypertension	510/4180	12.2	5060/23 691	21.4	<.0001
Maternal race					
Black	622/4254	14.6	3282/23 841	13.8	<.0001
Hispanic	2148/4254	50.5	11 039/23 841	46.3	–
Non-Hispanic white	935/4254	22	6282/23 841	26.3	–
Asian/Pacific Islander	418/4254	9.8	2603/23 841	10.9	–
Native American	29/4254	0.7	160/23 841	0.7	–
Other	102/4254	2.4	475/23 841	2	–
Cesarean delivery	2699/4290	62.9	17 306/23 956	72.2	<.0001
Gestational age at birth, wk					
24	671/4290	15.6	3370/23 962	14.1	.0698
25	725/4290	16.9	4038/23 962	16.9	–
26	840/4290	19.6	4710/23 962	19.7	–
27	962/4290	22.4	5441/23 962	22.7	–
28	1092/4290	25.5	6403/23 962	26.7	–
Sex					
Female	1962/4290	45.7	11 255/23 958	47	.1327
Male	2328/4290	54.3	12 703/23 958	53	–
Multiple gestation	780/4290	18.2	6025/23 962	25.1	<.0001
Location of birth					
Inborn	2936/4290	68.4	21 580/23 962	90.1	<.0001
Outborn	1354/4290	31.6	2382/23 962	9.9	–
Apgar score at 5 min					
<3	491/4136	11.9	1400/23 915	5.9	<.0001
4-7	1939/4136	46.9	9720/23 915	40.6	–
7-10	1706/4136	41.2	12 795/23 915	53.5	–
Birth weight, g					
≤750	1007/4290	23.5	6632/23 962	27.7	<.0001
751-1000	1632/4290	38	9118/23 962	38.1	–
1001-1250	1193/4290	27.8	6148/23 962	25.7	–
>1250	458/4290	10.7	2064/23 962	8.6	–
Any IVH	1852/4290	43.2	7393/23 962	30.9	<.0001
Severe IVH	898/4290	20.9	2603/23 962	10.9	<.0001
Mortality	680/4290	15.9	2412/23 962	10.1	<.0001
Delivery room intubation	3176/4278	74.2	15 672/23 949	65.4	<.0001

steroids (trend test $P = .01$ for hypertension; not significant for IUGR). Women who did not receive antenatal steroids were more likely to be <20 years old, not receiving prenatal care, and having infants who were outborn, with lower Apgar scores, and were more often intubated in the delivery room.

To assess the overall risk status of the 2 cohorts and examine the hypothesis that the observed lack of improvement in women who did not receive antenatal steroids in regard to death and severe IVH was in part due to a differential increase in the known risk profile of women who did not receive antenatal steroids, we calculated the predicted probability of outcomes for each time period by antenatal steroid status. Both maternal risk factors and the recently identified mediator, intubation in the delivery room, were included for each period's estimate. Across all study periods, the average predicted probability for severe IVH and neonatal death was greater in women who did not receive antenatal steroids (**Figure 1**, A and B). However, for both outcomes, there was little change over the 2005-2016 study periods for the group without antenatal steroids (**Figure 1**, A and B: trend test not significant). Although the antenatal steroid group experienced stable risk for death, there was a decrease in the estimated probability for severe IVH ($P < .001$) for antenatal steroids. These findings reject the hypothesis that as the population's percentage of antenatal steroid use increased, the observed lack of improvement in women who did not receive antenatal steroids was in part due to a progressive increase in their known risk status.

To assess the widening gap in the outcomes of the women who received and the women who did not receive antenatal steroids on the potential effectiveness of antenatal steroids, we estimated the adjusted rates of severe IVH and neonatal death in these 2 cohorts and their ORs using mixed logistic regression with location of birth designated as a random effect and 13 risk factors, birth year, and antenatal steroid administration as fixed effects. The interaction of antenatal steroids and birth year also was included to examine whether the trend of the outcome rates was different between the group that received and did not receive antenatal steroids. For both outcomes, the adjusted rates for women who received the intervention decreased ($P < .0001$), whereas the rates for the women who did not receive antenatal steroids showed no improvement ($P = .27$ for severe IVH, $P = .94$ for neonatal death, **Figure 2**, A and B [available at

