Antenatal Corticosteroids and Outcomes in Preterm Twins

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Short title

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Précis

Antenatal corticosteroids for preterm twins improve outcomes similar to those in singletons,

irrespective of chorionicity or birth order.

Abstract

OBJECTIVE: To estimate whether improvement in outcomes from antenatal corticosteroid (ACS) treatment in extremely and very preterm twins is similar to that observed in singletons, and to investigate whether ACS treatment has different effects according to chorionicity or birth order.

METHODS: This population-based study was based on an analysis of data collected by the Neonatal Research Network of Japan from 2003 to 2015 of neonates weighing 1,500 g or less at birth, from gestational ages of 24 and 0/7 weeks to 31 and 6/7 weeks. After propensity score matching, univariate logistic and interaction analyses were performed to compare short-term (neonatal period) and medium-term (3 years of age) outcomes of the infants of mothers who received ACS with those of infants of mothers who did not receive ACS. We focused on differences between singletons and twins, between monochorionic and dichorionic twins and between the first and second twin.

RESULTS: The study comprised 23,502 singletons and 6,546 twins. Antenatal corticosteroid treatment was associated with a significant decreased short-term neurological outcomes in both singletons and twins. However, ACS treatment was associated with significantly decreased mortality (OR 0.61; 95% CI [0.53–0.70]), respiratory distress syndrome (0.71 [0.67–0.76]),

and cerebral palsy (0.85 [0.72–0.99]) in singletons but not in twins (0.89 [0.68–1.17], 0.99 [0.87–1.12], and 0.82 [0.61–1.11], respectively). No association was found between chorionicity and the efficacy of ACS treatment on outcomes. Further, no association was found between birth order and the efficacy of ACS treatment on outcomes, except for periventricular leukomalacia and necrotizing enterocolitis (interaction: $p = 0.02$ and $p = 0.04$, respectively).

CONCLUSION: Antenatal corticosteroid treatment in twins was associated with a beneficial effect on short-term neurological outcomes only, without improvement in other short- and medium-term outcomes. There was no difference related to chorionicy.

INTRODUCTION

The incidence of twin births has increased substantially in the past few decades throughout the world, mainly as a result of older maternal age and widespread use of fertility treatments.(1) More than 60% of twin pregnancies are complicated by preterm birth, and approximately 10% of twins are delivered at less than 32 weeks' gestation, which is estimated to be approximately 8.6 times the incidence of preterm birth of singletons.(2)

A single course of antenatal corticosteroid (ACS) has become the standard of care for women at risk of imminent preterm birth at less than 34 weeks of pregnancy for reducing rates of neonatal mortality and morbidity.(3, 4) However, the efficacy of ACS treatment among certain subgroups of pregnant women, such as those with multiple pregnancy, fetal growth restriction, and chorioamnionitis, has not been fully evaluated.(3, 5, 6)

According to a recent Cochrane review in 2017, ACS treatment was associated with a significant reduction in the incidences of perinatal death by 31%, respiratory distress syndrome (RDS) by 32%, and intraventricular hemorrhage (IVH) by 44% in twins; these reductions were similar in magnitude to those observed in singletons.(3) On the other hand, according to the recommendations of the World Health Organization in 2015, ACS treatment is recommended in cases of multiple pregnancy, but its effectiveness remains uncertain.(7) Furthermore, recent studies with large populations have demonstrated that ACS treatment in preterm twins was

associated with decreased risk of mortality; however, ACS treatment was unrelated to benefit in rates of neurodevelopmental impairment or short-term morbidity.(8, 9) Current evidence on the effectiveness of ACS treatment in twins regarding neonatal complications, except for mortality, remains limited. In addition, little evidence is available regarding the effect of ACS treatment on early childhood outcomes in preterm twins.

Our aim was to evaluate the association of ACS treatment on short-term (neonatal period) and medium-term (3 years of age) outcomes in extremely and very preterm twins by using propensity score matching. Propensity score matching analysis is a useful tool for reducing risk of bias, which is often observed in retrospective observational studies. In addition, we sought to investigate whether ACS treatment has different effects according to chorionicity and birth order.

METHODS

In this population-based study, we analyzed data from a registry on extremely and very preterm neonates from the Neonatal Research Network of Japan (NRNJ) from January 2003 to December 2015. Approximately 200 facilities with levels II and III NICUs, which are similar to the level designations in the US, participate in the NRNJ. More than 4,000 infants born before the age of 32 gestational weeks and weighing 1,500 g or less are registered in the database each year. Exclusion criteria were gestational age of less than 24 weeks, higher-order

multiple birth infants (such as triplets and quadruplets), major congenital abnormality, transfer from other facilities, co-twin fetal death, and incomplete medical record. In this study, only women with complete data about maternal and neonatal characteristics were eligible to perform propensity score matching and for the improvement of data reliability. Appendix 1, available online at http://links.lww.com/xxx, lists the baseline characteristics of singletons and twins with and without complete data.

Information included maternal and neonatal characteristics and offspring complications during the neonatal period and at 3 years of age; information was anonymized before analysis. Data administrators in the NRNJ data center checked the data quality of clinical information, and asked the data abstractors at each facility to verify the correction of these data if necessary. Informed consent was obtained from all parents at each facility. The use of data in this study was authorized by the Japan Neonatal Network Executive Committee, and this study protocol was approved by the Institutional Ethics Board of Nagoya University (approval number 2018-0026).

The guideline for obstetric practice in Japan recommends two intramuscular doses of 12 mg of betamethasone given 24 hours apart as ACS treatment.(10) Although information about the dose, type of corticosteroid, and administration-to-birth interval of ACS treatment was not available in the NRNJ database, we assumed that the majority of women in this study received

a single course of betamethasone following the guidelines because Japanese health insurance covered only a single course of betamethasone as ACS treatment.

Hypertensive disorders of pregnancy were defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or both after 20 weeks of gestation.(11) Clinical chorioamnionitis was defined as the presence of maternal fever (body temperature, ≥38.0°C) accompanied by one or more of the following: (1) maternal tachycardia (heart rate, ≥100 beats/min); (2) uterine tenderness; (3) malodorous vaginal discharge or amniotic fluid leakage; and (4) maternal leukocytosis (leukocyte count, ≥15,000 cells/μL).(10, 12) Small for gestational age was defined as birth weight and length below the 10th percentile for gestational age according to a sex-specific Japanese neonatal anthropometric chart from 2000.(13) The diagnosis of RDS was based on clinical manifestations and chest radiography. Chronic lung disease was defined as the infant’s need for supplemental oxygen at 36 weeks of corrected gestational age. IVH was diagnosed according to the classification of Papile et al,(14) and periventricular leukomalacia (PVL) was diagnosed with intracranial ultrasonography or magnetic resonance imaging. Neonatal sepsis was defined as clinical symptoms of bacteremia with the presence of a pathogenic bacterium from a blood culture. Necrotizing enterocolitis was diagnosed as stage 2 or higher of Bell’s criteria.(15) Treatments for retinopathy of prematurity included laser photocoagulation, cryotherapy, or anti-vascular endothelial growth

147 factor therapy. When children were 36 months of age, their neurodevelopmental status was
148 assessed at each facility with the Kyoto Scale of Psychological Development, which is widely
149 used in Japan and was reported to be comparable in scope with the Bayley Scales of Infant and
150 Toddler Development, Third Edition.(16, 17) The basic management for preterm neonates was
151 standardized across the NRNJ participating facilities, regardless of plurality of pregnancy.
152
153 The short-term outcome measures included (1) in-hospital death; (2) respiratory morbidity,
154 including RDS and chronic lung disease; (3) neurological impairment, including IVH (grade
155 III or IV) and PVL; (4) neonatal sepsis; (5) necrotizing enterocolitis; (6) treated retinopathy of
156 prematurity; and (7) composite adverse outcomes (in-hospital death, severe IVH [grade III or
157 IV], or PVL). The medium-term outcome measures at 3 years of age included (1) death after
158 NICU discharge; (2) home oxygen therapy or home respiratory therapy; (3) visual impairment;
159 (4) hearing impairment; (5) cerebral palsy; (6) development quotient of less than 70; and (7)
160 composite adverse outcomes (death after NICU discharge, cerebral palsy, or development
161 quotient of less than 70).
162
163 To generate the propensity score, maternal and neonatal characteristics were included in a
164 logistic model (ACS treatment, maternal age, parity, gestational age, mode of delivery, diabetes
165 mellitus or gestational diabetes mellitus, hypertensive disorders of pregnancy, clinical

chorioamnionitis, nonreassuring fetal status, gender, birth weight, small for gestational age, plurality of pregnancy, chorionicity, birth order, and year of delivery). Greedy nearest-neighbor matching without replacement and one-to-one pair matching were used in this study. A caliper width of 0.2 of the standard deviation of the logit of the propensity score was used for the developed propensity score, as previously recommended.(18) To evaluate the success of balancing the baseline characteristics between the matched groups (singletons and twins, monochorionic and dichorionic twins, and the first and second twin), standardized differences were estimated. In general, standardized differences with a value of less than 0.10 suggested that the variable was sufficiently balanced between the two matched groups.(19) After propensity score matching, univariate logistic regression analysis was performed to explore the association of ACS treatment and outcomes. Subgroup analysis was conducted to investigate whether the chorionicity and birth order altered the effect of ACS treatment on outcomes in twins.

