Title

Impact of postnatal dexamethasone timing on preterm mortality and bronchopulmonary dysplasia: a propensity score analysis

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Word count (excluding title page, abstract, references, figures and tables): 2,998 words

Figures and Tables: 2 figures, 3 tables, 9 supplementary tables, 2 supplementary figures, 1 supplementary text

Keywords: bronchopulmonary dysplasia, preterm, respiratory, dexamethasone

Take home message (256 characters):

The ideal timing of postnatal dexamethasone to prevent BPD is unclear. After minimising residual confounding, first dexamethasone use at >5 weeks old is associated with a higher incidence of severe BPD/death and later extubation than use at 2–3 weeks old.

ABSTRACT

Introduction

Postnatal dexamethasone (PND) is used in high-risk preterm infants after the first week of life to facilitate extubation and prevent bronchopulmonary dysplasia (BPD) but the optimal treatment timing remains unclear.

Objective

Explore the association between the timing of PND commencement with mortality and respiratory outcomes.

Methods

Retrospective National Neonatal Research Database study of 84,440 premature infants born below 32 weeks of gestational age from 2010–2020 in England and Wales. Propensity score weighting analysis was used to explore the impact of PND commenced at three timepoints (two to three weeks ($PND^{2/3}$), four to five weeks ($PND^{4/5}$) and after five weeks (PND^{6+}) of chronological age) on the primary composite outcome of death before neonatal discharge and/or severe BPD (defined as respiratory pressure support at 36 weeks) alongside other secondary respiratory outcomes.

Results

3,469 infants received PND. Compared to $PND^{2/3}$, infants receiving PND^{6+} were more likely to die and/or develop severe BPD (OR 1.68, 95% CI 1.28–2.21), extubate at later postmenstrual age (mean difference 3.1 weeks, 95% CI 2.9–3.4), potentially require respiratory support at discharge (OR 1.34, 95% CI (1.06–1.70), but had lower mortality before discharge (OR 0.38, 95% CI 0.29–0.51). $PND^{4/5}$ was not associated with severe BPD or discharge respiratory support.

Conclusion

PND treatment after five weeks of age was associated with worse respiratory outcomes although residual bias cannot be excluded. A definitive clinical trial to determine the optimal PND treatment window, based on early objective measures to identify high-risk infants, is needed.

ABBREVIATION

BPD – Bronchopulmonary dysplasia

GA – Gestational age

IQR – Interquartile range

IPTW – Inverse probability of treatment weighted

NNRD – National Neonatal Research Database

PMA – Postmenstrual age

PND – Postnatal dexamethasone

$PND^{2/3}$ – Postnatal dexamethasone commenced at two to three weeks of chronological age

$PND^{4/5}$ – Postnatal dexamethasone commenced at four to five weeks of chronological age

PND^{6+} – Postnatal dexamethasone commenced after five weeks of chronological age

INTRODUCTION

Preterm infants born below 32 weeks of gestational age (GA) are at high risk of developing bronchopulmonary dysplasia (BPD) which is associated with a higher risk of mortality and morbidity [1], chronic pulmonary diseases in adulthood [2, 3], as well as long-term neurodevelopmental impairment [2]. With increasing BPD severity, the risk of late death after 36 weeks postmenstrual age (PMA), severe respiratory morbidity or moderate/severe neurodevelopmental impairment are up to seven times higher compared to preterm infants without BPD [4].

Postnatal dexamethasone (PND) is frequently used [5] to facilitate the extubation of preterm infants and reduce BPD and mortality risk [6, 7]. However, there is insufficient evidence as to which group of infants would benefit from PND and the optimal time to start treatment [6, 7], leading to variation in practice [8]. PND use, especially in the first week of life, in infants at low risk of BPD is associated with poor neurodevelopmental outcomes and cerebral palsy [9], alongside other adverse effects including hypertension and gastrointestinal perforation [10]. Conversely, delaying treatment may expose infants likely to benefit from treatment to a longer duration of invasive ventilation leading to further lung inflammation and injury [11] so missing the therapeutic window.

Most studies to date examining the optimal timing of PND treatment have been small, underpowered or terminated early [6, 7, 12]. A recent Cochrane review found that PND commenced after 7 days of life in preterm infants reduced mortality and BPD risk (n=553 infants, 12 trials) but was unable to examine optimal timing [7]. Additionally, a network meta-analysis of 14 corticosteroid BPD prevention regimes suggested a moderate dose of PND on days 8–14 of life was most effective (n=660 infants) in preventing mortality or BPD [12]. Conversely, another network meta-analysis [13] of five corticosteroids for BPD (n=6,747 infants) found aggressive early PND initiation in the first week of life to be beneficial, but did not break down the late (after 7 days) PND group to explore optimal timing. However, in all three analyses combined, only 139 infants were recruited since 2003,

with most studies undertaken 20-35 years ago, before modern neonatal intensive care approaches to reduce mortality and BPD. Therefore, this study aims to explore the impact of the chronological age when PND was commenced on preterm mortality and respiratory outcomes in a large contemporary national cohort.

MATERIAL AND METHODS

Study design

This population-based retrospective cohort study uses de-identified data from the National Neonatal Research Database (NNRD), a population-level dataset containing detailed information entered at the point of care. The data cover the entire clinical stay across multiple neonatal units, encompassing once-only demographic information including gestation, birthweight and sex as well as daily data including respiratory support and drugs received (without doses). Over 90% of neonatal units in England in 2010 contributed data to the NNRD with 100% coverage in England and Wales by 2012 and 2014 respectively. Ethical approval was granted by the Sheffield Research Ethics Committee (REC reference 19/YH/0115). The study was reported using the Strengthening the Reporting of Observational Studies in Epidemiology guideline [14], Lederer et al [15] and propensity score checklists [16].

Patient population

We included all infants born below 32 weeks GA admitted to 185 neonatal units in England and Wales from 01 January 2010 to 31 December 2020. In line with current PND recommendations in premature infants [10], infants who received PND after the first seven days of life but before 36 weeks PMA and who were invasively ventilated when PND was first commenced were included in the propensity score analysis. Infants with a birthweight for GA z-score greater than 4 standard deviations above or below the mean, or who were discharged to non-participating units, were

excluded as they likely represent erroneous or incomplete entries respectively. Infants with major congenital anomalies as defined previously [17] (**Supplementary Table 1**) or missing data on our primary composite outcome of death before discharge and/or severe BPD were also excluded.

Definition of clinical practices and outcomes

PND use was defined as more than two consecutive days of receiving PND, based on a recent survey [8], to ensure their intended use to treat or prevent BPD. A seven-day washout period was used to define new PND courses. The primary outcome was the composite outcome of death before discharge and/or severe BPD. Secondary respiratory outcomes included the individual outcomes of death, BPD, severe BPD, respiratory support requirement at discharge, duration of invasive ventilation, percentage of infants who were successfully extubated for at least 7 days within 14 days of receiving PND, and PMA when successfully extubated.

Severe BPD was defined using the Grade 2/3 BPD definition by Jensen et al 2019 [4], which is respiratory pressure support (non-invasive (including high flow above 2Lpm) and invasive ventilation) requirement at 36 weeks PMA due to its stronger association with long-term pulmonary and neurodevelopmental sequelae [4, 18]. These were assessed over three days (36 weeks PMA ± 1 day) to allow for missing data or fluctuating requirements. If infants were discharged before 36 weeks PMA, respiratory support at discharge was used. Infants who died before discharge were excluded from the respiratory support at discharge and BPD definitions. Further definitions of the variables are described in **Supplementary Table 2**.

Statistical analyses

All statistical analyses were performed using STATA SE 17 [19] and RStudio [20] with Bonferroni-corrected significance level for multiple testing. Summary statistics, such as median, interquartile

range (IQR) and percentages, were used to describe the infant characteristics in the overall cohort and those who received PND. Trends over time were analysed using the chi-squared test for trend [21] and a Wilcoxon rank-sum test extension [22] for categorical and continuous data respectively.

Propensity score weighting analysis was performed using the "Twang" package [23, 24] to minimise bias by confounding in exploring the association of the timing of commencing PND on respiratory outcomes. The cohort was split into three groups based on the chronological age they received PND: two to three weeks ($PND^{2/3}$); four to five weeks ($PND^{4/5}$); and after five weeks old (PND^{6+}). The three groups were chosen to assess the impact of commencing PND before, at and after the median chronological age when PND was commenced (**Figure 1**).

The propensity for the infants to be assigned to each of the three PND groups was then estimated based on a-priori variables [10, 25] (**Supplementary Table 2**) using the generalized boosted model, a machine learning approach which relies on iterative tree-based regression models [24]. The estimated propensity scores were subsequently used as inverse weights in estimating the treatment effects based on the inverse probability of treatment weighted (IPTW) approach [16]. The success of the IPTW approach was assessed by examining the balance of the a-priori variables across the three groups. Missing values (**Supplementary Table 3**) were controlled for by including missing value indicators and balancing rates of missingness in the three groups. Finally, the difference in weighted means was used to estimate the association between treatment groups and outcomes as the a-priori variables were balanced across the three groups after IPTW. **Supplementary Text 1** described the propensity score weighting approach in further detail.

Four sensitivity analyses were performed. Firstly, to minimise potential lead time bias, infants who received PND after 32 weeks PMA were excluded to allow PND at least 4 weeks to take effect before BPD was diagnosed at 36 weeks PMA. Secondly, to minimise survival bias, infants who died before 6

weeks of age were excluded so that infants will have at least survived to the earliest time point as infants in the late PND^{6+} group. As the GA at birth was not balanced after IPTW for the first two sensitivity analyses, a double adjustment [27] was performed for GA at birth. Thirdly, to minimise unmeasured bias [26], infants with propensity scores outside the 5th–95th centile ranges of all three PND groups were excluded. Lastly, to partially account for PND courses for BPD that may have been terminated early, PND use was defined as at least seven consecutive days of treatment, which is two-thirds of the duration of the most commonly used PND regime for BPD [8].