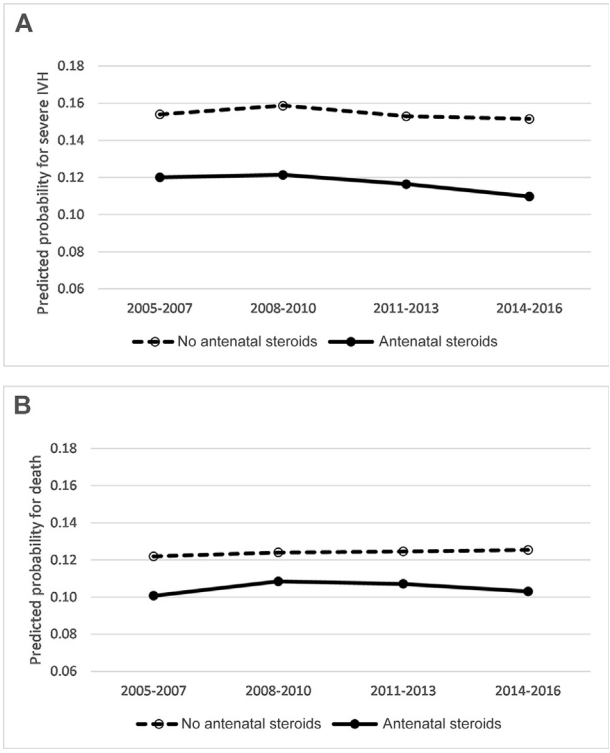

Figure 1. Predicted probability by antenatal steroid status for **A,** severe IVH—trend test $P < .001$ for antenatal steroid group/not significant for no antenatal steroid group; and **B,** neonatal death—trend test not significant for both groups.

www.jpeds.com]). The change in risk aORs over the study period is shown in **Table III**. Note that as the population's percent of antenatal steroids increases, there is also an apparent increase in the effectiveness of the intervention. We designate this apparent increase as the "population improvement bias."

In sensitivity analysis, E-values (CI limit that is closer to the null in parenthesis) were 2.86 (2.51) and 2.21 (1.87) during the overall study periods for severe IVH and neonatal death, respectively. This suggests that considerable unmeasured confounders would be needed to fully explain away the observed findings between antenatal steroids and outcomes.

Table III. Risk aORs for outcomes by antenatal steroid status

Years	% Antenatal steroids	OR	95% CI
Severe IVH			
2005-2007	79.5%	0.67	(0.57-0.80)
2008-2010	84.4%	0.57	(0.48-0.68)
2011-2013	86.7%	0.50	(0.41-0.61)
2014-2016	89.2%	0.53	(0.42-0.67)
Death			
2005-2007	79.5%	0.82	(0.69-0.99)
2008-2010	84.4%	0.69	(0.57-0.85)
2011-2013	86.7%	0.59	(0.47-0.75)
2014-2016	89.2%	0.62	(0.49-0.80)

Over the time period 2005-2016, the improvements in perinatal care have resulted in an overall decreasing incidence of key neonatal outcomes including death, severe IVH, nosocomial infection, NEC, and severe ROP.[11] However, when infants were placed into groups based on antenatal steroid exposure, no improvements in the rates of severe IVH and neonatal death were seen in infants who had not been exposed to antenatal steroids. To examine whether factors that have held back improvement in severe IVH and death in these infants also would hold back improvement in other neonatal morbidities, the outcomes of nosocomial infection, severe ROP, and NEC were examined by maternal antenatal steroid status (**Figure 3**, A-C; available at www.jpeds.com). For the 2 cohorts, observed improvements were similar for nosocomial infection over all 4 study periods and for NEC and severe ROP over the first 3 periods. This suggests that in large part, the unidentified risk factors and mediators that are responsible for the lack of temporal improvement in severe IVH and death are specific for these 2 outcomes.