Patients' categorical variables were compared in chi-squared tests, and continuous variables were compared in Student's *t* test. Univariate logistic regression analyses were performed for the binary outcomes to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the prognostic variables. To investigate whether the efficacy of ACS treatment varied across different groups (singletons versus twins, monochorionic twins versus dichorionic twins, and the first twin versus second twin), we assessed the interaction between

the group and the treatment (i.e., ACS) among propensity score-matched pairs in the multivariate models (Fig. 1). The multivariate logistic model included maternal age, parity, gestational age, mode of delivery, diabetes mellitus or gestational diabetes mellitus, hypertensive disorders of pregnancy, clinical chorioamnionitis, nonreassuring fetal status, gender, birth weight, small for gestational age, plurality of pregnancy, chorinonicity, birth order, year of delivery and ACS treatment. A *p*-value of less than 0.05 for the interaction indicated a significant difference in the effect of ACS treatment between the two groups. All analyses performed in this study were exploratory; therefore, we did not adjust the multiplicity of testing. Further, we performed additional analysis to evaluate the incidence of offspring short- and medium-term adverse outcomes stratified by gestational weeks without adjustment of covariates. In this study, a *p*-value of less than 0.05 indicated a significant difference. Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

During the study period, 44,674 neonates were born before 32 weeks of gestational age and with birth weights of 1,500 g or less; of these infants, a total of 14,626 were excluded from the study on the basis of exclusion criteria (Fig. 1). The study included 23,502 singletons (with ACS, n = 13,073; without ACS, n = 10,429) and 6,546 twins (with ACS, n = 3,824; without ACS, n = 2,722). After propensity score matching (the ratio of the number of mothers who

received ACS [ACS group] to the number of those who did not [no-ACS group] = 1:1) among singletons and among twins to adjust potential confounding variables, 18,700 singletons (in the ACS group, *n* = 9,350; in the no-ACS group, *n* = 9,350) and 5,122 twins (in the ACS group, *n* = 2,561; in the no-ACS group, *n* = 2,561) were selected for the first analysis. Of the total of 23,822 children, 10,262 children were assessed for medium-term outcomes at 3 years of age. After propensity score matching (ratio of ACS group to no-ACS group = 1:1) 1,246 monochorionic first twin, 1,230 monochorionic second twin, 1,262 dichorionic first twin, and 1,320 dichorionic second twin were selected for the second analysis. Of the total of 5,058, 2,133 were assessed for medium-term outcomes (Fig. 1).

Table 1 lists the baseline characteristics in singletons and twins, stratified by ACS treatment, after propensity score matching. Before propensity score matching, maternal and neonatal characteristics in the ACS and no-ACS groups were considerably different for both singletons and twins (Appendix 2, available online at http://links.lww.com/xxx). The propensity score matching algorithm largely reduced the initial imbalance of all variables, and no significant difference in any variables was observed between the ACS and no-ACS groups in singletons or twins. Standardized differences of all variables were between -0.024 and 0.013 in the first analysis, which indicated that propensity score matching was successful. Appendix 3, available online at http://links.lww.com/xxx, lists the characteristics of the matched and un-matched cohorts.

Table 2 lists the short- and medium-term adverse outcomes in singletons and twins, stratified by ACS treatment. Both singletons and twins born to mothers who received ACS treatment had lower rates of IVH (grade III or IV), PVL, and short-term composite adverse outcomes than did the children born to mothers who did not receive ACS treatment (Table 2). ACS treatment in singletons significantly decreased the rates of in-hospital death, RDS, and sepsis in short-term and cerebral palsy and composite adverse outcomes in medium-term, whereas it did not do so in twins. However, the interaction analysis revealed no statistically significant difference between singletons and twins in the efficacy of ACS treatment on short- and medium-term outcomes except for in-hospital death, RDS and short-term composite adverse outcomes. An additional analysis on neonatal respiratory morbidities showed that the effects of ACS treatment on intubation at birth, surfactant use, and chronic lung disease were also different between singletons and twins (, Appendix 4, available online at http://links.lww.com/xxx).

With regard to medium-term outcomes, ACS treatment was associated with a significant decrease in cerebral palsy, composite adverse outcomes, and increase in home oxygen therapy or home respiratory therapy at 3 years of age in singletons; no additional association was observed in twins (Table 2). However, the interaction analysis showed no significant difference between singletons and twins with regard to the efficacy of ACS treatment in medium-term infants. Appendixes 5 and 6, available online at

http://links.lww.com/xxx, lists the baseline characteristics and outcomes of singletons and twins with and without medium-term outcomes.

Appendixes 7 and 8, available online at http://links.lww.com/xxx, lists the baseline characteristics in monochorionic and dichorionic twins, stratified by birth order and ACS treatment after propensity score matching. No significant difference in any variables was observed between the ACS and no-ACS groups, and propensity score matching was successfully performed.

Table 3 lists the ORs of the short- and medium-term outcomes in monochorionic and dichorionic twins, stratified by birth order and ACS treatment (the details are shown in Appendixes 9 and 10, available online at http://links.lww.com/xxx). ACS treatment was not associated with decreased short- and medium-term outcomes in the first twin in both monochorionic and dichorionic twins. However, the second twin in both monochorionic and dichorionic twins in the ACS group had lower rates of PVL and short-term composite adverse outcomes than that in the no-ACS group. Regarding birth order, interaction analysis revealed that there was no significant difference in the effect of ACS treatment on short- and medium-term outcomes between the first and second twin, except for PVL and necrotizing enterocolitis. Regarding chorionicity, the interaction analysis revealed that there was no significant difference in the short- and medium-term effect of ACS treatment on outcomes between monochorionic and dichorionic twins.

Figure 2 shows the rates of short- and medium-term outcomes by gestational age at birth in singletons and twins according to exposure to ACS. Short- and medium-term adverse outcomes decreased with each additional week of gestation; however, efficacy of ACS was decreased in relation to several short-term outcomes in twins in comparison with singletons.

DISCUSSION

In this propensity score-matched cohort study, we demonstrated that ACS treatment was associated with improvement of short-term neurological outcomes similarly in singletons and twins. However, ACS treatment was associated with a significant decreased morality, respiratory morbidities, and cerebral palsy in singletons but not in twins. In addition, we demonstrated that the difference in chorionicity and birth order did not alter the efficacy of ACS treatment on most of the short- and medium-term offspring outcomes.

Our study differs from previous studies because we could not demonstrate a sufficient protective effect of ACS treatment against RDS in twins.(3, 20) Additional analysis also showed that ACS treatment was not associated with improvement of the rates of intubation at birth and surfactant use in twins, which is compatible with the lack of protective effect against RDS. These discrepancies regarding the efficacy of ACS treatment on RDS between singletons and twins might be associated with the following: (1) the rate of incomplete ACS treatment or an administration-to-birth interval of more than 7 days (21); (2) the rate of mothers who

experienced labor before cesarean section, which can reduce approximately 20%–30% OR for RDS (22); and (3) a dose-dependent effect of ACS treatment on protecting against or reducing the rate of respiratory morbidities in twins. However, the NRNJ database did not include this information.

In this study, increased ORs of chronic lung disease and home oxygen therapy or home respiratory therapy were observed in the ACS group in singletons, which is consistent with a previous report using the same database within a different period (2003–2007).(23) This can be attributed to the fact that improved survival rate by ACS treatment might increase the number of severe neonates requiring prolonged mechanical ventilation, oxygen administration, and artificial nutrition.

In addition, we could not demonstrate an association between reduction of mortality and ACS treatment in twins, in disagreement with previous studies.(8, 20) Although the underlying reasons for this remain unclear, there is a possibility that a single course of ACS treatment may lead to a concentration of betamethasone that is subtherapeutic against preventing or reducing mortality and morbidities. So far, adjustment of ACS dose or course adjusted to maternal body weight or to the plurality of pregnancy have been discussed from the viewpoint of pharmacokinetics. A previous report demonstrated shortened half-life (7.2 ± 2.4 hours for twins versus 9.0 ± 2.7 hours for singletons; $p < 0.017$) and increased clearance of betamethasone (8.6 ± 6.4 L/h in twins versus 5.7 ± 3.1 L/h in singletons; $p = 0.06$).(24) Taking

into consideration the reduced effect of a single course and dose of ACS treatment in twins on neonatal mortality and morbidity compared to singletons in this study, larger or repeated doses might be necessary to yield a therapeutic level in twins.(9) However, several studies have demonstrated that the serum concentrations of betamethasone in maternal blood and umbilical cord blood were not different between singletons and twins or between obese and nonobese mothers(25) and that the efficacy of ACS treatment against adverse neonatal outcomes was not altered by maternal body mass index.(26, 27)

Overall, the effect of ACS treatment on short-term neurological adverse outcomes in twins was similar to those observed in singletons, which is in accordance with a recent Cochrane review regarding IVH (relative risk, 0.56; 95% CI, 0.40 to 0.77).(7) However, to date, findings regarding the neuroprotective effect of ACS treatment in twins have been contradictory.(8, 9, 20, 28) Contrary to the retrospective studies showing insufficient neuroprotective effect of ACS treatment,(8, 9) our study demonstrated approximately 30% reduction of severe neurodevelopmental impairment (IVH grade [III or IV] or PVL) in twins. Our findings were consistent with a recent well-designed retrospective cohort study.(20)

The first strength of this study is that we used propensity score matching analysis to reduce risk of bias, which is often observed in retrospective observational studies. Second, we evaluated the effect of ACS treatment on both short- and medium-term outcomes in extremely and very preterm twins. In addition, the sample size of this study is larger than those in previous

studies.(20, 28) Furthermore, additional analyses evaluated the difference in ACS efficacy between monochorionic and dichorionic twins and between the first and second twin.