RESULTS

Infant cohort

84,440 premature infants born below 32 weeks GA were admitted into 185 neonatal units within the NNRD from 2010 to 2020. 3,469 (4%) infants fulfilled the inclusion criteria for the propensity score analysis of PND use (**Figure 2** and **Table 1**). 16% (n=541) of these infants died at a median (IQR) chronological age of 49 days (28–91). 2,827 (81%) infants developed the composite outcome of death and/or severe BPD. Among the 2,928 survivors to discharge, 2,018 (69%) infants required respiratory support at discharge (**Table 1**).

Dexamethasone use

PND use in ventilated infants between eight days of age and 36 weeks PMA increased from 3% in 2010 to 5% in 2020 ($p<0.001$) and was commenced earlier from a median (IQR) of 28 days (20–40) of chronological age in 2010 to 24 days (18–32) in 2020 ($p<0.001$). There was an increasing trend in the percentage of infants receiving multiple PND courses from 25% in 2010 to 34% in 2020 ($p=0.04$). Infants born at earlier gestations ($p<0.001$) and lower birthweights ($p<0.001$) were more likely to receive PND later (**Table 2** and **Supplementary Table 4**).

Propensity score analysis

All a-priori variables were balanced across the three groups after weighting (**Supplementary Table 4, Supplementary Figure 1–2, Supplementary Text 1**). After weighting, PND^{6+} infants were more likely to develop the composite outcome of death before discharge and/or severe BPD (odds ratio (OR) 1.68, 95% confidence interval (CI) 1.28–2.21) but were less likely to die before discharge (OR 0.38, 95% CI 0.29–0.51) when compared to $PND^{2/3}$ infants. In infants who survived to discharge, PND^{6+} infants received a longer duration of invasive ventilation (mean difference (MD) 17.5 days, 95% CI 15.3–19.7) and were extubated at a later PMA after commencing PND (MD 3.1 weeks, 95% CI 2.9–3.4) when compared to $PND^{2/3}$ infants. Although not achieving the conservative Bonferroni-corrected statistical significance, there was an increasing trend of respiratory support requirement at neonatal discharge in PND^{6+} infants who survived to discharge than in $PND^{2/3}$ infants (OR 1.34, 95% CI 1.06–1.70). There was no statistically significant difference in the odds of BPD among the three PND groups. Compared to $PND^{2/3}$, $PND^{4/5}$ and PND^{6+} infants were more likely to be successfully extubated within 14 days of starting PND, but this did not translate into differences with severe BPD or respiratory support at discharge (**Table 3**).

Sensitivity analyses

All four sensitivity analyses found similar findings of more severe BPD and extubation at a later PMA in PND^{6+} infants than in $PND^{2/3}$ infants (**Supplementary Tables 5 – 8**). In the first two sensitivity analyses, more PND^{6+} infants required respiratory support at discharge than in $PND^{2/3}$ infants, achieving Bonferroni-corrected statistical significance (**Supplementary Tables 5, 6**). The odds of death among all three groups were not different when excluding infants who died before 6 weeks old to minimise survival bias (**Supplementary Table 6**).

DISCUSSION

This large population-based cohort study, representing over 90% of live births of premature infants born below 32 weeks GA in England and Wales, describes the PND use and the association between the timing of PND commencement with respiratory morbidities and mortality. This provides a true reflection of current practices and valuable data for healthcare professionals caring for these infants during the neonatal stay and those in the post-discharge phase, including respiratory specialists.

Trend of postnatal dexamethasone (PND) use

PND use to prevent BPD or aid extubation in premature infants born below 32 weeks GA in England and Wales has nearly doubled over the last 11 years, demonstrating a fluctuating trend of PND use from a high dose protracted course in the 1990s to reduced use in the 2000s [29], and finally to the current increased use. Despite this increasing trend, BPD rates continue to increase [30]. This may reflect the difficulty in balancing the risk-benefit of PND use and the lack of evidence in determining the ideal timing of using PND in high risk infants. In 2020, PND was typically commenced more than two weeks later than the earliest age suggested by national guidance [10], with a further 34% of infants requiring repeated PND courses.

Timing of commencement of postnatal dexamethasone

Our study suggests that PND commenced between 8 and 35 days of chronological age was associated with a lower incidence of severe BPD, extubation at an earlier PMA and potentially lower need for respiratory support at discharge. These findings persisted after minimising the lead time, survival and residual bias (**Strengths and limitations**) via the sensitivity analyses performed. This suggests that the anti-inflammatory effect of PND may become less effective the later PND is commenced, possibly reflecting more severe lung injury secondary to prolonged ventilation, which is known to be a good predictor of severe BPD during the first month of life [31] and the generalised pro-inflammatory state of premature infants.

The higher odds of death before discharge with earlier PND use cannot be fully explored with the present study methodology. This may be partly explained by the selection bias of infants receiving PND earlier that was not accounted for in our modelling, rather than a true casual effect. The association was not seen in the sensitivity analysis to minimise survival bias. This may explain the competing findings of the association found between later PND use with higher odds of severe BPD and/or death but lower mortality odds. Acutely unwell infants are more likely to receive dexamethasone earlier while infants who received dexamethasone later had already survived longer by definition. A previous meta-analysis found that the commencement of postnatal corticosteroids after 7 days of age demonstrated a trend towards a reduction in mortality without significant impact on long-term neurodevelopmental outcomes [7].

Our findings were consistent with those found by Harmon et al [32] and Cuna et al [33]. Harmon et al [32] concluded that postnatal corticosteroids should be considered before 50 days old for the lowest associated odds of severe BPD in their NICHD Neonatal Research Network cohort of 951 infants born between 2006 and 2012. The later age of 50 days suggested may be partly explained by the combination of the different PNC types (dexamethasone and hydrocortisone) used in their study which may have different anti-inflammatory effects. Cuna et al [33] found that delayed commencement of PND at 29–42 days vs 14–28 days old was associated with worse short-term outcomes, including longer duration of invasive ventilation and oxygen requirement although this was a single centre cohort of just 55 infants born between 2011 and 2016.

A recent network meta-analysis found that moderate PND dose given at 8–14 days was superior to 13 other BPD preventative regimes, including a range of PND doses given later at 14–28 days, although the evidence was of low certainty and included only two studies recruiting 117 infants within the last 20 years (i.e. 2006–2010 and 2012–2013). Furthermore, the authors concluded that the top three most

beneficial BPD preventative regimes were moderate dose and high dose PND given at 8–14 days as well as high dose PND given at 14–28 days [12]. Previous randomised controlled trials comparing the different timing of commencing PND found no difference in respiratory outcomes at 36 weeks PMA between PND use at 7 vs 14 days [34, 35] and 2 weeks vs 4 weeks [36] respectively. However, these trials were undertaken in the 1990s, whereby neonatal respiratory practices have changed significantly since with increased surfactant use and lung injury minimisation ventilation strategies.

Strengths and limitations

The key strengths of this study include the large population with point-of-care data collected and the true reflection of contemporary practice with babies discharged as late as 2021. Due to the retrospective nature of the study, causation cannot be drawn from the associations seen. While a-priori factors from the literature [10, 25] were accounted for in our propensity score estimation, including birth years to minimise confounding by changes in practices over time, there may be further unmeasured confounders, including confounding by indication and lead time bias due to different follow-up periods in the three PND groups before BPD is diagnosed at 36 weeks PMA. However, sensitivity analyses to minimise these biases revealed similar results, supporting the main study findings. Although neurodevelopmental outcomes were not available, previous meta-analyses [7] and observational studies [32, 37] found that the risk for neurodevelopmental impairment did not differ significantly by the chronological age of dexamethasone exposure after 7 days old. We did however choose severe BPD as an outcome as this is known to be associated with worse neurodevelopmental outcomes [4] and preterm infants discharged from hospital on respiratory support have significantly more respiratory morbidity compared with those discharged without respiratory support [38].

Though the dose and indication of PND were not available, the definition of PND used was based on the current clinical practice [8], ensuring that the PND was intended to facilitate extubation and prevent BPD. Although the use of other postnatal corticosteroids may affect the results, this is

unlikely to change the findings as dexamethasone remained the predominantly used postnatal corticosteroid for BPD [39]. Data inaccuracies and missing data could not be controlled for as data were entered at the point-of-care. However, the missing data rate was balanced across the three treatment groups after weighting. The study did not explore the potential impact of morbidities associated with poor respiratory outcomes [1], such as necrotising enterocolitis and treated retinopathy of prematurity, as it was beyond the study's aim. These morbidities often occurred after PND was commenced and it was difficult to ascertain with certainty the onset of these morbidities. Besides respiratory support requirement at discharge, further long-term respiratory outcomes that are important for parents [40], such as hospital readmissions and exercise limitation, were not available and warrant investigation in prospective studies.

Conclusion

Clinicians are increasingly using PND to prevent BPD in high-risk preterm infants despite the lack of evidence on the optimal time to commence PND. Although our study suggests that the optimal window for PND use was between 8 and 35 days of chronological age, which is in line with previous smaller studies, residual confounding and survival bias cannot be excluded. This highlights a need for both a definitive adequately powered clinical trial, including long-term outcomes, on the optimal timing for PND use, and objective measures to support the early identification of high-risk infants for timely PND treatment.

COMPETING INTERESTS

All authors declare no competing interests.

FUNDING

TCK received the Action Medical Research training fellowship, supported by the Albert Gubay Foundation, as part of this study.

ACKNOWLEDGEMENTS

Electronic patient data recorded at participating neonatal units are transmitted to the Neonatal Data Analysis Unit (NDAU) to form the NNRD. Professor Don Sharkey had full access to all the data in the study. We are grateful to all the families that agreed to include their baby's data in the NNRD, the health professionals who recorded data and the NDAU team (**Supplementary Table 9**).