Discussion

The main objective of this study was to examine the phenomenon of population improvement bias. This bias would result if when an increasing percentage of a population receives an intervention, the risk profile of those who do not receive the intervention also increases. This risk profile consists of both known and unknown risk factors and mediators. We hypothesized that in the case of antenatal steroids, as the intervention became more prevalent, an increasing risk profile of those who did not receive the intervention would increase the estimation of the relative risk (ie, the relative effectiveness) of the intervention. The effectiveness of antenatal steroids for preterm birth has been shown in meta-analyses of randomized trials, including reduction of death, IVH, and respiratory distress syndrome.[12] Observational studies extend the populations and outcomes assessed in randomized trials.[13-15] These more recent observational studies, performed after a period of increasing uptake of antenatal steroids, may be prone to population improvement bias.

We found that over the 12-year period, as the proportion of the population who received antenatal steroids increased, severe IVH and neonatal death showed dramatic improvement in the infants exposed to antenatal steroids but failed to improve in the infants who did not receive antenatal steroids. Because the improvement was seen in infants with antenatal steroid exposure throughout the 12-year time period, the improvement was most likely the result of the introduction of new approaches to care designed to reduce the risk of severe IVH and resultant mortality, such as better fluid management, decreased stimulation, midline head control, and other neuro-centric practices.[16] As location of care was modeled as a random effect, there should have been no

major influence of differences in access of patients who received and did not receive antenatal steroids to these advancements in care. Therefore, the lack of improvement in the group of infants that did not receive antenatal steroids could be due to a lack of responsiveness to these improvements in care. Alternatively, they may have potentially benefited from these improvements, but their greater risk profile counterbalanced the benefits. This risk profile may be a combination of measured and unmeasured factors.

An unexpected finding was that predicted probability for severe IVH and death in the group of infants that did not receive antenatal steroids was not elevated as the population's rate of antenatal steroids increased, suggesting that their increased risk status was due to unidentified factors. A second unexpected finding was that these factors were highly specific for severe IVH and death. Over the 12-year period, the improvement in the observed rates of nosocomial infection, NEC and ROP were similar regardless of maternal antenatal steroid status.

Identifying the source of the increased risk, that is, identifying those factors that held back improvement in the rates of severe IVH and death in those who did not receive antenatal steroids requires further inquiry. It is notable that the infants who did not receive antenatal steroids tended to have a profile of identified risk factors that was quite different from those who received antenatal steroids (**Table II**). For example, their greater rate of teen pregnancy, poor prenatal care, and outborn status may have limited opportunity to receive antenatal steroids. However, the pattern of these endowments was unchanged as population levels of antenatal steroids use increased. Furthermore, even after adjusting for the 13 known risks and mediators, the rates of severe IVH and neonatal death still failed to show improvement in the infants who were not exposed to antenatal steroids. It may be possible that some of their unidentified risk factors are related to conditions that lead to relatively quick delivery after onset of preterm labor, forestalling the ability to receive antenatal steroids. Infants not exposed to antenatal steroids in later time periods may indicate a situation in which they may have not received or responded to other interventions that led to improvement in infants that were exposed to antenatal steroids. The likelihood of receiving a beneficial treatment may be correlated with antenatal steroid exposure, and such a treatment may be an intervention that is not measured or can be simplified into one variable. Sensitivity analysis using E-value indicated that such an unmeasured confounder needs to be associated with both antenatal steroids and severe IVH or neonatal death by an OR of at least 2.0 to explain away the association.

A limitation of our study is the lack of timing of antenatal steroid administration. The benefit of antenatal steroids in preterm birth for various outcomes may depend on timing, with some indication that the outcome of IVH may be most influenced when the timing of administration occurs between 24 and 48 hours before birth.[17] Differential trends in timing of antenatal steroid administration among groups also could introduce bias. We also lacked data on whether there was a decision before birth for withholding resuscitation or intensive care, a case in which there also may be withholding of antenatal steroids. We did exclude delivery room deaths, a situation that could signify a plan on the part of the family and clinical team to withhold interventions. We also excluded infants born before 24 weeks of gestational age, a population that may benefit significantly from antenatal steroids.

Finally, this study emphasizes that even when there is strong clinical and laboratory evidence of a causal relationship between an intervention and an outcome, a modeled relative risk or OR should not be assumed to reflect the entire causal impact. As in the case of antenatal steroids, the observed association also may depend upon benefit derived from associated but unidentified factors and mediators. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

More Than 50 Years of the "Thoracic Squeeze"

Adams FH, Yanagisawa M, Kuzela D, Martinek H. The Disappearance of Fetal Lung Fluid Following Birth. J Pediatr 1971;78:837-43.