Several limitations of this study should be acknowledged. First, the NRNJ database did not include information on the type, dose, and course of ACS treatment or the interval between administration of ACS treatment and birth. However, only a single course of betamethasone was covered as ACS treatment by Japanese health insurance. A recent study of information from a national inpatient database showed that only 1.1% of mothers received a repeated course of ACS treatment and that the interval between the last injection of ACS treatment and preterm birth was 3 days (median) in Japan.(29) Moreover, the study also demonstrated that of the patients who received ACS treatment, 50.2% delivered within 7 days after the last injection of betamethasone; this percentage was similar to those in the United States and Canada.(20, 29, 30) Second, the reasons for omissions of ACS treatment (e.g. placental abruption, precipitate delivery, and eclampsia) were not documented in the NRNJ database, which may affect subsequent offspring outcomes. Third, approximately 60% of the infants registered in the NRNJ were lost to follow-up at 3 years of age, indicating that we cannot exclude the possibility of selection bias. Finally, we could not appropriately adjust our results by suitable methods, considering the intra-twin correlation of events because each set of twins shares many risk characteristics.

ACS treatment in twins is associated with a beneficial effect on short-term outcomes with a slightly decreased effect compared with those observed in singletons. In addition, the effect of ACS treatment on offspring outcomes did not differ according to chorionicity or birth order.

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Table 1. Demographic and obstetric characteristics of the study population

	Singletons				Twins			
Variable	ACS (n = 9,350)	No-ACS (n = 9,350)	*p*-value	standardized difference	ACS (n = 2,561)	No-ACS (n = 2,561)	*p*-value	standardized difference
Maternal characteristics								
Maternal age (year)	31.6 ± 5.3	31.7 ± 5.5	0.44	−0.011	31.1 ± 5.0	31.1 ± 5.0	0.94	−0.002
Primiparous (%)	4,644 (49.7)	4,612 (49.3)	0.64	0.007	1,548 (60.4)	1,543 (60.2)	0.89	0.004
Gestational age (wks)	28.2 ± 2.1	28.1 ± 2.2	0.83	0.003	28.6 ± 2.0	28.6 ± 2.1	0.90	−0.003
Cesarean section (%)	7,175 (76.7)	7,220 (77.2)	0.43	0.011	2,367 (92.4)	2,358 (92.1)	0.64	−0.013
GDM or DM (%)	253 (2.7)	262 (2.8)	0.69	0.006	99 (3.9)	89 (3.5)	0.46	−0.021
HDP (%)	2,212 (23.7)	2,209 (23.6)	0.96	−0.001	198 (7.7)	201 (7.8)	0.88	0.004
Clinical CAM (%)	2,047 (21.9)	2,054 (22.0)	0.90	0.002	297 (11.6)	293 (11.4)	0.86	−0.005
NRFS (%)	2,668 (28.5)	2,693 (28.8)	0.69	0.006	485 (18.9)	491 (19.2)	0.83	0.006
Monochorionicity (%)	NA	NA	NA	NA	1,218 (47.6)	1,235 (48.2)	0.89	0.013
First twin (%)	NA	NA	NA	NA	1,300 (50.8)	1,269 (49.6)	0.39	−0.024
Year of delivery			0.69				0.92	
2003−2007 (%)	2,632 (28.1)	2,643 (28.3)			888 (34.7)	897 (35.0)		
2008−2011 (%)	3,653 (39.1)	3,598 (38.5)			915 (35.7)	919 (35.9)		
2012−2015 (%)	3,065 (32.8)	3,109 (33.3)			758 (29.6)	745 (29.1)		
Neonatal characteristics								
Male (%)	4,886 (52.3)	4,880 (52.2)	0.93	−0.001	1,284 (50.1)	1,301 (50.8)	0.63	0.013
Birth weight (g)	1,004 ± 280	1,005 ± 283	0.80	−0.004	1,048 ± 276	1,049 ± 275	0.92	−0.003
SGA (%)	2,086 (22.3)	2,059 (22.0)	0.63	−0.007	501 (19.6)	505 (19.7)	0.89	0.004

GDM; gestational diabetes mellitus, DM; diabetes mellitus, HDP; hypertensive disorders of pregnancy, CAM; chorioamnionitis, NRFS; nonreassuring fetal status, SGA; small for gestational age,

ACS; antenatal corticosteroids, NA; not applicable. Data are presented as mean ± standard deviation or n (%).

Table 2. Short- and medium-term outcomes in singletons and twins

	Singletons			Twins			
Variable	ACS	No-ACS	OR (95% CI)	ACS	No-ACS	OR (95% CI)	Interaction
Short-term outcomes	(n=9,350)	(n=9,350)		(n=2,561)	(n=2,561)		
In-hospital death (%)	304/9,340 (3.3)	489/9,334 (5.2)	**0.61 (0.53-0.70)**	104/2,559 (4.1)	116/2,555 (4.5)	0.89 (0.68-1.17)	0.02
Respiratory distress syndrome (%)	5,566/9,317 (59.7)	6,266/9,283 (67.5)	**0.71 (0.67-0.76)**	1,858/2,549 (72.9)	1,855/2,536 (73.1)	0.99 (0.87-1.12)	<0.01
Chronic lung disease (%)	2,176/9,216 (23.6)	1,842/9,157 (20.1)	**1.23 (1.14-1.32)**	528/2,533 (20.8)	492/2,490 (19.8)	1.07 (0.93-1.23)	0.04
Intraventricular hemorrhage (III or IV) (%)	252/9,289 (2.7)	473/9,279 (5.1)	**0.52 (0.44-0.61)**	92/2,549 (3.6)	128/2,536 (5.0)	**0.70 (0.54-0.93)**	0.06
Periventricular leukomalacia (%)	283/9,309 (3.0)	394/9,300 (4.2)	**0.71 (0.61-0.83)**	95/2,548 (3.7)	143/2,546 (5.6)	**0.65 (0.50-0.85)**	0.57
Sepsis (%)	637/9,302 (6.8)	789/9,258 (8.5)	**0.79 (0.71-0.98)**	164/2,541 (6.5)	168/2,525 (6.7)	0.97 (0.78-1.21)	0.10
Necrotizing enterocolitis (%)	117/9,301 (1.3)	137/9,275 (1.5)	0.85 (0.66-1.09)	38/2,544 (1.5)	38/2,531 (1.5)	1.00 (0.63-1.57)	0.59
Treated retinopathy of prematurity (%)	1,379/9,025 (15.3)	1,431/8,858 (16.2)	0.94 (0.86-1.02)	394/2,487 (15.8)	409/2,414 (16.9)	0.92 (0.79-1.07)	0.93
Composite adverse outcomes (%)	730/9,346 (7.8)	1,149/9,350 (12.3)	**0.61 (0.55-0.67)**	249/2,561 (9.7)	332/2,561 (12.6)	**0.75 (0.63-0.90)**	0.04
Medium-term outcomes	(n=4,270)	(n=3,857)		(n=1,091)	(n=1,044)		
Death after NICU discharge (%)	35/4,270 (0.8)	37/3,857 (1.0)	0.85 (0.54-1.36)	7/1,091 (0.6)	11/1,044 (1.1)	0.61 (0.23-1.57)	0.46
Home oxygen therapy or home respiratory therapy (%)	88/3,428 (2.6)	56/3,099 (1.8)	**1.43 (1.02-2.01)**	20/817 (2.4)	11/802 (1.4)	1.80 (0.86-3.79)	0.42
Visual impairment (%)	243/3,908 (6.2)	189/3,547 (5.3)	1.18 (0.97-1.43)	60/998 (6.0)	54/950 (5.7)	1.06 (0.73-1.55)	0.46
Hearing impairment (%)	21/3,192 (0.7)	31/2,737 (1.1)	0.58 (0.23-1.01)	4/816 (0.5)	7/723 (1.0)	0.50 (0.15-1.73)	0.72
Cerebral palsy (%)	313/4,042 (7.7)	332/3,693 (9.0)	**0.85 (0.72-0.99)**	92/1,034 (8.9)	105/990 (10.6)	0.82 (0.61-1.11)	0.79
Developmental quotient <70 (%)	391/2,687 (14.6)	395/2,496 (15.8)	0.91 (0.78-1.05)	109/633 (17.2)	99/630 (15.7)	1.12 (0.83-1.50)	0.17
Composite adverse outcomes (%)	661/4,270 (15.5)	674/3,857 (17.5)	**0.87 (0.77-0.97)**	185/1,091 (17.0)	187/1,044 (17.9)	0.94 (0.75-1.17)	0.61

ACS, antenatal corticosteroids; OR, odds ratio; short-term composite adverse outcomes: in-hospital death, intraventricular hemorrhage (grade III or IV) and periventricular leukomalacia, medium-term composite adverse outcomes: death after NICU discharge, cerebral palsy or developmental quotient <70. Bold indicates a significant association. A *p*-value for interaction < 0.05 indicates a

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significant difference in the effect of ACS treatment between singletons and twins.