TABLES

Demographics and characteristics	All infants (n = 84,440)	Received PND[1] (n = 3,469)
Gestation at birth (weeks), median (IQR)[2]	29^{+3} (27^{+2} – 30^{+6})	25^{+0} (24^{+1} – 26^{+2})
Birthweight (g), median (IQR)[2]	1,197 (900 – 1,490)	700 (609 – 815)
Small for gestational age, n (%)[2,3]	12,589 (15)	766 (22)
Sex, n (%)[2]		
Male	46,118 (55)	2,077 (60)
Received antenatal corticosteroids, n (%)[2]	75,637 (90)	3,125 (91)
Received surfactant, n (%)	52,225 (62)	3,360 (97)
Duration of invasive ventilation (days), median (IQR)	2 (0 – 6)	38 (27 – 52)
Death, n (%)[4]	7,529 (9)	541 (16)
Severe bronchopulmonary dysplasia or death, n (%)[2,4]	19,399 (23)	2,827 (81)
Respiratory support at 36 weeks PMA, n (%)[2,5]		
None	52,453 (68)	133 (5)
Oxygen only	12,157 (16)	509 (17)
Pressure support	11,870 (15)	2,286 (78)
Respiratory support at discharge, n (%)[2,5]		
None	64,077 (83)	893 (31)
Oxygen only	10,051 (13)	1,637 (56)
Pressure support	2,048 (3)	381 (13)

Table 1 Demographics and clinical characteristics of all infants extracted from the National Neonatal Research Database (N = 84,440) as well as infants who received a course of postnatal dexamethasone (PND) (N=3,469). n = total number of infants. PMA = postmenstrual age.

[1] PND was defined as dexamethasone use for more than two consecutive days in ventilated infants between 8 days of chronological age and 36 weeks PMA.

[2] Number (percentage) of infants with missing data in the full cohort for the following variables: gestation 2 (<0.01%), birthweight 11 (0.0%), small for gestational age 116 (0.1%), sex 62 (0.1%), antenatal corticosteroids 715 (0.9%), severe bronchopulmonary dysplasia and/or death 431 (0.5%), respiratory support at 36 weeks PMA 431 (0.6%) and respiratory support at discharge 735 (1.0%).

[3] Small for gestational age was defined as birthweight <10^{th} centile based on the UK-WHO growth chart [28].

[4] Death was defined as death before discharge from the neonatal unit.

[5] Infants who died before discharge were excluded from the analysis of respiratory support at 36 weeks PMA and discharge respectively.

Age (weeks) when PND[1] started	GA at birth, weeks median (IQR)	Birthweight, g median (IQR)	Sex n (%) male	Antenatal corticosteroids n (%)[3]	Surfactant n (%)	Duration of first PND course, days median (IQR)	Total days on PND, days median (IQR)	Multiple PND courses n (%)
2 (n = 344)	25^{+1} (24^{+1} – 26^{+4})	730 (630 – 855)	212 (62)	303 (88)	338 (98)	10 (6 – 19)	14 (8 – 29.5)	115 (33)
3 (n = 911)	25^{+1} (24^{+1} – 26^{+2})	705 (600 – 820)	552 (61)	802 (88)	878 (96)	11 (8 – 17)	15 (10 – 27)	323 (35)
4 (n = 854)	25^{+2} (24^{+2} – 26^{+3})	710 (614 – 830)	517 (61)	794 (93)	840 (98)	10 (8 – 15)	13 (9 – 23)	250 (29)
5 (n = 517)	25^{+0} (24^{+1} – 26^{+1})	705 (617 – 810)	306 (59)	471 (92)	498 (96)	10 (7 – 14)	12 (9 – 20)	121 (23)
6 (n = 337)	25^{+0} (24^{+1} – 26^{+1})	685 (600 – 780)	200 (59)	307 (91)	317 (94)	10 (7 – 13)	12 (9 – 19)	81 (24)
7 (n = 237)	24^{+5} (24^{+0} – 26^{+1})	665 (580 – 780)	141 (59)	206 (88)	231 (97)	10 (7 – 13)	12 (9 – 21)	63 (27)
8 (n = 121)	25^{+0} (24^{+1} – 26^{+2})	680 (592 – 815)	66 (55)	107 (90)	116 (96)	10 (7 – 14)	12 (9 – 19)	29 (24)
9 (n = 67)	24^{+5} (24^{+0} – 25^{+4})	658 (600 – 770)	37 (55)	59 (88)	66 (99)	11 (7 – 12)	11 (9 – 16)	16 (24)
≥10 (n = 81)	24^{+3} (23^{+6} – 25^{+0})	650 (570 – 750)	46 (57)	76 (95)	76 (94)	10 (6 – 14)	12 (7 – 23)	21 (26)
p value for trend[2]	<0.001*	<0.001*	0.1	0.2	0.06	0.001*	<0.001*	<0.001*

Table 2 Demographics and clinical characteristics of the 3,469 infants who received postnatal dexamethasone (PND) stratified by the chronological age in weeks they first received PND. n = total number of infants. * = statistically significant after Bonferroni correction.

[1] A course of PND was defined as PND use for more than two consecutive days in ventilated infants between 8 days of chronological age and 36 weeks PMA.

[2] Extension of Wilcoxon rank-sum test or chi-squared test for trend was performed to examine the association of continuous or categorical variables respectively by the chronological age of infants first receiving PND in weeks.

[3] Data on complete antenatal corticosteroids course were missing for 17 (0.5%) infants.

Characteristics	Chronological age when postnatal dexamethasone was commenced (n=3,469)							
	Unweighted cohort			Weighted cohort[1]				
	PND$^{2/3}$ (n = 1,255)	PND$^{4/5}$ (n = 1,371)	PND^{6+} (n = 843)	PND$^{2/3}$ (ES = 1,098)	PND$^{4/5}$ (ES = 1,298)	PND^{6+} (ES = 636)	Treatment effect OR/MD (95% CI)	p value
Primary outcome								
Severe bronchopulmonary dysplasia and/or death, n (%)	991 (79.0)	1,098 (80.1)	738 (87.5)	79.6	79.9	86.8	PND$^{2/3}$: Reference PND$^{4/5}$: 1.02 (0.84 – 1.24) PND^{6+}: 1.68 (1.28 – 2.21)	 0.851 <0.001*
Secondary outcomes								
Death, n (%)	273 (21.8)	177 (12.9)	91 (10.8)	21.6	13.1	9.6	PND$^{2/3}$: Reference PND$^{4/5}$: 0.55 (0.44 – 0.68) PND^{6+}:0.38 (0.29 – 0.51)	 <0.001* <0.001*
Severe bronchopulmonary dysplasia, n (%)[2]	718 (73.1)	921 (77.1)	647 (86.0)	74.0	76.9	85.4	PND$^{2/3}$: Reference PND$^{4/5}$: 1.17 (0.95 – 1.43) PND^{6+}: 2.05 (1.55 – 2.71)	 0.135 <0.001*
Bronchopulmonary dysplasia, n (%)[2]	928 (94.5)	1,138 (95.3)	729 (96.9)	94.8	95.3	96.1	PND$^{2/3}$: Reference PND$^{4/5}$: 1.11 (0.74 – 1.66) PND^{6+}: 1.34 (0.77 – 2.34)	 0.608 0.304
Duration of invasive ventilation (days), median (IQR)[2]	30 (22 – 43)	35 (28 – 45)	51 (41 – 64)	30 (22 – 44)	35 (28 – 46)	49 (40 – 60)	PND$^{2/3}$: Reference PND$^{4/5}$: 4.3 (2.6 – 6.0) PND^{6+}: 17.5 (15.3 – 19.7)	 <0.001* <0.001*
Successful extubation within 14 days of starting PND, n (%)[2]	609 (62.0)	899 (75.3)	591 (78.6)	60.2	74.7	79.6	PND$^{2/3}$: Reference PND$^{4/5}$: 2.0 (1.6 – 2.4) PND^{6+}: 2.6 (2.0 – 3.3)	 <0.001* <0.001*
PMA when successfully extubated after receiving PND (weeks), median (IQR)[2]	29^{+5} (28^{+4} – 31^{+2})	30^{+4} (29^{+3} – 31^{+6})	32^{+6} (31^{+3} – 34^{+3})	29^{+5} (28^{+4} – 31^{+3})	30^{+4} (29^{+2} – 31^{+6})	32^{+6} (31^{+3} – 34^{+3})	PND$^{2/3}$: Reference PND$^{4/5}$: 0.7 (0.5 – 0.9) PND^{6+}: 3.1 (2.9 – 3.4)	 <0.001* <0.001*
Respiratory support at discharge, n (%)[2]	658 (67.0)	807 (67.6)	553 (73.5)	67.4	67.8	73.2	PND$^{2/3}$: Reference PND$^{4/5}$: 1.04 (0.86 – 1.25) PND^{6+}: 1.34 (1.06 – 1.70)	 0.713 0.015

Table 3 Neonatal outcomes between infants who received postnatal dexamethasone (PND) at the chronological age of two to three weeks (PND$^{2/3}$); four to five weeks (PND$^{4/5}$); and after five weeks (PND^{6+}) in the unweighted (n=3,469) and weighted infant cohort (effective sample size (ES) =3,032). n = number of infants. OR = Odds ratio. MD = Mean difference. CI = confidence interval. IQR = interquartile range. * = statistically significant after Bonferroni correction.

[1] Only the percentage of infants with the respective categorical neonatal outcomes was depicted for the weighted infant cohort.

[2] Infants who died before discharge were excluded from the analysis.

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FIGURE LEGENDS

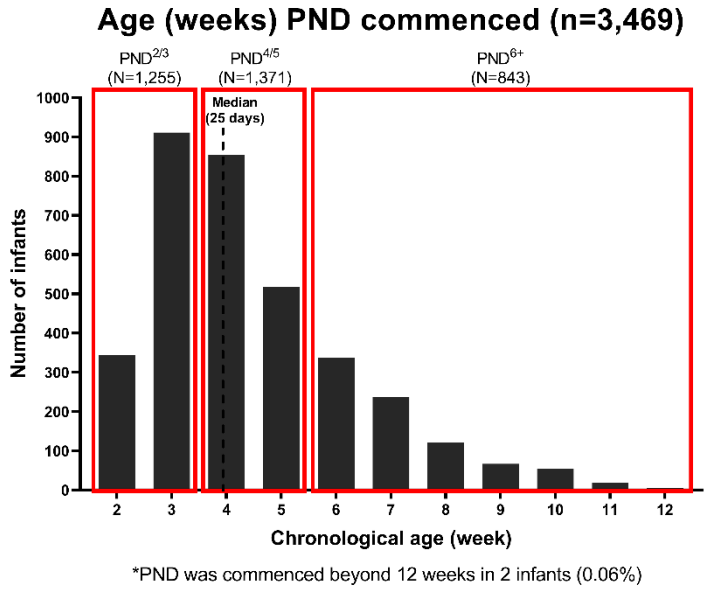

Figure 1: Histogram showing the chronological age in weeks when postnatal dexamethasone (PND) was commenced in 3,469 infants who met the study inclusion criteria with a median of 25 days and the three groups of infants receiving PND at two to three weeks ($PND^{2/3}$), four to five weeks ($PND^{4/5}$) and after five weeks old (PND^{6+}).