In utero, lung development is facilitated through the secretion of lung fluid and fetal breathing movements that move fluid in and out of the airways. This fetal lung fluid must be cleared rapidly at the time of birth to enable gas exchange with the first breaths. Understanding how this amazing process occurs so quickly has been of longstanding interest to pediatricians. Fifty years ago in *The Journal of Pediatrics*, Adams et al reported clearance of lung fluid in fetal and neonatal rabbits delivered vaginally and by cesarean. They found that the lungs of some rabbits born by cesarean were not fully aerated until after 6 hours of breathing, whereas those who delivered vaginally seemed to be completely aerated after 10 minutes. Adams et al speculated that these immediate differences in lung fluid may have been at least partially due to the compression of the thorax that had recently been demonstrated during vaginal birth.

Similar to newborn rabbits, human infants delivered by cesarean have higher rates of retained fetal lung fluid and higher rates of transient tachypnea of the newborn. During the 50 years since the publication of this study, the lack of a "thoracic squeeze" during cesarean deliveries has been an intuitive explanation to many parents of infants with transient tachypnea. However, additional research has shown that the process is more complex and begins during late gestation with changes in the epithelial sodium channels.[1] Although transient tachypnea is generally regarded as a benign condition, more research is needed on this illness because it is a common reason for neonatal intensive care unit admission. Finding ways to decrease the incidence or severity of transient tachypnea would give more infants a healthy start and decrease the separation of families at this important time of life.

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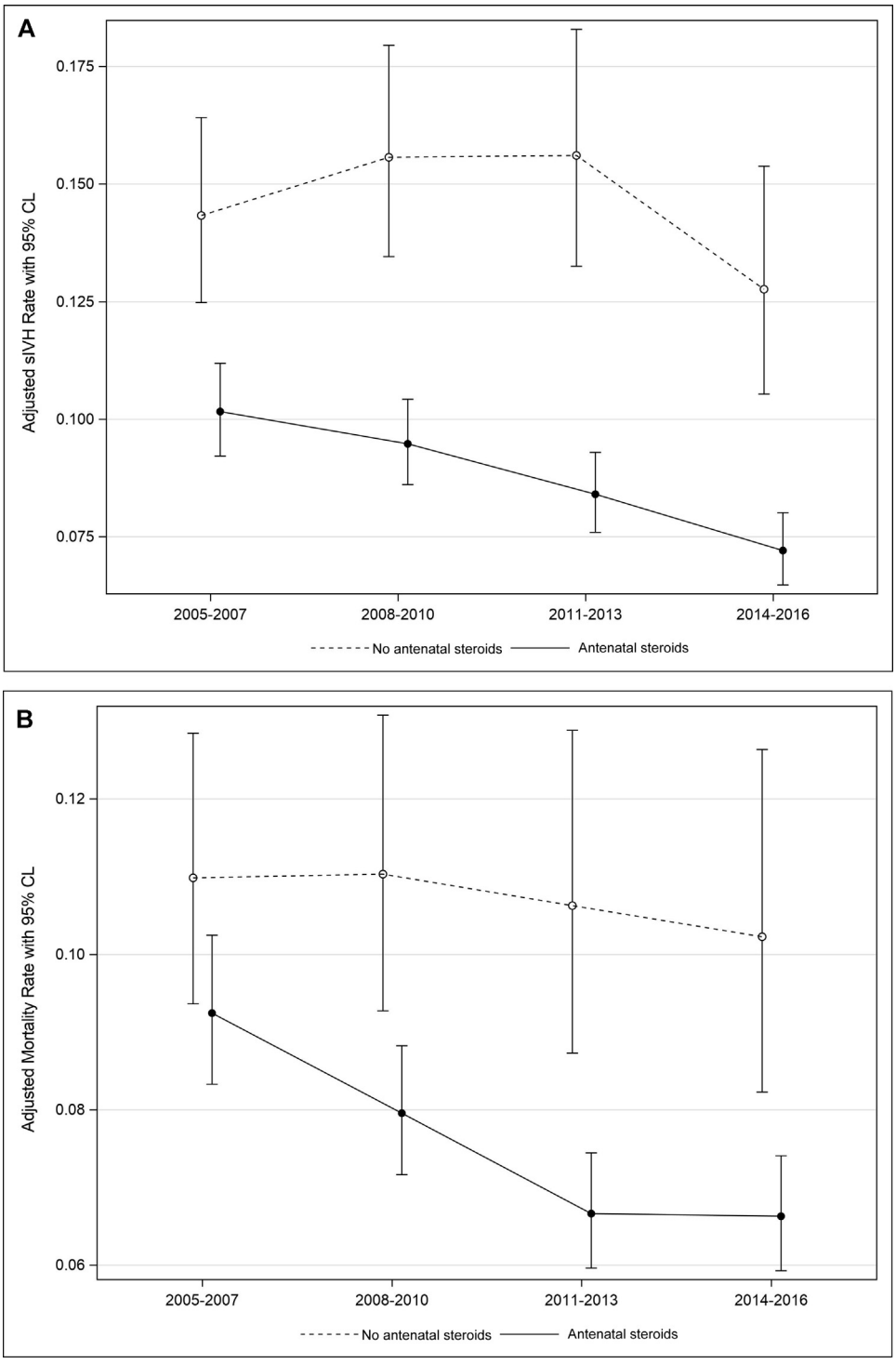