Table 3. Short- and medium-term outcomes of twins stratified by the chorionicity and birth order

Variable	Monochorionic 1st twins ACS vs No-ACS OR (95% CI)	Monochorionic 2nd twins ACS vs No-ACS OR (95% CI)	Dichorionic 1st twins ACS vs No-ACS OR (95% CI)	Dichorionic 2nd twins ACS vs No-ACS OR (95% CI)	Interaction Chorionicity*ACS *p*-value	Interaction Birth order*ACS *p*-value
Short-term outcomes						
In-hospital death (%)	0.82 (0.49-1.36)	**0.57 (0.34-0.97)**	0.82 (0.44-1.52)	1.10 (0.60-2.00)	0.24	0.71
Respiratory distress syndrome (%)	1.11 (0.86-1.44)	0.93 (0.72-1.19)	1.00 (0.79-1.28)	1.13 (0.88-1.45)	0.73	0.70
Chronic lung disease (%)	1.06 (0.80-1.40)	1.09 (0.83-1.42)	1.19 (0.89-1.60)	1.00 (0.76-1.31)	0.81	0.57
Intraventricular hemorrhage (III or IV) (%)	0.64 (0.39-1.04)	0.61 (0.35-1.09)	0.75 (0.41-1.37)	**0.53 (0.29-0.95)**	0.92	0.57
Periventricular leukomalacia (%)	1.02 (0.65-1.58)	**0.47 (0.27-0.83)**	0.69 (0.38-1.26)	**0.45 (0.24-0.85)**	0.31	0.02
Sepsis (%)	1.09 (0.71-1.68)	0.90 (0.57-1.41)	1.12 (0.72-1.73)	0.99 (0.64-1.52)	0.89	0.44
Necrotizing enterocolitis (%)	1.60 (0.72-3.55)	0.39 (0.15-1.02)	1.57 (0.61-4.08)	1.12 (0.43-2.92)	0.39	0.04
Treated retinopathy of prematurity (%)	0.90 (0.67-1.22)	1.04 (0.76-1.41)	0.89 (0.65-1.21)	0.83 (0.61-1.12)	0.30	0.89
Composite adverse outcomes (%)	0.86 (0.63-1.17)	**0.56 (0.39-0.80)**	0.77 (0.52-1.13)	**0.61 (0.42-0.90)**	0.78	0.05
Medium-term outcomes						
Death after NICU discharge (%)	0.44 (0.08-2.41)	4.30 (0.50-37.1)	0.47 (0.04-5.26)	0.75 (0.17-3.38)	0.50	0.16
Home oxygen therapy or home respiratory therapy (%)	1.38 (0.38-4.95)	1.08 (0.29-4.09)	12.7 (0.71-229)	2.06 (0.37-11.4)	0.34	0.51
Visual impairment (%)	1.32 (0.66-2.67)	0.73 (0.34-1.53)	0.66 (0.25-1.76)	1.73 (0.81-3.72)	0.85	0.83
Hearing impairment (%)	NA	0.58 (0.10-3.49)	0.43 (0.04-4.75)	0.18 (0.01-3.76)	0.34	0.78
Cerebral palsy (%)	1.04 (0.62-1.75)	0.53 (0.28-1.01)	0.91 (0.49-1.68)	0.68 (0.36-1.29)	0.61	0.10
Developmental quotient <70 (%)	1.04 (0.59-1.85)	1.16 (0.66-2.05)	1.68 (0.90-3.15)	1.04 (0.58-1.88)	0.78	0.59
Composite adverse outcomes (%)	1.18 (0.77-1.81)	0.90 (0.58-1.40)	1.12 (0.70-1.77)	0.82 (0.52-1.28)	0.30	0.20

ACS, antenatal corticosteroids; OR, odds ratio; NA, not available; short-term composite adverse outcomes: in-hospital death, intraventricular hemorrhage (grade III or IV) and periventricular

leukomalacia, medium-term composite adverse outcomes: death after NICU discharge, cerebral palsy or developmental quotient <70. Bold indicates a significant association. A *p*-value for interaction < 0.05 indicates a significant difference in the effect of ACS treatment between monochorionic and dichorionic twins and between the first and second twin.