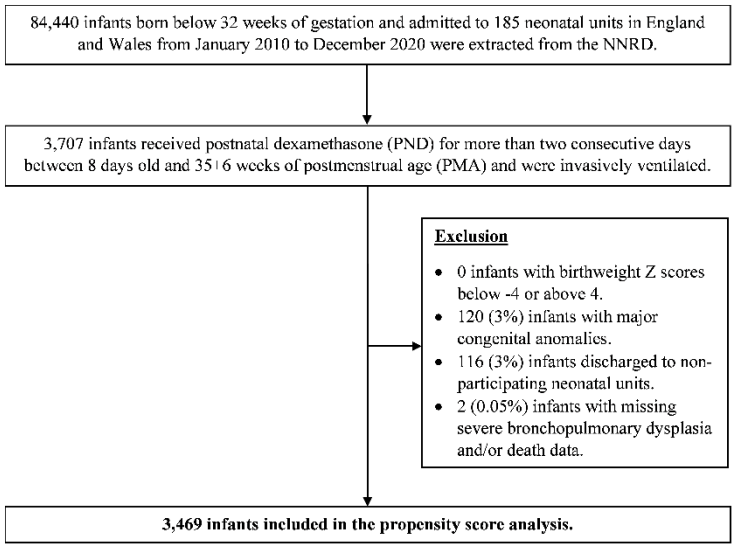

Figure 2: Participant flow diagram for the analysis of the trend of postnatal dexamethasone use from 2010 to 2020 as well as the propensity score analysis on the timing of commencing postnatal dexamethasone (PND). NNRD = National Neonatal Research Database. PMA = postmenstrual age

SUPPLEMENTARY MATERIAL

Supplementary Table 1 ICD-10 codes used to identify major congenital anomaly exclusions and the associated number of babies excluded. [1]Sum exceeds the total number of exclusions as some infants had more than one anomaly.

ICD-10 code	Anomaly	Number of infants excluded[1]
Q00	Anencephaly and similar malformations	0
Q01	Encephalocele and similar malformations	1
Q05	Spina bifida and similar malformations	0
Q20	Congenital malformations of cardiac chambers and connections	0
Q20.3	Transposition of great arteries	0
Q21.2	Atrioventricular septal defect (AVSD)	1
Q21.3	Tetralogy of Fallot	3
Q21.91	Single atrium	0
Q21.92	Single ventricle	0
Q22	Congenital malformations of pulmonary and tricuspid valves	28
Q23	Congenital malformations of aortic and mitral valves	12
Q23.4	Hypoplastic left heart	1
Q25.1	Coarctation of aorta	8
Q25.4	Other congenital malformations of aorta	1
Q25.5	Atresia of pulmonary artery	0
Q25.6	Stenosis of pulmonary artery (PS)	22
Q25.8	Other congenital malformations of great arteries	0
Q26.2	Total anomalous pulmonary venous connection (TAPVD)	1
Q30.0	Choanal atresia	3
Q32	Congenital malformations of trachea and bronchus	6
Q33.0	Congenital cystic lung	8
Q33.2	Sequestration of lung	1
Q33.3	Agenesis of lung	0
Q33.4	Congenital bronchiectasis	0
Q33.5	Ectopic tissue in lung	0
Q33.6	Hypoplasia and dysplasia of lung	2
Q34.0	Anomaly of pleura	0
Q34.1	Congenital cyst of mediastinum	0
Q34.8	Other specified congenital malformations of respiratory system	1
Q35/Q36/Q37	Cleft lip and/or palate	27
Q39	Oesophageal atresia	7
Q41	Congenital absence, atresia and stenosis of small intestine	0
Q42	Congenital absence, atresia and stenosis of large intestine	0
Q60.1	Bilateral renal agenesis	0
Q60.6	Potter's syndrome	0
Q61.1	Polycystic kidney, infantile type	0
Q61.2	Polycystic kidney, adult type	0
Q64.1	Exstrophy of urinary bladder	0
Q64.2	Posterior urethral valves (PUV)	1
Q64.5	Congenital absence of bladder and urethra	0
Q77.1	Thanatophoric short stature	1
Q79.0	Congenital diaphragmatic hernia	2
Q79.1	Eventration of diaphragmatic hernia	2
Q79.2	Exomphalos	10
Q79.3	Gastroschisis	0
Q90	Down's syndrome	5
Q91	Edwards' syndrome and Patau's syndrome	0

Supplementary Table 2 Definition of the variables and the associated data items extracted from the National Neonatal Research Database.

Treatment	
Variable	**Data Items**
Postnatal dexamethasone (PND)	**Definition**: Dexamethasone treatment for more than two consecutive days in ventilated infants between 8 days of chronological age and 36 weeks of postmenstrual age (PMA). Dexamethasone eye drops were excluded from this definition. This definition is based on current practices [1] to ensure that they are intended to treat or prevent BPD rather than for other reasons. A washout period of 7 days was used to define repeated courses. • Data extracted from "DRUGSDAY" variable in the "DAILY" dataset. • Dichotomous (Yes/No)
A-priori variables used for propensity score estimation [2, 3]	
Variable	**Data Items**
Gestational age	• Data extracted from "GESTATIONDAYS" and "GESTATIONWEEKS" variables in the "EPISODES" dataset. • Continuous in days
Birthweight z score	**Definition**: Birthweight z score derived from the UK-WHO growth chart [4]. • Data extracted from "BIRTHWEIGHT", "GESTATIONDAYS", "GESTATIONWEEKS" and "GENDER" variables in the "EPISODES" dataset. • Continuous
Sex	• Data extracted from "GENDER" variable in the "EPISODES" dataset. • Dichotomous (Male/Female)
Multiple gestation	• Data extracted from "FETUSNUMBER" variable of more than 1 in the "EPISODES" dataset. • Dichotomous (Yes/No)
Maternal antenatal corticosteroids course	**Definition**: Any maternal antenatal corticosteroids received before delivery • Data extracted from "STEROIDSANTENATALCOURSES" variable in the "EPISODES" dataset. • Dichotomous (Yes/No)
Prolonged rupture of membrane	**Definition**: Rupture of membrane for more than 18 hours. • Data extracted from "ROMTIMEANON" variable or "Prolonged rupture membranes" response from the "PROBLEMSDURINGPREGNANCY" variable in the "EPISODES" dataset. • Dichotomous (Yes/No)
Maternal chorioamnionitis	**Definition**: Clinically suspected maternal chorioamnionitis by the obstetrics team. • Data extracted from "Chorioamnionitis" response from the "PROBLEMSDURINGPREGNANCY" variable in the "EPISODES" dataset as well as the "DIAGNOSISATADMISSION" and "PRINCIPALDIAGNOSISATDISCHARGE" variables in the "EPISODES" dataset for "Chorioamnionitis". • Dichotomous (Yes/No)
Maternal gestational diabetes	• Data extracted from "Gestational diabetes" response from the "PROBLEMSDURINGPREGNANCY" variable in the "EPISODES" dataset.

	• Dichotomous (Yes/No)
Maternal diabetes	• Data extracted from "Diabetes" response from the "PROBLEMSMEDICALMOTHER" variable in the "EPISODES" dataset. • Dichotomous (Yes/No)
Maternal pre-eclampsia	• Data extracted from "Pregnancy induced hypertension", "Pre-eclampsia" and "Maternal HELLP" responses from the "PROBLEMSDURINGPREGNANCY" variable in the "EPISODES" dataset. • Dichotomous (Yes/No)
Maternal hypertension	• Data extracted from "Chronic hypertension" response from the "PROBLEMSMEDICALMOTHER" variable in the "EPISODES" dataset. • Dichotomous (Yes/No)
Maternal age	• Data extracted from "BIRTHYEARMOTHER" and "BIRTHYEAR" variables in the "EPISODES" dataset. • Continuous
Level of care of neonatal unit at birth	• Data extracted from "POBNDAUCODE" variable in the "EPISODES" dataset and the "UNITLEVEL" variable in the "UNITLEVELSANDNDAUCODES" dataset. • Categorical (1/2/3)
Neonatal network at birth	• Data extracted from "POBNDAUCODE" variable in the "EPISODES" dataset and the "NEONATAL_ODN" variable in the "ODNMAPPINGANDNDAUCODES" dataset. • Categorical (14 networks)
Apgar score at 5 minutes	• Data extracted from "APGAR_5MIN" variable in the "EPISODES" dataset. • Continuous
Cardiopulmonary resuscitation at birth in infants <30 weeks	**Definition**: Cardiopulmonary resuscitation provided at birth in infants born below 30 weeks of gestation • Data extracted from "METHODSOFRESUSCITATION" variable in the "EPISODES" dataset if the "GESTATIONWEEKS" variables in the "EPISODES" dataset is <30. • Dichotomous (Yes/No)
Admission temperature below 35ºC	**Definition**: Admission temperature below 35ºC on the <u>first</u> neonatal admission. • Data extracted from "ADMITTEMPERATURE" variable from the "EPISODES" dataset if "EPISODENUMBERBABY" variable in the "EPISODES" dataset is 1. • Dichotomous (Yes/No)
Inotrope requirement in the first week of life	**Definition**: Inotrope (Dopamine, dobutamine, adrenaline, noradrenaline and milrinone) requirement in the first week of life. • Data extracted from "DRUGSDAY" and "INOTROPESGIVEN" variables from the "DAILY" dataset in the first week of age. • Dichotomous (Yes/No)
Invasive ventilation in the first week of life	**Definition**: Invasive ventilation in the first week of life. • Data extracted from "RESPIRATORYSUPPORT", "ADDEDO2", "VENTILATIONMODE" and "NONINVASIVERESPIRATORYSUPPORT" variables from the "DAILY" dataset in the first week of age. • Dichotomous (Yes/No)