Figure 2. Adjusted rates by antenatal steroid status for **A,** severe IVH—trend test $P < .0001$ for antenatal steroid group/not significant for no antenatal steroid group; and **B,** neonatal death—trend test $P < .0001$ for antenatal steroid group/not significant for no antenatal steroid group. *CL*, confidence limit.

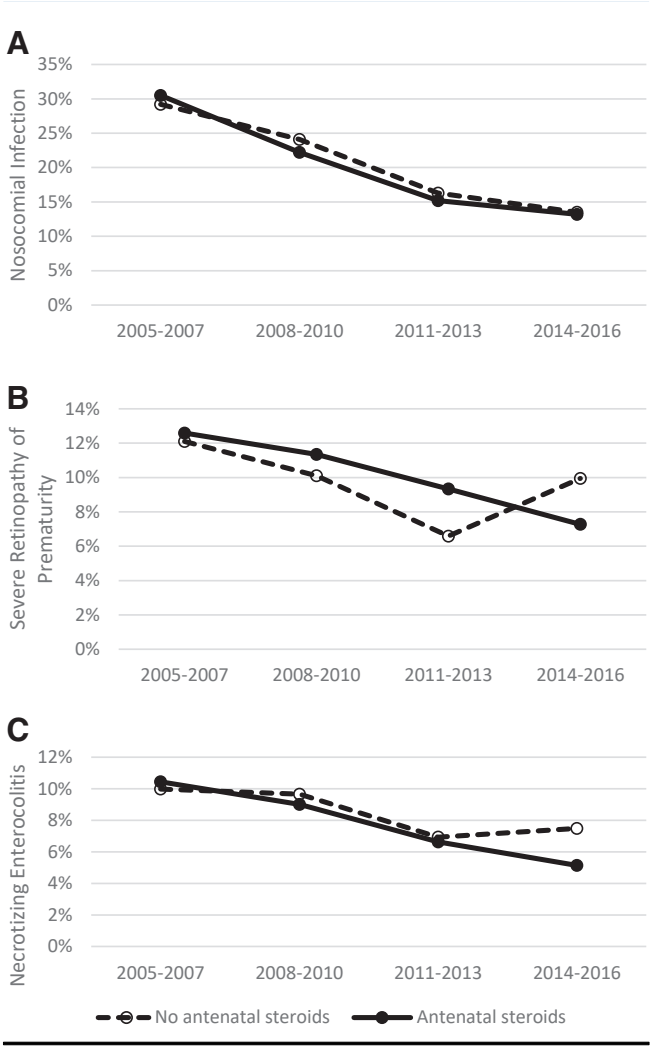

Figure 3. Trends in outcomes over time by antenatal steroid status for **A,** nosocomial infection; **B,** severe ROP; and **C,** NEC.