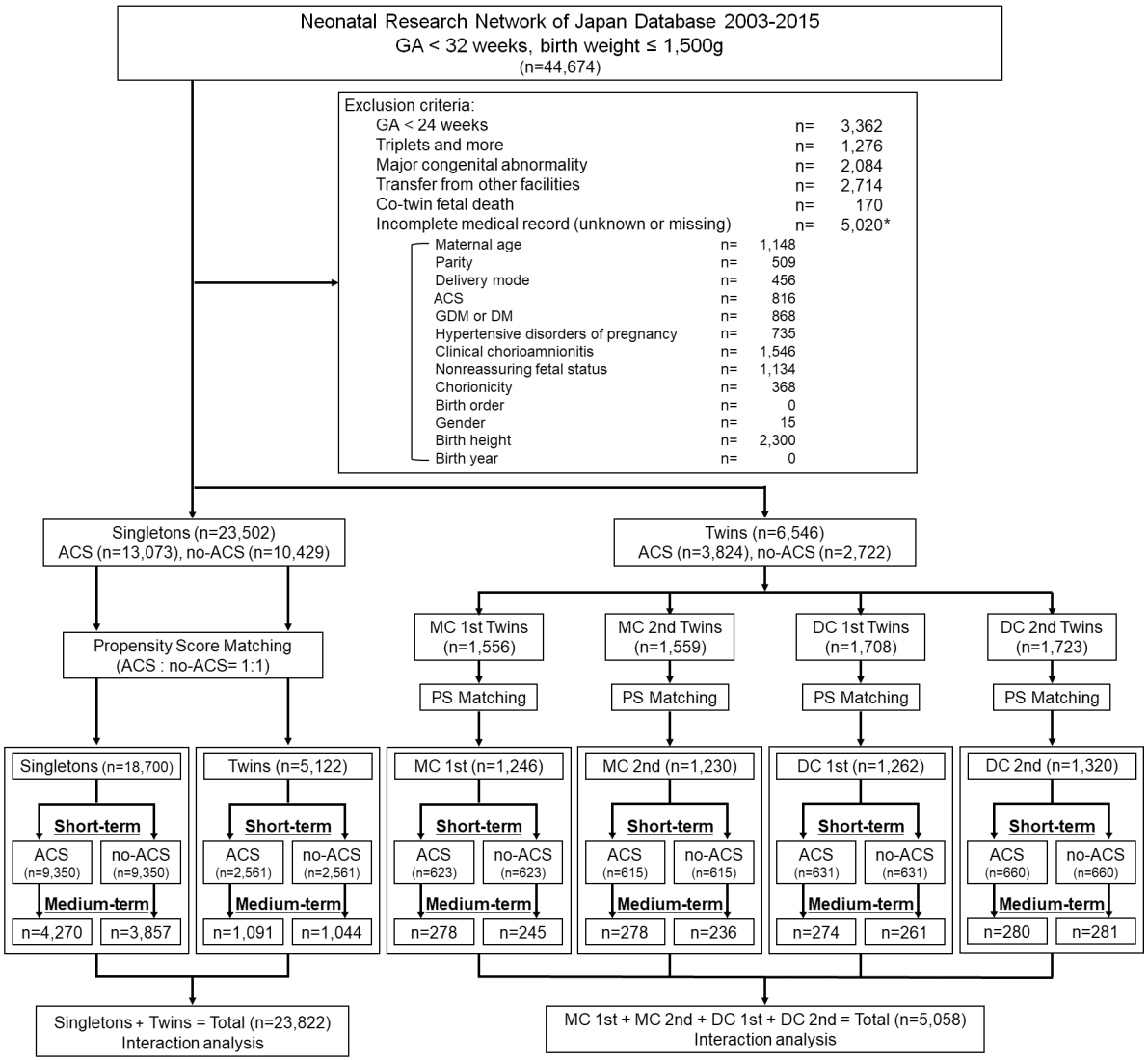
Figure legends

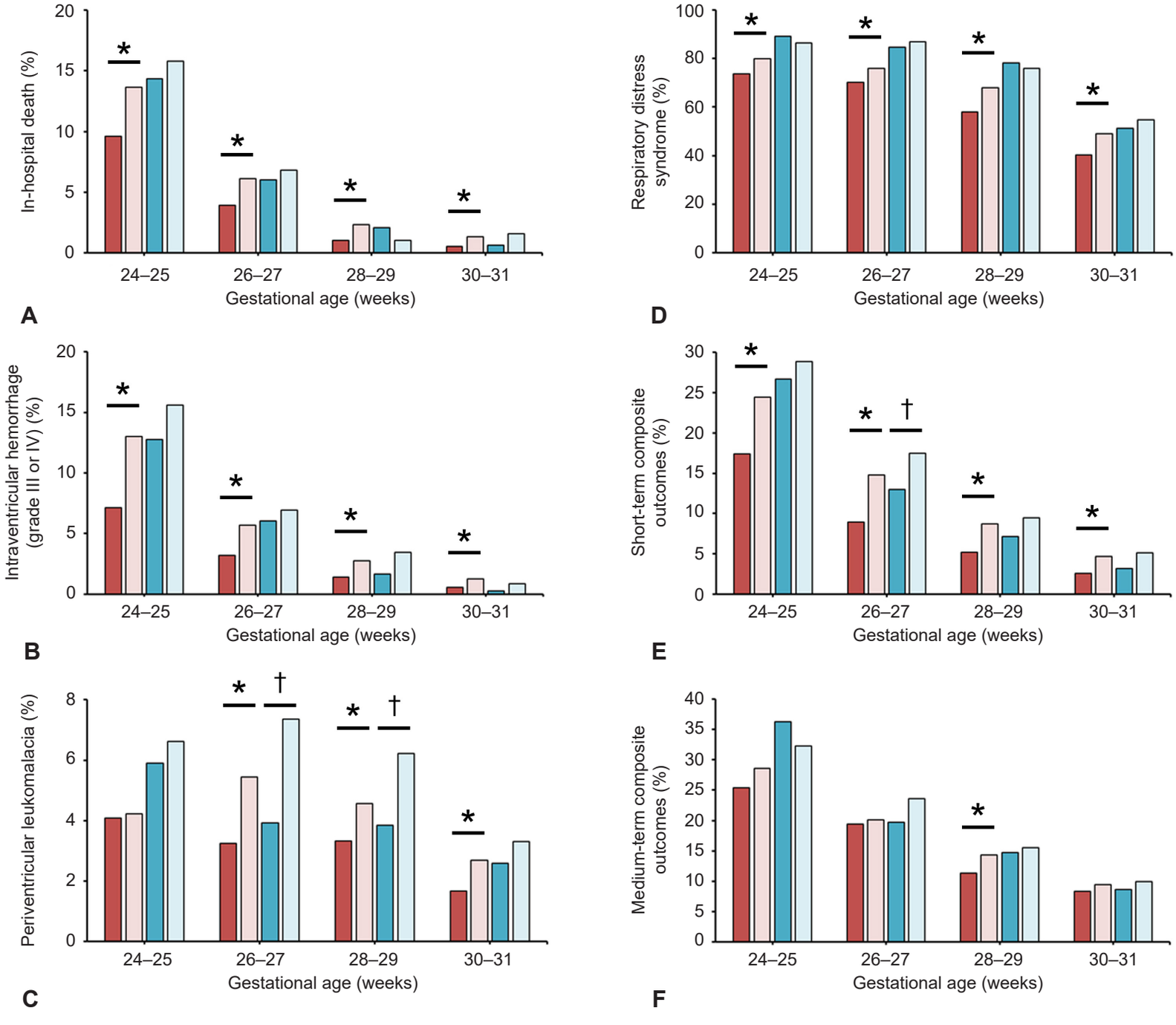
Fig. 1. Flow diagram of the propensity score–matched study population.

Data on 44,674 neonates were collected from the Neonatal Research Network of Japan database. Propensity score matching (ratio of ACS group to no-ACS group = 1:1) was performed. Interaction analyses were performed to evaluate whether ACS treatment produced significantly different effects between singletons and twins, between monochorionic and dichorionic twins and between the first and second twin. GA, gestational age; ACS, antenatal corticosteroids; GDM, gestational diabetes mellitus; DM, diabetes mellitus; DC, dichorionic; MC, monochorionic; PS, propensity score.

Fig. 2. Rates of short- and medium-term outcomes by gestational week at birth in singletons and twins according to exposure to antenatal corticosteroids (ACS).

The outcomes shown include in-hospital death, IVH (grade III or IV), PVL, RDS, and short- and medium-term composite outcomes by gestational age at birth in singletons and twins according to exposure to ACS. Short-term composite adverse outcomes: in-hospital death, severe IVH (grade III or IV), and PVL. Medium-term composite adverse outcomes: death after discharge from NICUs, cerebral palsy, and developmental quotient of less than 70. *$p < 0.05$ for ACS treatment versus no ACS treatment in singletons. †$p < 0.05$ for ACS treatment versus no ACS treatment in twins. IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome.


Neonatal Research Network of Japan Database 2003-2015
GA < 32 weeks, birth weight ≤ 1,500g
(n=44,674)
Exclusion criteria:
GA < 24 weeks n= 3,362
Triplets and more n= 1,276
Major congenital abnormality n= 2,084
Transfer from other facilities n= 2,714
Co-twin fetal death n= 170
Incomplete medical record (unknown or missing) n= 5,020*
Maternal age n= 1,148
Parity n= 509
Delivery mode n= 456
ACS n= 816
GDM or DM n= 868
Hypertensive disorders of pregnancy n= 735
Clinical chorioamnionitis n= 1,546
Nonreassuring fetal status n= 1,134
Chorionicity n= 368
Birth order n= 0
Gender n= 15
Birth height n= 2,300
Birth year n= 0
Singletons (n=23,502)
ACS (n=13,073), no-ACS (n=10,429)
Twins (n=6,546)
ACS (n=3,824), no-ACS (n=2,722)
Propensity Score Matching
(ACS : no-ACS= 1:1)
MC 1st Twins (n=1,556)
MC 2nd Twins (n=1,559)
DC 1st Twins (n=1,708)
DC 2nd Twins (n=1,723)
PS Matching
PS Matching
PS Matching
PS Matching
Singletons (n=18,700)
Twins (n=5,122)
MC 1st (n=1,246)
MC 2nd (n=1,230)
DC 1st (n=1,262)
DC 2nd (n=1,320)
Short-term
ACS (n=9,350)
no-ACS (n=9,350)
ACS (n=2,561)
no-ACS (n=2,561)
ACS (n=623)
no-ACS (n=623)
ACS (n=615)
no-ACS (n=615)
ACS (n=631)
no-ACS (n=631)
ACS (n=660)
no-ACS (n=660)
Medium-term
n=4,270
n=3,857
n=1,091
n=1,044
n=278
n=245
n=278
n=236
n=274
n=261
n=280
n=281
Singletons + Twins = Total (n=23,822)
Interaction analysis
MC 1st + MC 2nd + DC 1st + DC 2nd = Total (n=5,058)
Interaction analysis


In-hospital death (%)
Gestational age (weeks)
24–25
26–27
28–29
30–31
A
Respiratory distress syndrome (%)
D
Intraventricular hemorrhage (grade III or IV) (%)
B
Short-term composite outcomes (%)
E
Periventricular leukomalacia (%)
C
Medium-term composite outcomes (%)
F
Singletons, ACS
Singletons, no ACS
Twins, ACS
Twins, no ACS

Supplementary Table 1. Baseline characteristics of singletons and twins with and without complete data

	Singletons			Twins		
Variable	Complete data (n=23,502)	Incomplete data (n=3,898)	*p*-value	Complete data (n=6,546)	Incomplete data (n=1,122)	*p*-value
Maternal characteristics						
Maternal age (year)	31.7 ± 5.4	31.8 ± 5.7	0.51	31.3 ± 5.0	31.5 ± 5.3	0.18
Primiparous (%)	11,714 (49.8)	1,837/3,433 (53.5)	<0.01	4,015 (61.3)	682/1,083 (63.0)	0.31
Gestational age (wks)	28.1 ± 2.2	28.1 ± 2.2	0.61	28.6 ± 2.0	28.5 ± 2.1	0.24
Cesarean section (%)	18,045 (76.8)	2,451/3,472 (70.6)	<0.01	6,046 (92.4)	963/1,092 (88.2)	<0.01
GDM or DM (%)	691 (2.9)	82/3,114 (2.8)	0.32	232 (3.5)	19/1,038 (1.8)	<0.01
HDP (%)	5,381 (22.9)	595/3,253 (18.3)	<0.01	549 (8.4)	78/1,032 (7.6)	0.37
Clinical CAM (%)	5,325 (22.7)	483/2,607 (18.5)	<0.01	717 (11.0)	80/867 (9.2)	0.12
ACS (%)	13,073 (55.6)	1,387/3,188 (43.5)	<0.01	3,824 (58.4)	519/1,016 (51.1)	<0.01
NRFS (%)	6,583 (28.0)	694/2,933 (23.7)	<0.01	1,207 (18.4)	128/953 (13.4)	<0.01
Monochorionicity (%)	NA	NA	NA	3,115 (47.6)	347/754 (46.0)	0.42
First twin (%)	NA	NA	NA	3,264 (49.9)	595/1,122 (53.0)	0.05
Year of delivery			<0.01			<0.01
2003-2007 (%)	6,266 (26.7)	1,117 (28.7)		2,012 (30.7)	433 (38.6)	
2008-2011 (%)	8,383 (35.7)	1,258 (32.3)		2,200 (33.6)	368 (32.8)	
2012-2015 (%)	8,853 (37.7)	1,523 (39.1)		2,334 (35.7)	321 (28.6)	
Neonatal characteristics						
Male (%)	12,253 (52.1)	2,064/3,884 (53.1)	0.25	3,326 (50.8)	582/1,121 (51.9)	0.49
Birth weight (g)	997 ± 282	991 ± 287	0.27	1,045 ± 277	1,028 ± 280	0.06
SGA (%)	5,217 (22.2)	522/1,998 (26.1)	<0.01	1,328 (20.3)	158/695 (22.7)	0.13