Clinical sepsis with or without positive blood or CSF culture in the first week of life	**Definition**: Clinically suspected sepsis receiving at least five consecutive days of antibiotics (Benzylpenicillin, amoxicillin, flucloxacillin, gentamicin, metronidazole, meropenem, cefotaxime, ceftazidime, cefradine, ceftriaxone and vancomycin) or blood/CSF culture that grew organism of clear pathogenicity as defined by the National Neonatal Audit Programme 2021 [5] in the first week of age. • Data extracted from "DRUGSDAY" variable in the "DAILY" dataset as well as "PATHOGENSBLOODFORDBSYNCS" and "PATHOGENSCSFFORDBSYNCS" variables in the "SEPSIS SCREENS" dataset. • Dichotomous (Yes/No)
Enteral feed type in the first week of life	• Data extracted from "DAYENTERALFEEDS" and "FORMULANAME" variables in the "DAILY" dataset in the first week of age. • Categorical (Breast milk only, formula milk only, mixed formula and breast milk, nil by mouth)
Surfactant treatment	**Definition**: Surfactant treatment received at resuscitation or after admission to the neonatal unit. • Data extracted from "SURFACTANTGIVENRESUSCITATION" variable in the "EPISODES" dataset and "DAYSURFACTANTGIVEN" and "DRUGSDAY" variables in the "DAILY" dataset. • Dichotomous (Yes/No)
Birth year	• Data extracted from BIRTHYEAR" variable in the "EPISODES" dataset. • Continuous
Other variable	
Variable	**Data Items**
NMR-2000 score	**Definition**: Neonatal mortality risk score derived from birthweight, highest level of respiratory support at any point within 24 hours of birth and oxygen saturation on admission [6]. • Data extracted from "BIRTHWEIGHT" and "ADMISSIONOXYGENSATURATION" variables in the "EPISODES" dataset as well as from "RESPIRATORYSUPPORT", "ADDEDO2", "VENTILATIONMODE" and "NONINVASIVERESPIRATORYSUPPORT" variables from the "DAILY" dataset on day 1 of age. • Continuous
Outcome	
Variable	**Data Items**
Death	**Definition**: Death before discharge from the neonatal unit. • Data extracted from "DATEOFDEATH" and "DISCHARGEDESTINATION" variables from the "EPISODES" dataset. • Dichotomous (Yes/No)
Bronchopulmonary dysplasia (BPD)	**Definition**: Respiratory support or oxygen requirement over a three-day period at 36 weeks PMA or at discharge (if discharged before 36 weeks PMA [7, 8]). • Data extracted from "RESPIRATORYSUPPORT", "ADDEDO2", "VENTILATIONMODE" and "NONINVASIVERESPIRATORYSUPPORT" variables from

	the "DAILY" dataset over a three-day period at 36 weeks PMA or at discharge. • Dichotomous (Yes/No)
Severe BPD	**Definition**: Non-invasive (including high flow) and invasive ventilation requirement at 36 weeks PMA or at discharge (if discharged before 36 weeks PMA [7, 8]). • Data extracted from "RESPIRATORYSUPPORT", "ADDEDO2", "VENTILATIONMODE" and "NONINVASIVERESPIRATORYSUPPORT" variables from the "DAILY" dataset over a three-day period at 36 weeks PMA or at discharge. • Dichotomous (Yes/No)
Respiratory support at discharge	**Definition**: Respiratory support or oxygen requirement at discharge. • Data extracted from "RESPIRATORYSUPPORT", "ADDEDO2", "VENTILATIONMODE" and "NONINVASIVERESPIRATORYSUPPORT" variables from the "DAILY" dataset at discharge. • Dichotomous (Yes/No)
Days of invasive ventilation	**Definition**: Duration of invasive ventilation in days • Data extracted from "RESPIRATORYSUPPORT", "ADDEDO2", "VENTILATIONMODE" and "NONINVASIVERESPIRATORYSUPPORT" variables from the "DAILY" dataset. • Continuous in days
Successful extubation within 14 days of starting postnatal dexamethasone	**Definition**: Successfully extubated for at least 7 days within 14 days after the start of dexamethasone course • Data extracted from "RESPIRATORYSUPPORT", "ADDEDO2", "VENTILATIONMODE" and "NONINVASIVERESPIRATORYSUPPORT" variables from the "DAILY" dataset. • Dichotomous (Yes/No)
Postmenstrual age when successfully extubated after receiving postnatal dexamethasone	**Definition**: PMA when successfully extubated for at least 7 days after the dexamethasone course • Data extracted from "GESTATIONDAYS" and "GESTATIONWEEKS" variables in the "EPISODES" dataset as well as "RESPIRATORYSUPPORT", "ADDEDO2", "VENTILATIONMODE" and "NONINVASIVERESPIRATORYSUPPORT" variables from the "DAILY" dataset. • Continuous in weeks

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Supplementary Table 3 Missing cases for the a-priori variables and outcomes used in the propensity score analysis.

Characteristics	Number of missing cases, n (%)
A-priori variables	
Birthweight Z score	33 (0.9)
Maternal antenatal corticosteroids	17 (0.5)
Maternal age	10 (0.3)
Admission temperature	86 (2.4)
Ventilated in the first 7 days of age	2 (0.1)
Inotrope requirement in the first 7 days of age	2 (0.1)
Enteral feed in the first 7 days of age	2 (0.1)
Apgar at 5 minutes	499 (14.1)
Neonatal network at birth	58 (1.6)
Outcomes	
Respiratory support at discharge	17 (0.5)

Supplementary Table 1 Characteristics of infants in the overall cohort (N=84,440), unweighted (N=3,469) and weighted infant cohort (effective sample size (ES)=3,032) depending on chronological age when infants received postnatal dexamethasone (two to three weeks ($PND^{2/3}$); four to five weeks ($PND^{4/5}$); and after six weeks (PND^{6+})). IQR = interquartile range.

Characteristics	Overall cohort (n=84,440)	Chronological age when postnatal dexamethasone was commenced (n=3,469)						
		Unweighted cohort				Weighted cohort[1]		
		$PND^{2/3}$ (N = 1,255)	$PND^{4/5}$ (N = 1,371)	PND^{6+} (N = 843)	p value[2]	$PND^{2/3}$ (ES = 1,098)	$PND^{4/5}$ (ES = 1,298)	PND^{6+} (ES = 636)
Infant factors at birth								
Gestational age (weeks), median (IQR)	29^{+3} (27^{+2} – 30^{+6})	25^{+1} (24^{+1} – 26^{+3})	25^{+1} (24^{+2} – 26^{+2})	24^{+5} (24^{+0} – 26^{+0})	<0.001	25^{+0} (24^{+1} – 26^{+2})	25^{+0} (24^{+1} – 26^{+1})	25^{+0} (24^{+1} – 26^{+1})
Missing data, n (%)	2 (0.0)	0 (0)	0 (0)	0 (0)		0	0	0
Birthweight (g), median (IQR)	1,197 (900 – 1,490)	710 (610 – 830)	707 (615 – 820)	670 (590 – 780)	<0.001	700 (610 – 817)	700 (610 – 815)	691 (601 – 805)
Missing data, n (%)	11 (0.0)	0 (0)	0 (0)	0 (0)		0	0	0
Birthweight Z score, median (IQR)	-0.26 (-0.88 – 0.26)	-0.56 (-1.17 – -0.06)	-0.58 (-1.18 – -0.11)	-0.63 (-1.18 – -0.19)	0.035	-0.57 (-1.17 – -0.11)	-0.59 (-1.18 – -0.11)	-0.59 (-1.16 – -0.12)
Missing data, n (%)	314 (0.4)	11 (0.9)	10 (0.7)	12 (1.4)		0.8	1.0	0.8
Male, n (%)	46,118 (54.6)	764 (60.9)	823 (60.0)	490 (58.1)	0.447	60.8	59.8	58.5
Missing data	62 (0.1)	0 (0)	0 (0)	0 (0)		0	0	0
Birth year, n (%)								
2010	7,519 (8.9)	59 (4.7)	83 (6.1)	71 (7.9)	0.002	5.1	6.1	6.6
2011	7,848 (9.3)	95 (7.6)	104 (7.6)	60 (7.1)		7.8	7.9	7.7
2012	7,915 (9.4)	108 (8.6)	98 (7.1)	89 (10.6)		8.2	7.4	8.7
2013	7,873 (9.3)	118 (9.4)	111 (8.1)	76 (9.0)		9.3	8.4	8.6
2014	7,765 (9.2)	99 (7.9)	125 (9.1)	67 (7.9)		8.4	8.6	8.0
2015	8,016 (9.5)	98 (7.8)	149 (10.9)	79 (9.4)		9.0	10.1	9.9
2016	8,064 (9.5)	113 (9.0)	145 (10.6)	75 (8.9)		10.0	9.9	9.3
2017	7,937 (9.4)	137 (10.9)	133 (9.7)	93 (11.0)		10.5	10.0	10.9
2018	7,396 (8.8)	149 (11.9)	139 (10.1)	87 (10.3)		10.9	10.5	11.3
2019	7,380 (8.7)	166 (13.2)	148 (10.8)	85 (10.1)		12.3	11.6	10.5
2020	6,727 (8.0)	113 (9.0)	136 (9.9)	61 (7.2)		8.5	9.5	8.6
Multiple pregnancy, n (%)	22,130 (26.2)	271 (21.6)	330 (24.1)	213 (25.3)	0.119	21.8	23.4	24.5
Missing data	22 (0.0)	0 (0)	0 (0)	0 (0)		0	0	0