GDM; gestational diabetes mellitus, DM; diabetes mellitus, HDP; hypertensive disorders of pregnancy, CAM; chorioamnionitis, ACS; antenatal corticosteroids, NRFS; nonreassuring fetal status,

SGA; small for gestational age, NA; not applicable. Data are presented as mean ± standard deviation or n (%).

Supplementary Table 2. Demographic and obstetric characteristics of the study population before propensity score matching

	Singletons			Twins		
Variable	ACS (n=13,073)	No-ACS (n=10,429)	*p*-value	ACS (n=3,824)	No-ACS (n=2,722)	*p*-value
Maternal characteristics						
Maternal age (year)	31.8 ± 5.4	31.6 ± 5.5	<0.01	31.3 ± 5.1	31.1 ± 5.0	0.10
Primiparous (%)	6,570 (50.3)	5,144 (49.3)	0.16	2,408 (63.0)	1,607 (59.0)	<0.01
Gestational age (wks)	28.0 ± 2.1	28.2 ± 2.2	<0.01	28.6 ± 2.0	28.6 ± 2.1	0.82
Cesarean section (%)	9,969 (76.3)	8,076 (77.4)	0.03	3,543 (92.7)	2,503 (92.0)	0.29
GDM or DM (%)	398 (3.0)	293 (2.8)	0.29	136 (3.6)	96 (3.5)	0.95
HDP (%)	2,793 (21.4)	2,588 (24.8)	<0.01	336 (8.8)	213 (7.8)	0.17
Clinical CAM (%)	3,106 (23.8)	2,219 (21.3)	<0.01	396 (10.4)	321 (11.8)	0.07
NRFS (%)	3,514 (26.9)	3,069 (29.4)	<0.01	675 (17.7)	532 (19.5)	0.05
Monochorionicity (%)	NA	NA	NA	1,816 (47.5)	1,299 (47.7)	0.86
First twin (%)	NA	NA	NA	1,920 (50.2)	1,344 (49.4)	0.51
Year of delivery			<0.01			<0.01
2003-2007 (%)	2,665 (20.4)	3,601 (34.5)		964 (25.2)	1,048 (38.5)	
2008-2011 (%)	4,666 (35.7)	3,717 (35.6)		1,271 (33.2)	929 (34.1)	
2012-2015 (%)	5,742 (43.9)	3,111 (29.8)		1,589 (41.6)	745 (27.4)	
Neonatal characteristics						
Male (%)	6,853 (52.4)	5,400 (51.8)	0.33	1,953 (51.1)	1,373 (50.4)	0.62
Birth weight (g)	984 ± 281	1,012 ± 283	<0.01	1,040 ± 279	1,053 ± 275	0.06
SGA (%)	2,943 (22.5)	2,274 (21.8)	0.19	802 (21.0)	526 (19.3)	0.10

GDM; gestational diabetes mellitus, DM; diabetes mellitus, HDP; hypertensive disorders of pregnancy, CAM; chorioamnionitis, NRFS; nonreassuring fetal status, SGA; small for gestational age, ACS; antenatal corticosteroids, NA; not applicable. Data are presented as mean ± standard deviation or n (%).

Supplementary Table 3. Baseline characteristics of singletons and twins in the PS-matched and un-matched cohorts

	Singletons			Twins		
Variable	PS-matched (n=18,700)	PS-un-mached (n=4,802)	*p*-value	PS-matched (n=5,122)	PS-un-mached (n=1,424)	*p*-value
Maternal characteristics						
Maternal age (year)	31.7 ± 5.4	32.0 ± 5.4	<0.01	31.3 ± 5.0	31.7 ± 5.2	<0.01
Primiparous (%)	9,256 (49.5)	2,458(51.2)	0.04	3,091 (60.3)	924 (64.9)	<0.01
Gestational age (wks)	28.1 ± 2.1	27.9 ± 2.1	<0.01	28.6 ± 2.1	28.7 ± 2.0	0.13
Cesarean section (%)	1,4395 (77.0)	3,650 (76.0)	0.16	4,725 (92.2)	1,321 (92.8)	0.52
GDM or DM (%)	515 (2.8)	176 (3.7)	<0.01	188 (3.7)	44 (3.1)	0.29
HDP (%)	4,421 (23.6)	960 (20.0)	<0.01	399 (7.8)	150 (10.5)	<0.01
Clinical CAM (%)	4,101 (21.9)	1,224 (25.5)	<0.01	590 (11.5)	127 (8.9)	<0.01
ACS (%)	9,350 (50.0)	3,723 (77.5)	<0.01	2,561 (50.0)	1,263 (88.7)	<0.01
NRFS (%)	5,361 (28.7)	1,222 (25.4)	<0.01	976 (19.1)	231 (16.2)	0.01
Monochorionicity (%)	NA	NA	NA	2,453 (47.9)	662 (46.5)	0.35
First twin (%)	NA	NA	NA	2,569 (50.2)	695 (48.8)	0.37
Year of delivery			<0.01			<0.01
2003-2007 (%)	5,275 (28.2)	991 (20.6)		1,785 (34.8)	227 (15.9)	
2008-2011 (%)	7,251 (38.8)	1,132 (23.6)		1,834 (35.8)	366 (25.7)	
2012-2015 (%)	6,174 (33.0)	2,679 (55.8)		1,503 (29.3)	831 (58.4)	
Neonatal characteristics						
Male (%)	9,766 (52.2)	2,487 (51.8)	0.59	2,585 (50.5)	741 (52.0)	0.29
Birth weight (g)	1,004 ± 281	965 ± 282	<0.01	1,048 ± 275	1,034 ± 284	0.09
SGA (%)	4,145 (22.2)	1,072 (22.3)	0.81	1,006 (19.6)	322 (22.6)	0.01

GDM; gestational diabetes mellitus, DM; diabetes mellitus, HDP; hypertensive disorders of pregnancy, CAM; chorioamnionitis, ACS; antenatal corticosteroids, NRFS; nonreassuring fetal status,

SGA; small for gestational age, NA; not applicable, PS; propensity score. Data are presented as mean ± standard deviation or n (%).

Supplementary Table 4. Short- and medium-term respiratory outcomes of singletons and twins

	Singletons			Twins			
Variable	ACS	No-ACS	OR (95% CI)	ACS	No-ACS	OR (95% CI)	Interaction
Short-term outcomes	(n=9,350)	(n=9,350)		(n=2,561)	(n=2,561)		
Intubation at birth (%)	5,461/9,330 (58.5)	6,158/9,334 (66.0)	**0.73 (0.69–0.77)**	1,516/2,556 (59.3)	1,619/2,553 (63.4)	**0.84 (0.75–0.94)**	0.02
Surfactant use (%)	5,614/9,295 (60.4)	6,253/9,270 (67.5)	**0.74 (0.69–0.78)**	1,814/2,548 (71.1)	1,830/2,528 (72.4)	0.94 (0.83–1.07)	<0.01
Respiratory distress syndrome (%)	5,566/9,317 (59.7)	6,266/9,283 (67.5)	**0.71 (0.67–0.76)**	1,858/2,549 (72.9)	1,855/2,536 (73.1)	0.99 (0.87–1.12)	<0.01
Chronic lung disease (%)	2,176/9,216 (23.6)	1,842/9,157 (20.1)	**1.23 (1.14–1.32)**	528/2,533 (20.8)	492/2,490 (19.8)	1.07 (0.93–1.23)	0.04
Medium-term outcome	(n=4,270)	(n=3,857)		(n=1,091)	(n=1,044)		
Home oxygen therapy or home respiratory therapy (%)	88/3,428 (2.6)	56/3,099 (1.8)	**1.43 (1.02–2.01)**	20/817 (2.4)	11/802 (1.4)	1.80 (0.86–3.79)	0.42

ACS, antenatal corticosteroids; OR, odds ratio; CI, confidence interval. Bold indicates a significant association. A *p*-value for interaction <0.05 indicates a significant difference in the effect of ACS treatment between singletons and twins.