Antenatal corticosteroids, n (%)	75,637 (89.6)	1,105 (88.0)	1,265 (92.3)	755 (89.6)	0.001	89.9	90.5	91.1
Missing data	715 (0.8)	3 (0.2)	9 (0.7)	5 (0.6)		0.3	0.5	0.5
Maternal factors								
Prolonged rupture of membrane, n (%)	9,727 (11.5)	158 (12.6)	199 (14.5)	98 (11.6)	0.116	12.6	13.3	11.5
Chorioamnionitis, n (%)	3,534 (4.2)	81 (6.5)	93 (6.8)	60 (7.1)	0.836	7.0	6.7	6.7
Maternal diabetes, n (%)	1,528 (1.8)	15 (1.2)	24 (1.8)	10 (1.2)	0.394	1.4	1.5	1.5
Gestational diabetes, n (%)	3,064 (3.6)	11 (0.9)	26 (1.9)	13 (1.5)	0.087	0.6	1.6	1.4
Maternal hypertension, n (%)	1,145 (1.4)	20 (1.6)	35 (2.6)	16 (1.9)	0.209	1.9	2.2	1.5
Gestational hypertension, n (%)	9,377 (11.1)	134 (10.7)	148 (10.8)	82 (9.7)	0.703	11.3	10.7	10.0
Maternal age (years), median (IQR)	31 (26 – 35)	30 (26 – 35)	30 (26 – 35)	30 (26 – 34)	0.669	30 (26 – 35)	30 (26 – 35)	30 (26 – 34)
Missing data, n (%)	584 (0.7)	3 (0.2)	2 (0.1)	4 (0.5)		0.4	0.2	0.5
Infant factors after birth								
Cardiopulmonary resuscitation at birth, n (%)	2,826 (3.3)	92 (7.3)	97 (7.1)	48 (5.7)	0.311	6.8	6.9	6.1
5 minute Apgar score, median (IQR)	8 (7 – 9)	7 (5 – 8)	7 (5 – 8)	7 (5 – 8)	0.095	7 (5 – 8)	7 (5 – 8)	7 (5 – 8)
Missing data, n (%)	9,286 (11.0)	209 (16.7)	197 (14.4)	90 (10.7)		14.6	13.7	12.7
Admission temperature <35ºC, n (%)	1,455 (1.7)	58 (4.6)	40 (2.9)	42 (5.0)	0.034	4.0	3.6	4.1
Missing data	1,040 (1.2)	35 (2.8)	37 (2.7)	14 (1.7)		2.5	2.5	1.6
Invasive ventilation in first 7 days, n (%)	53,845 (63.8)	1,252 (99.8)	1,357 (99.0)	837 (99.3)	0.146	99.7	99.3	99.3
Missing data	393 (0.5)	0 (0.0)	1 (0.1)	1 (0.1)		0.0	0.1	0.1
Inotrope use in first 7 days, n (%)	15,949 (18.9)	721 (57.5)	760 (55.4)	490 (58.1)	0.527	57.2	56.7	55.9
Missing data	393 (0.5)	0 (0.0)	1 (0.1)	1 (0.1)		0.0	0.1	0.1
Sepsis in first 7 days, n (%)	33,993 (40.3)	897 (71.5)	983 (71.7)	652 (77.3)	0.005	72.7	72.7	73.9
Feed type in first 7 days, n (%)								
Nil by mouth	6,139 (7.3)	118 (9.4)	159 (11.6)	113 (12.5)	0.008	9.9	11.4	12.2
Breast milk only	54,599 (64.7)	1,095 (87.3)	1,132 (82.6)	704 (83.5)		86.2	84.2	83.9
Mixed breast and formula milk	18,332 (21.7)	34 (2.7)	62 (4.5)	21 (2.5)		3.2	3.3	2.9
Formula milk only	3,713 (4.4)	8 (0.6)	17 (1.2)	8 (0.9)		0.8	1.0	0.9
Missing data	1,657 (2.0)	0 (0.0)	1 (0.1)	1 (0.1)		0.0	0.1	0.1
Surfactant use, n (%)	52,225 (61.8)	1,216 (96.9)	1,338 (97.6)	806 (95.6)	0.034	96.9	97.1	96.6
NMR-2000 score [1], median (IQR)	10 (7 – 14)	5 (4 – 7)	5 (4 – 7)	5 (4 – 6)	<0.0001	5 (4 – 6)	5 (4 – 7)	5 (4 – 6)
Missing data, n (%)	9,281 (11.0)	129 (10.3)	129 (9.4)	90 (10.7)		10.1	9.4	11.0

Mortality risk based on NMR-2000 [1], n (%)								
Low risk	10,785 (12.8)	3 (0.2)	2 (0.1)	1 (0.1)		0.2	0.1	0.2
Moderate risk	54,747 (64.8)	515 (41.0)	588 (42.9)	295 (35.0)	0.021	40.3	41.3	38.4
High risk	9,627 (11.4)	608 (48.4)	652 (47.6)	457 (54.2)		49.4	49.2	50.4
Missing data	9,281 (11.0)	129 (10.3)	129 (9.4)	90 (10.7)		10.1	9.4	11.0
Organisational factor								
Neonatal unit level at birth, n (%)								
Level 1	6,395 (7.6)	58 (4.6)	78 (5.7)	56 (6.6)	0.306	4.7	5.6	5.5
Level 2	31,433 (37.2)	258 (20.6)	267 (19.5)	157 (18.6)		19.7	19.6	20.1
Level 3	46,595 (55.2)	939 (74.8)	1,026 (74.8)	630 (74.7)		75.5	74.8	74.3
Missing data	17 (0)	0 (0)	0 (0)	0 (0)		0	0	0
Neonatal network at birth, n (%)	82,955 (98.2)							
% spread across networks, median (IQR)	N/A	6.3 (3.6 – 9.8)	6.8 (5.2 – 9.3)	6.8 (4.5 – 9.8)	<0.001	5.9 (4.4 – 8.9)	6.6 (4.7 – 9.3)	6.7 (5.2 – 9.5)
Missing data	1,485 (1.8)	26 (2.1)	18 (1.3)	13 (1.5)		1.6	1.5	1.4

[1] Only the percentage of infants with the corresponding categorical variables was depicted for the weighted infant cohort.

[2] Chi-squared test and Kruskal-Wallis rank sum test were used to compare the categorical and continuous infant characteristics respectively across the three postnatal dexamethasone treatment groups.

References

1. Medvedev MM, Brotherton H, Gai A, Tann C, Gale C, Waiswa P, Elbourne D, Lawn JE, Allen E. Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 g or less (NMR-2000): an analysis using data from the UK and The Gambia. *The Lancet Child & Adolescent Health* 2020: 4(4): 299-311.

Supplementary Table 5 Neonatal outcomes between infants who received postnatal dexamethasone (PND) at the chronological age of two to three weeks ($PND^{2/3}$); four to five weeks ($PND^{4/5}$); and after six weeks (PND^{6+}) in the unweighted and weighted infant cohort after excluding infants who received PND after 32 weeks of postmenstrual age (PMA) (N=2,986). n = number of infants. OR = Odds ratio. MD = Mean difference. CI = confidence interval. IQR = interquartile range. * = statistically significant after Bonferroni correction.

Characteristics	Chronological age when PND was commenced excluding PND >32 weeks PMA (N=2,986)							
	Unweighted cohort			Weighted cohort[1]				
	$PND^{2/3}$ (n = 1,239)	$PND^{4/5}$ (n = 1,275)	PND^{6+} (n = 472)	$PND^{2/3}$	$PND^{4/5}$	PND^{6+}	Treatment effect OR/MD (95% CI)	p value
Primary outcome								
Severe bronchopulmonary dysplasia and/or death, n (%)	979 (79.0)	1014 (79.5)	399 (84.5)	79.6	79.2	84.8	$PND^{2/3}$: Reference $PND^{4/5}$: 0.98 (0.80 – 1.20) PND^{6+}: 1.46 (1.06 – 2.03)	 0.868 0.022
Secondary outcomes								
Death, n (%)	270 (21.8)	158 (12.4)	44 (9.3)	21.7	12.7	8.2	$PND^{2/3}$: Reference $PND^{4/5}$: 0.52 (0.41 – 0.65) PND^{6+}: 0.30 (0.21 – 0.44)	 <0.001* <0.001*
Severe bronchopulmonary dysplasia, n (%)[2]	709 (73.2)	856 (76.6)	355 (82.9)	73.9	76.2	83.4	$PND^{2/3}$: Reference $PND^{4/5}$: 1.14 (0.93 – 1.41) PND^{6+}: 1.85 (1.33 – 2.59)	 0.211 <0.001*
Bronchopulmonary dysplasia, n (%)[2]	917 (94.6)	1067 (95.5)	416 (97.2)	94.9	95.3	96.8	$PND^{2/3}$: Reference $PND^{4/5}$: 1.09 (0.72 – 1.64) PND^{6+}: 1.59 (0.76 – 3.32)	 0.682 0.219
Duration of invasive ventilation (days), median (IQR)[2]	30 (22 – 44)	35 (28 – 45)	49 (41 – 58)	31 (22 – 45)	35 (28 – 46)	46 (40 – 55)	$PND^{2/3}$: Reference $PND^{4/5}$: 3.3 (1.7 – 5.0) PND^{6+}: 12.2 (10.1 – 14.4)	 <0.001* <0.001*
Successful extubation within 14 days of starting PND, n (%)[2]	598 (61.7)	838 (75.0)	339 (79.2)	58.8	74.4	79.9	$PND^{2/3}$: Reference $PND^{4/5}$: 2.3 (2.0 – 2.8) PND^{6+}: 3.8 (2.9 – 5.1)	 <0.001* <0.001*
PMA when successfully extubated after receiving PND (weeks), median (IQR)[2]	29^{+5} (28^{+3} – 31^{+2})	30^{+3} (29^{+2} – 31^{+5})	31^{+4} (30^{+5} – 32^{+3})	29^{+4} (28^{+3} – 31^{+2})	30^{+2} (29^{+2} – 31^{+4})	31^{+5} (30^{+6} – 32^{+4})	$PND^{2/3}$: Reference $PND^{4/5}$: 0.7 (0.5 – 0.9) PND^{6+}: 2.3 (2.0 – 2.5)	 <0.001* <0.001*
Respiratory support at discharge, n (%)[2]	649 (67.0)	750 (67.1)	313 (73.1)	67.3	67.3	75.4	$PND^{2/3}$: Reference $PND^{4/5}$: 1.01 (0.84 – 1.23) PND^{6+}: 1.52 (1.13 – 2.05)	 0.896 0.005*

[1] Only the percentage of infants with the respective categorical neonatal outcomes was depicted for the weighted infant cohort.