Supplementary Table 5. Baseline characteristics of singletons and twins with and without medium-term outcomes

	Singletons			Twins		
Variable	With medium-term data (n=8,054)	Without medium-term data (n=9,781)	*p*-value	With medium-term data (n=2,117)	Without medium-term data (n=2,767)	*p*-value
Maternal characteristics						
Maternal age (year)	31.7 ± 5.3	31.6 ± 5.6	0.06	31.1 ± 5.0	31.2 ± 5.0	0.64
Primiparous (%)	4,125 (51.2)	4,712 (48.2)	<0.01	1,331 (62.9)	1,617 (58.4)	<0.01
Gestational age (wks)	28.1 ± 2.1	28.3 ± 2.1	<0.01	28.5 ± 2.0	28.8 ± 2.0	<0.01
Cesarean section (%)	6,231 (77.4)	7,487 (76.5)	0.20	1,968 (93.0)	2,552 (92.2)	0.33
GDM or DM (%)	214 (2.7)	283 (2.9)	0.34	73 (3.4)	109 (3.9)	0.37
HDP (%)	1,949 (24.2)	2,308 (23.6)	0.35	163 (7.7)	222 (8.0)	0.68
Clinical CAM (%)	1,816 (22.5)	2,095 (21.4)	0.07	230 (10.9)	331 (12.0)	0.23
ACS (%)	4,234 (52.6)	4,777 (48.8)	<0.01	1,084 (51.2)	1,366 (49.4)	0.20
NRFS (%)	2,269 (28.2)	2,737 (28.0)	0.78	411 (19.4)	483 (17.5)	0.08
Monochorionicity (%)	NA	NA	NA	992 (46.9)	1,323 (47.8)	0.51
First twin (%)	NA	NA	NA	1,060 (50.1)	1,395 (50.4)	0.81
Year of delivery			<0.01			<0.01
2003-2007 (%)	2,567 (31.9)	2,366 (24.2)		856 (40.4)	830 (30.0)	
2008-2011 (%)	3,518 (43.7)	3,407 (34.8)		856 (40.4)	896 (32.4)	
2012-2015 (%)	1,969 (24.4)	4,008 (41.0)		405 (19.2)	1,041 (37.6)	
Neonatal characteristics						
Male (%)	4,204 (52.2)	5,065 (51.8)	0.58	1,053 (49.7)	1,391 (50.3)	0.71
Birth weight (g)	995 ± 274	1,036 ± 276	<0.01	1,043 ± 268	1,080 ± 267	<0.01
SGA (%)	1,855 (23.0)	2,001 (20.5)	<0.01	397 (18.8)	523 (18.9)	0.89

GDM; gestational diabetes mellitus, DM; diabetes mellitus, HDP; hypertensive disorders of pregnancy, CAM; chorioamnionitis, ACS; antenatal corticosteroids, NRFS; nonreassuring fetal status,

SGA; small for gestational age, NA; not applicable. Data are presented as mean ± standard deviation or n (%).

Supplementary Table 6. Short-term outcomes in singletons and twins with and without medium-term outcomes

	Singletons			Twins		
Variable	With medium-term data (n=8,054)	Without medium-term data (n=9,781)	*p*-value	With medium-term data (n=2,117)	Without medium-term data (n=2,767)	*p*-value
Short-term outcomes						
Respiratory distress syndrome (%)	5,020/7,995 (62.8)	6,189/9,754 (63.5)	0.36	1,511/2,094 (72.2)	2,009/2,760 (72.8)	0.62
Chronic lung disease (%)	1,795/8,010 (22.4)	2,111/9,660 (21.9)	0.37	418/2,097 (19.9)	572/2,732 (20.9)	0.39
Intraventricular hemorrhage (III or IV) (%)	207/8,007 (2.6)	317/9,714 (3.3)	<0.01	64/2,105 (3.0)	90/2,751 (3.3)	0.65
Periventricular leukomalacia (%)	248/8,032 (3.1)	388/9,734 (4.0)	<0.01	94/2,115 (4.4)	126/2,753 (4.6)	0.82
Sepsis (%)	530/7,985 (6.6)	616/9,723 (6.3)	0.42	116/2,092 (5.5)	145/2,745 (5.3)	0.69
Necrotizing enterocolitis (%)	71/7,993 (0.9)	87/9,733 (0.9)	0.97	17/2,094 (0.8)	27/2,751 (1.0)	0.54
Treated retinopathy of prematurity (%)	1,335/7,854 (17.0)	1,424/9,344 (15.2)	<0.01	345/2,058 (16.8)	435/2,658 (16.4)	0.72
Composite adverse outcomes (%)	423/8,052 (5.3)	650/9,779 (6.6)	<0.01	150/2,117 (7.1)	196/2,767 (7.1)	1

Short-term composite adverse outcomes: in-hospital death, intraventricular hemorrhage (grade III or IV) and periventricular leukomalacia.

Supplementary Table 7. Baseline characteristics of monochorionic first and second twin

	Monochorionic first twins				Monochorionic second twins			
Variable	ACS (n=623)	No-ACS (n=623)	*p*-value	standardized difference	ACS (n=615)	No-ACS (n=615)	*p*-value	standardized difference
Maternal characteristics								
Maternal age (year)	30.8 ± 5.0	30.8 ± 5.0	0.96	0.003	30.5 ± 5.0	30.7 ± 5.2	0.56	–0.032
Primiparous (%)	349 (56.0)	357 (57.3)	0.65	–0.026	361 (58.7)	359 (58.4)	0.91	0.007
Gestational age (wks)	28.6 ± 2.0	28.5 ± 2.0	0.81	0.013	28.7 ± 1.9	28.7 ± 2.0	0.95	–0.004
Cesarean section (%)	578 (92.8)	581 (93.3)	0.74	0.019	582 (94.6)	580 (94.3)	0.80	–0.014
GDM or DM (%)	22 (3.5)	22 (3.5)	1	0	18 (2.9)	19 (3.1)	0.87	0.009
HDP (%)	44 (7.1)	45 (7.2)	0.91	0.006	46 (7.5)	41 (6.7)	0.58	–0.031
Clinical CAM (%)	43 (6.9)	44 (7.1)	0.91	0.006	43 (7.0)	44 (7.2)	0.91	0.007
NRFS (%)	145 (23.3)	147 (23.6)	0.89	0.008	156 (25.4)	148 (24.1)	0.60	–0.03
Year of delivery			0.75				0.95	
2003-2007 (%)	181 (29.1)	191 (30.7)			200 (32.5)	201 (32.7)		
2008-2011 (%)	245 (39.3)	246 (39.5)			221 (35.9)	225 (36.6)		
2012-2015 (%)	197 (31.6)	186 (29.9)			194 (31.5)	189 (30.7)		
Neonatal characteristics								
Male (%)	316 (50.7)	309 (49.6)	0.69	–0.022	310 (50.4)	311 (50.6)	0.95	0.003
Birth weight (g)	1,066 ± 271	1,053 ± 265	0.40	0.048	1,009 ± 281	1,013 ± 282	0.79	–0.015
SGA (%)	108 (17.3)	113 (18.1)	0.71	0.021	184 (29.9)	176 (28.6)	0.62	–0.029

GDM; gestational diabetes mellitus, DM; diabetes mellitus, HDP; hypertensive disorders of pregnancy, CAM; chorioamnionitis, NRFS; nonreassuring fetal status, SGA; small for gestational age, ACS; antenatal corticosteroids. Data are presented as mean ± standard deviation or n (%).

Supplementary Table 8. Baseline characteristics of dichorionic first and second twin

	Dichorionic first twins				Dichorionic second twins			
Variable	ACS (n=631)	No-ACS (n=631)	*p*-value	standardized difference	ACS (n=660)	No-ACS (n=660)	*p*-value	standardized difference
Maternal characteristics								
Maternal age (year)	31.3 ± 4.9	31.5 ± 4.7	0.46	–0.042	31.6 ± 5.0	31.7 ± 4.9	0.66	–0.024
Primiparous (%)	397 (62.9)	392 (62.1)	0.77	0.016	422 (63.9)	419 (63.5)	0.86	0.009
Gestational age (wks)	28.5 ± 2.1	28.5 ± 2.1	0.63	0.027	28.5 ± 2.1	28.6 ± 2.1	0.59	–0.029
Cesarean section (%)	568 (90.0)	573 (90.8)	0.74	0.019	609 (92.3)	603 (91.4)	0.55	–0.032
GDM or DM (%)	27 (4.3)	26 (4.1)	0.89	–0.008	21 (3.2)	23 (3.5)	0.76	0.016
HDP (%)	53 (8.4)	53 (8.4)	1	0	58 (8.8)	63 (9.5)	0.63	–0.026
Clinical CAM (%)	100 (15.8)	101 (16.0)	0.94	0.004	102 (15.5)	100 (15.2)	0.88	–0.009
NRFS (%)	82 (13.0)	86 (13.6)	0.74	0.019	102 (15.5)	104 (15.8)	0.88	0.008
Year of delivery			0.70				0.72	
2003-2007 (%)	241 (38.2)	231 (36.6)			245 (37.1)	246 (37.3)		
2008-2011 (%)	205 (32.5)	219 (34.7)			214 (32.4)	225 (34.1)		
2012-2015 (%)	185 (29.3)	181 (28.7)			201 (30.5)	189 (28.6)		
Neonatal characteristics								
Male (%)	326 (51.7)	322 (51.0)	0.82	–0.013	332 (50.3)	340 (51.5)	0.66	0.024
Birth weight (g)	1,072 ± 268	1,075 ± 269	0.84	–0.011	1,052 ± 280	1,053 ± 277	0.94	–0.004
SGA (%)	87 (13.8)	92 (14.6)	0.69	0.022	112 (17.0)	118 (17.9)	0.66	0.023

GDM; gestational diabetes mellitus, DM; diabetes mellitus, HDP; hypertensive disorders of pregnancy, CAM; chorioamnionitis, NRFS; nonreassuring fetal status, SGA; small for gestational age, ACS; antenatal corticosteroids. Data are presented as mean ± standard deviation or n (%).