[2] Infants who died before discharge were excluded from the analysis.

Supplementary Table 6 Neonatal outcomes between infants who received postnatal dexamethasone (PND) at the chronological age of two to three weeks ($PND^{2/3}$); four to five weeks ($PND^{4/5}$); and after six weeks (PND^{6+}) in the unweighted and weighted infant cohort after excluding infants who received PND after 32 weeks of postmenstrual age (PMA) or infants who died before 6 weeks old (N=2,760). N = number of infants. OR = Odds ratio. MD = Mean difference. CI = confidence interval. IQR = interquartile range. * = statistically significant after Bonferroni correction.

Characteristics	Chronological age when PND was commenced excluding PND >32 weeks PMA or died <6 weeks old (N=2,760)							
	Unweighted cohort			Weighted cohort[1]				
	$PND^{2/3}$ (n = 1,070)	$PND^{4/5}$ (n = 1,220)	PND^{6+} (n = 470)	$PND^{2/3}$	$PND^{4/5}$	PND^{6+}	Treatment effect OR/MD (95% CI)	p value
Primary outcome								
Severe bronchopulmonary dysplasia and/or death, n (%)	810 (75.7)	959 (78.6)	397 (84.5)	76.2	78.2	84.7	$PND^{2/3}$: Reference $PND^{4/5}$: 1.13 (0.92 – 1.39) PND^{6+}: 1.79 (1.29 – 2.48)	 0.238 <0.001*
Secondary outcomes								
Death, n (%)	101 (9.4)	103 (8.4)	42 (8.9)	9.2	8.6	7.5	$PND^{2/3}$: Reference $PND^{4/5}$: 0.92 (0.68 – 1.24) PND^{6+}:0.77 (0.51 – 1.17)	 0.582 0.227
Severe bronchopulmonary dysplasia, n (%)[2]	709 (73.2)	856 (76.6)	355 (82.9)	73.8	76.2	83.4	$PND^{2/3}$: Reference $PND^{4/5}$: 1.15 (0.93 – 1.41) PND^{6+}: 1.86 (1.34 – 2.59)	 0.200 <0.001*
Bronchopulmonary dysplasia, n (%)[2]	917 (94.6)	1067 (95.5)	416 (97.2)	94.9	95.3	96.8	$PND^{2/3}$: Reference $PND^{4/5}$: 1.09 (0.72 – 1.66) PND^{6+}: 1.60 (0.77 – 3.34)	 0.668 0.207
Duration of invasive ventilation (days), median (IQR)[2]	30 (22 – 44)	35 (28 – 45)	49 (41 – 58)	31 (22 – 45)	35 (28 – 46)	46 (40 – 55)	$PND^{2/3}$: Reference $PND^{4/5}$: 3.4 (1.7 – 5.0) PND^{6+}: 12.4 (10.3 – 14.5)	 <0.001* <0.001*
Successful extubation within 14 days of starting PND, n (%)[2]	598 (61.7)	838 (75.0)	339 (79.2)	58.4	74.4	79.8	$PND^{2/3}$: Reference $PND^{4/5}$: 2.2 (1.8 – 2.7) PND^{6+}: 3.4 (2.4 – 4.8)	 <0.001* <0.001*
PMA when successfully extubated after receiving PND (weeks), median (IQR)[2]	29^{+5} (28^{+3} – 31^{+2})	30^{+3} ($29^{+1}2$– 31^{+5})	31^{+4} (30^{+5} – 32^{+3})	29^{+4} (28^{+3} – 31^{+2})	30^{+2} (29^{+2} – 31^{+4})	31^{+5} (30^{+6} – 32^{+4})	$PND^{2/3}$: Reference $PND^{4/5}$: 0.9 (0.7 – 1.1) PND^{6+}: 2.6 (2.4 – 2.9)	 <0.001* <0.001*
Respiratory support at discharge, n (%)[2]	649 (67.0)	750 (67.1)	313 (73.1)	67.0	67.6	76.1	$PND^{2/3}$: Reference $PND^{4/5}$: 1.04 (0.86 – 1.26) PND^{6+}: 1.60 (1.20 – 2.15)	 0.672 0.002*

[1] Only the percentage of infants with the respective categorical neonatal outcomes was depicted for the weighted infant cohort.

[2] Infants who died before discharge were excluded from the analysis.

Supplementary Table 7 Neonatal outcomes between infants who received postnatal dexamethasone (PND) at the chronological age of two to three weeks ($PND^{2/3}$); four to five weeks ($PND^{4/5}$); and after six weeks (PND^{6+}) in the unweighted and weighted infant cohort after excluding infants with propensity scores outside the 5th – 95th centile range (N=2,564). n = number of infants. OR = Odds ratio. MD = Mean difference. CI = confidence interval. IQR = interquartile range. PMA = postmenstrual age. * = statistically significant after Bonferroni correction.

Characteristics	Chronological age when PND was commenced excluding infants outside 5th – 95th centile range (N=2,564)							
	Unweighted cohort			Weighted cohort[1]				
	$PND^{2/3}$ (n = 925)	$PND^{4/5}$ (n = 1,233)	PND^{6+} (n = 406)	$PND^{2/3}$	$PND^{4/5}$	PND^{6+}	Treatment effect OR/MD (95% CI)	p value
Primary outcome								
Severe bronchopulmonary dysplasia and/or death, n (%)	733 (79.2)	986 (80.0)	353 (86.9)	79.6	79.8	86.1	$PND^{2/3}$: Reference $PND^{4/5}$: 1.02 (0.82 – 1.26) PND^{6+}: 1.58 (1.13 – 2.21)	 0.892 0.007
Secondary outcomes								
Death, n (%)	183 (19.8)	159 (12.9)	48 (11.8)	19.5	13.0	11.8	$PND^{2/3}$: Reference $PND^{4/5}$: 0.62 (0.49 – 0.78) PND^{6+}:0.55 (0.39 – 0.78)	 <0.001* <0.001*
Severe bronchopulmonary dysplasia, n (%)[2]	550 (74.1)	827 (77.0)	305 (85.2)	74.7	76.8	84.2	$PND^{2/3}$: Reference $PND^{4/5}$: 1.12 (0.90 – 1.40) PND^{6+}: 1.81 (1.29 – 2.54)	 0.298 0.001*
Bronchopulmonary dysplasia, n (%)[2]	704 (94.9)	1025 (95.4)	347 (96.9)	94.9	95.6	96.9	$PND^{2/3}$: Reference $PND^{4/5}$: 1.15 (0.74 – 1.79) PND^{6+}: 1.67 (0.83 – 3.35)	 0.536 0.152
Duration of invasive ventilation (days), median (IQR)[2]	30 (22 – 43)	35 (28 – 45)	52 (41 – 66)	30 (22 – 43)	35 (28 – 45)	51 (41 – 66)	$PND^{2/3}$: Reference $PND^{4/5}$: 4.7 (3.0 – 6.5) PND^{6+}: 22.6 (19.5 – 25.6)	 <0.001* <0.001*
Successful extubation within 14 days of starting PND, n (%)[2]	471 (63.5)	814 (75.8)	271 (75.7)	63.1	75.5	76.3	$PND^{2/3}$: Reference $PND^{4/5}$: 1.8 (1.5 – 2.2) PND^{6+}: 1.9 (1.4 – 2.5)	 <0.001* <0.001*
PMA when successfully extubated after receiving PND (weeks), median (IQR)[2]	29^{+5} (28^{+3} – 31^{+1})	30^{+4} (29^{+3} – 31^{+6})	32^{+4} (31^{+2} – 34^{+4})	29^{+5} (28^{+3} – 31^{+2})	30^{+4} (29^{+3} – 31^{+6})	32^{+4} (31^{+2} – 34^{+4})	$PND^{2/3}$: Reference $PND^{4/5}$: 0.8 (0.6 – 1.0) PND^{6+}: 3.2 (2.8 – 3.5)	 <0.001* <0.001*
Respiratory support at discharge, n (%)[2]	505 (68.1)	727 (67.7)	265 (74.0)	68.3	67.4	73.7	$PND^{2/3}$: Reference $PND^{4/5}$: 0.97 (0.79 – 1.20) PND^{6+}: 1.33 (1.00 – 1.78)	 0.802 0.053

[1] Only the percentage of infants with the respective categorical neonatal outcomes was depicted for the weighted infant cohort.

[2] Infants who died before discharge were excluded from the analysis.

Supplementary Table 8 Neonatal outcomes between infants who received postnatal dexamethasone (PND) for at least seven consecutive days at the chronological age of two to three weeks ($PND^{2/3}$); four to five weeks ($PND^{4/5}$); and after six weeks (PND^{6+}) (N=2,686). n = number of infants. OR = Odds ratio. MD = Mean difference. CI = confidence interval. IQR = interquartile range. PMA = postmenstrual age. * = statistically significant after Bonferroni correction.