Supplementary Table 9. Short- and medium-term outcomes of monochorionic first and second twin

	Monochorionic first twins			Monochorionic second twins		
Variable	ACS	No-ACS	OR (95% CI)	ACS	No-ACS	OR (95% CI)
Short-term outcomes	(n=623)	(n=623)		(n=615)	(n=615)	
In-hospital death (%)	29/622 (4.7)	35/622 (5.6)	0.82 (0.49–1.36)	23/615 (3.7)	39/613 (6.4)	**0.57 (0.34–0.97)**
Respiratory distress syndrome (%)	475/620 (76.6)	461/617 (74.7)	1.11 (0.86–1.44)	439/609 (72.1)	449/610 (73.6)	0.93 (0.72–1.19)
Chronic lung disease (%)	129/617 (20.9)	119/597 (19.9)	1.06 (0.80–1.40)	144/608 (23.7)	133/598 (22.2)	1.09 (0.83–1.42)
Intraventricular hemorrhage (III or IV) (%)	29/620 (4.7)	44/617 (7.1)	0.64 (0.39–1.04)	20/610 (3.3)	32/612 (5.2)	0.61 (0.35–1.09)
Periventricular leukomalacia (%)	43/621 (6.9)	42/616 (6.8)	1.02 (0.65–1.58)	19/612 (3.1)	39/614 (6.4)	**0.47 (0.27–0.83)**
Sepsis (%)	47/620 (7.6)	43/615 (7.0)	1.09 (0.71–1.68)	39/609 (6.4)	43/607 (7.1)	0.90 (0.57–1.41)
Necrotizing enterocolitis (%)	16/622 (2.6)	10/615 (1.6)	1.60 (0.72–3.55)	6/609 (1.0)	15/608 (2.5)	0.39 (0.15–1.02)
Treated retinopathy of prematurity (%)	101/609 (16.6)	106/587 (18.1)	0.90 (0.67–1.22)	100/597 (16.8)	94/578 (16.3)	1.04 (0.76–1.41)
Composite adverse outcomes (%)	85/623 (13.6)	97/623 (15.6)	0.86 (0.63–1.17)	54/615 (8.8)	90/615 (14.6)	**0.56 (0.39–0.80)**
Medium-term outcomes	(n=278)	(n=245)		(n=278)	(n=236)	
Death after NICU discharge (%)	2/278 (0.7)	4/245 (1.6)	0.44 (0.08–2.41)	5/278 (1.8)	1/236 (0.4)	4.30 (0.50–37.1)
Home oxygen therapy or home respiratory therapy (%)	6/210 (2.9)	4/191 (2.1)	1.38 (0.38–4.95)	5/213 (2.3)	4/184 (2.2)	1.08 (0.29–4.09)
Visual impairment (%)	21/251 (8.4)	14/217 (6.5)	1.32 (0.66–2.67)	14/252 (5.6)	16/214 (7.5)	0.73 (0.34–1.53)
Hearing impairment (%)	0/200 (0)	0/163 (0)	NA	2/192 (1.0)	3/167 (1.8)	0.58 (0.10–3.49)
Cerebral palsy (%)	36/258 (14.0)	31/230 (13.5)	1.04 (0.62–1.75)	17/260 (6.5)	26/223 (11.7)	0.53 (0.28–1.01)
Developmental quotient <70 (%)	30/161 (18.6)	27/150 (18.0)	1.04 (0.59–1.85)	35/175 (20.0)	25/141 (17.7)	1.16 (0.66–2.05)
Composite adverse outcomes (%)	61/278 (21.9)	47/245 (19.2)	1.18 (0.77–1.81)	51/278 (18.3)	47/236 (19.9)	0.90 (0.58–1.40)

ACS, antenatal corticosteroids; OR, odds ratio; CI, confidence interval; NA, not available; short-term composite adverse outcomes: in-hospital death, intraventricular hemorrhage (grade III or IV) and periventricular leukomalacia, medium-term composite adverse outcomes: death after NICU discharge, cerebral palsy or developmental quotient <70. Bold indicates a significant association.

Supplementary Table 10. Short- and medium-term outcomes of dichorionic first and second twin

	Dichorionic first twins			Dichorionic second twins		
Variable	ACS	No-ACS	OR (95% CI)	ACS	No-ACS	OR (95% CI)
Short-term outcomes	(n=631)	(n=631)		(n=660)	(n=660)	
In-hospital death (%)	19/630 (3.0)	23/629 (3.7)	0.82 (0.44–1.52)	23/659 (3.5)	21/658 (3.2)	1.10 (0.60–2.00)
Respiratory distress syndrome (%)	441/628 (70.2)	438/624 (70.2)	1.00 (0.79–1.28)	503/659 (76.3)	484/653 (74.1)	1.13 (0.88–1.45)
Chronic lung disease (%)	121/621 (19.5)	104/617 (16.9)	1.19 (0.89–1.60)	129/658 (19.6)	127/645 (19.7)	1.00 (0.76–1.31)
Intraventricular hemorrhage (III or IV) (%)	19/629 (3.0)	25/624 (4.0)	0.75 (0.41–1.37)	18/659 (2.7)	33/654 (5.0)	**0.53 (0.29–0.95)**
Periventricular leukomalacia (%)	19/628 (3.0)	27/628 (4.3)	0.69 (0.38–1.26)	15/660 (2.3)	32/656 (4.9)	**0.45 (0.24–0.85)**
Sepsis (%)	46/628 (7.3)	41/620 (6.6)	1.12 (0.72–1.73)	45/658 (6.8)	45/651 (6.9)	0.99 (0.64–1.52)
Necrotizing enterocolitis (%)	11/628 (1.8)	7/624 (1.1)	1.57 (0.61–4.08)	9/656 (1.4)	8/652 (1.2)	1.12 (0.43–2.92)
Treated retinopathy of prematurity (%)	91/610 (14.9)	98/595 (16.5)	0.89 (0.65–1.21)	95/646 (14.7)	107/621 (17.2)	0.83 (0.61–1.12)
Composite adverse outcomes (%)	51/631 (8.1)	65/631 (10.3)	0.77 (0.52–1.13)	46/660 (7.0)	73/660 (11.1)	**0.61 (0.42–0.90)**
Medium-term outcomes	(n=274)	(n=261)		(n=280)	(n=281)	
Death after NICU discharge (%)	1/274 (0.4)	2/261 (0.8)	0.47 (0.04–5.26)	3/280 (1.1)	4/281 (1.4)	0.75 (0.17–3.38)
Home oxygen therapy or home respiratory therapy (%)	6/207 (2.9)	0/197 (0)	12.7 (0.71–229)	4/209 (1.9)	2/213 (0.9)	2.06 (0.37–11.4)
Visual impairment (%)	7/254 (2.8)	10/242 (4.1)	0.66 (0.25–1.76)	19/261 (7.3)	11/254 (4.3)	1.73 (0.81–3.72)
Hearing impairment (%)	1/214 (0.5)	2/184 (1.1)	0.43 (0.04–4.75)	0/211 (0)	2/190 (1.1)	0.18 (0.01–3.76)
Cerebral palsy (%)	22/258 (8.5)	23/248 (9.3)	0.91 (0.49–1.68)	17/271 (6.3)	24/267 (9.0)	0.68 (0.36–1.29)
Developmental quotient <70 (%)	29/156 (18.6)	19/159 (12.0)	1.68 (0.90–3.15)	26/160 (16.3)	27/172 (15.7)	1.04 (0.58–1.88)
Composite adverse outcomes (%)	46/274 (16.8)	40/261 (15.3)	1.12 (0.70–1.77)	42/280 (15.0)	50/281 (17.8)	0.82 (0.52–1.28)

ACS, antenatal corticosteroids; OR, odds ratio; CI, confidence interval; short-term composite adverse outcomes: in-hospital death, intraventricular hemorrhage (grade III or IV) and periventricular leukomalacia, medium-term composite adverse outcomes: death after NICU discharge, cerebral palsy or developmental quotient <70. Bold indicates a significant association.