Characteristics	Chronological age when PND for at least 7 consecutive days was commenced (N=2,686)							
	Unweighted cohort			Weighted cohort[1]				
	$PND^{2/3}$ (n = 894)	$PND^{4/5}$ (n = 1,073)	PND^{6+} (n = 719)	$PND^{2/3}$	$PND^{4/5}$	PND^{6+}	Treatment effect OR/MD (95% CI)	p value
Primary outcome								
Severe bronchopulmonary dysplasia and/or death, n (%)	711 (79.5)	866 (80.7)	635 (88.3)	80.3	80.4	87.5	$PND^{2/3}$: Reference $PND^{4/5}$: 1.01 (0.80 – 1.27) PND^{6+}: 1.73 (1.28 – 2.32)	 0.939 <0.001*
Secondary outcomes								
Death, n (%)	150 (16.8)	121 (11.3)	73 (10.2)	16.6	11.7	10.2	$PND^{2/3}$: Reference $PND^{4/5}$: 0.67 (0.51 – 0.87) PND^{6+}:0.57 (0.41 – 0.79)	 0.003* 0.001*
Severe bronchopulmonary dysplasia, n (%)[2]	561 (75.4)	745 (78.3)	562 (87.0)	76.4	77.8	86.1	$PND^{2/3}$: Reference $PND^{4/5}$: 1.09 (0.86 – 1.37) PND^{6+}: 1.92 (1.42 – 2.60)	 0.486 <0.001*
Bronchopulmonary dysplasia, n (%)[2]	712 (95.7)	916 (96.2)	631 (97.7)	96.0	96.1	97.4	$PND^{2/3}$: Reference $PND^{4/5}$: 1.02 (0.62 – 1.68) PND^{6+}: 1.55 (0.79 – 3.02)	 0.927 0.199
Duration of invasive ventilation (days), median (IQR)[2]	30 (22 – 44)	35 (28 – 44)	51 (42 – 64)	30 (22 – 45)	35 (28 – 44)	50 (41 – 61)	$PND^{2/3}$: Reference $PND^{4/5}$: 2.9 (0.9 – 4.8) PND^{6+}: 18.3 (15.9 – 20.7)	 <0.001* <0.001*
Successful extubation within 14 days of starting PND, n (%)[2]	467 (62.8)	752 (79.0)	515 (79.7)	61.5	78.5	80.4	$PND^{2/3}$: Reference $PND^{4/5}$: 2.3 (1.8 – 2.9) PND^{6+}: 2.6 (2.0 – 3.3)	 <0.001* <0.001*
PMA when successfully extubated after receiving PND (weeks), median (IQR)[2]	29^{+5} (28^{+3} – 31^{+2})	30^{+3} (29^{+2} – 31^{+5})	32^{+5} (31^{+2} – 34^{+3})	29^{+5} (28^{+3} – 31^{+2})	30^{+2} (29^{+2} – 31^{+5})	32^{+5} (31^{+2} – 34^{+3})	$PND^{2/3}$: Reference $PND^{4/5}$: 0.6 (0.4 – 0.8) PND^{6+}: 3.2 (2.9 – 3.5)	 <0.001* <0.001*
Respiratory support at discharge, n (%)[2]	515 (69.2)	673 (70.7)	495 (76.6)	69.6	70.4	76.1	$PND^{2/3}$: Reference $PND^{4/5}$: 1.06 (0.85 – 1.32) PND^{6+}: 1.41 (1.09 – 1.82)	 0.602 0.009

[1] Only the percentage of infants with the respective categorical neonatal outcomes was depicted for the weighted infant cohort.

[2] Infants who died before discharge were excluded from the analysis.

Supplementary Table 9 Participating neonatal units in England and Wales and their respective lead clinicians. The list was accessed from https://www.imperial.ac.uk/neonatal-data-analysis-unit/neonatal-data-analysis-unit/list-of-national-neonatal-units/ on 06/01/2022.

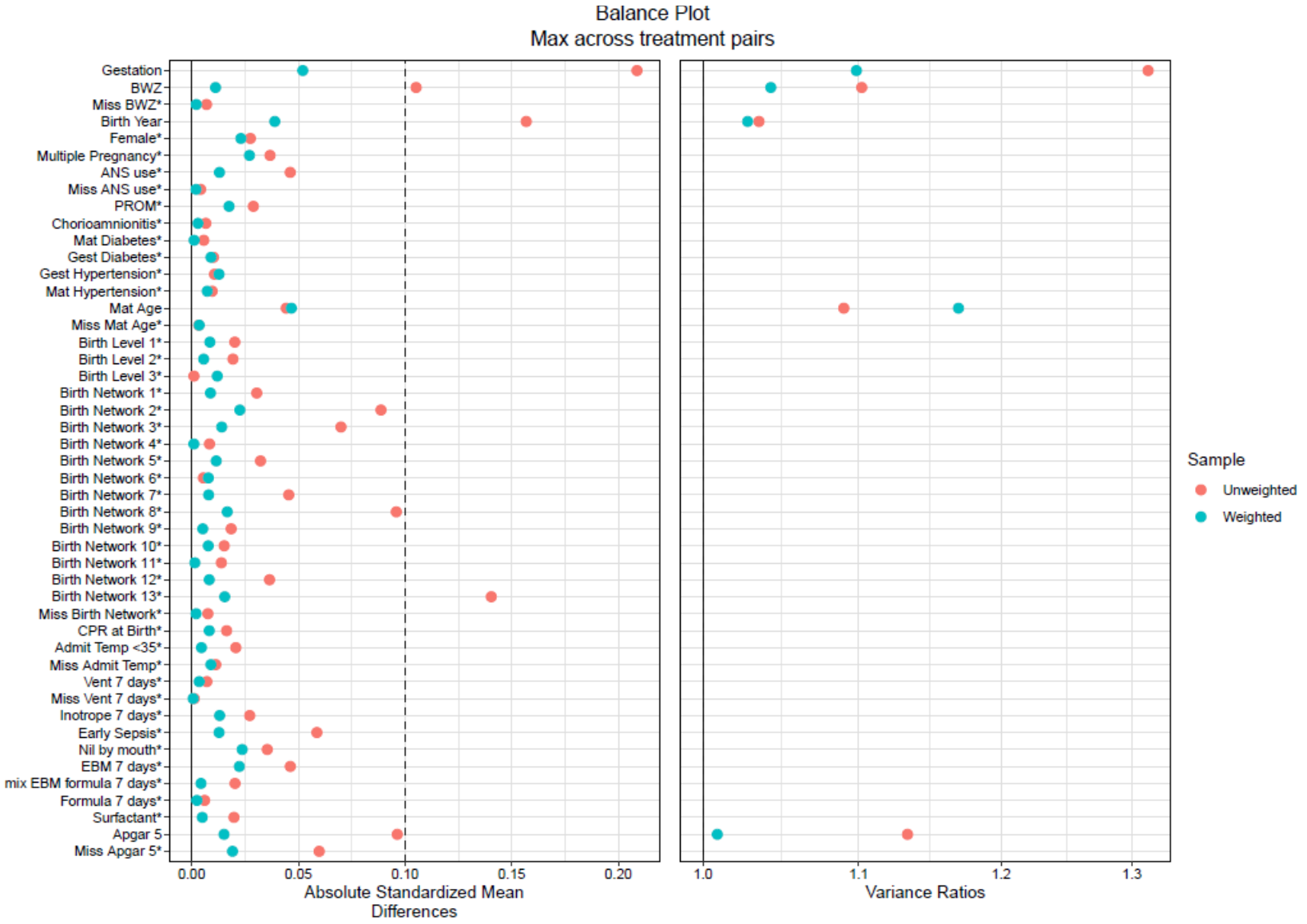
Institution	Lead clinician
Airedale General Hospital	Dr Matthew Babirecki
Arrowe Park Hospital	Dr Anand Kamalanathan
Barnet Hospital	Dr Tim Wickham
Barnsley District General Hospital	Dr Kavi Aucharaz
Basildon Hospital	Dr Aashish Gupta
Basingstoke & North Hampshire Hospital	Dr Nicola Paul
Bassetlaw District General Hospital	Dr L M Wong
Bedford Hospital	Dr Anita Mittal
Birmingham City Hospital	Dr Lindsay Halpern
Birmingham Heartlands Hospital	Dr Pinki Surana
Birmingham Women's Hospital	Dr Matt Nash
Bradford Royal Infirmary	Dr Sam Wallis
Broomfield Hospital, Chelmsford	Dr Ahmed Hassan
Calderdale Royal Hospital	Dr Karin Schwarz
Chelsea & Westminster Hospital	Dr Shu-Ling Chuang
Chesterfield & North Derbyshire Royal Hospital	Dr Aiwyne Foo
Colchester General Hospital	Dr Jo Anderson
Conquest Hospital	Dr Graham Whincup
Countess of Chester Hospital	Dr Stephen Brearey
Croydon University Hospital	Dr Morris
Croydon University Hospital	Dr Srirambhatla
Cumberland Infirmary	Dr Yee Aung
Darent Valley Hospital	Dr Abdul Hasib
Darlington Memorial Hospital	Dr Mehdi Garbash
Derriford Hospital	Dr Alex Allwood
Diana Princess of Wales Hospital	Dr Pauline Adiotomre
Doncaster Royal Infirmary	Dr Nigel Brooke
Dorset County Hospital	Dr Abby Deketelaere
East Surrey Hospital	Dr Abdul Khader
Epsom General Hospital	Dr Sonia Spathis
Frimley Park Hospital	Dr Sanghavi Rekha
Furness General Hospital	Dr Anas Olabi
George Eliot Hospital	Dr Mukta Jain
Glan Clwyd Hospital	Dr Ian Barnard
Glangwili General Hospital	Dr Prem Pitchaikani
Gloucester Royal Hospital	Dr Jennifer Holman
Good Hope Hospital	Dr Pinki Surana
Great Western Hospital	Dr Stanley Zengeya
Guy's & St Thomas' Hospital	Dr Geraint Lee
Harrogate District Hospital	Dr Sobia Balal

Hereford County Hospital	Dr Cath Seagrave
Hillingdon Hospital	Dr Tristan Bate
Hinchingbrooke Hospital	Dr Hilary Dixon
Homerton Hospital	Dr Narendra Aladangady
Hull Royal Infirmary	Dr Hassan Gaili
Ipswich Hospital	Dr Matthew James
James Cook University Hospital	Dr M Lal
James Paget Hospital	Dr Ambadkar
Kettering General Hospital	Dr Poornima Pandey
Kings College Hospital	Dr Ravindra Bhat
King's Mill Hospital	Dr Simon Rhodes
Kingston Hospital	Dr Jonathan Filkin
Lancashire Women and Newborn Centre	Dr Savi Sivashankar
Leeds Neonatal Service	Dr Lawrence Miall
Leicester General Hospital	Dr Jonathan Cusack
Leicester Royal Infirmary	Dr Venkatesh Kairamkonda
Leighton Hospital	Dr Michael Grosdenier
Lincoln County Hospital	Dr Ajay Reddy
Lister Hospital	Dr J Kefas
Liverpool Women's Hospital	Dr Christopher Dewhurst
Luton & Dunstable Hospital	Dr Jennifer Birch
Macclesfield District General Hospital	Dr Gail Whitehead
Manor Hospital	Dr Ashok Karupaiah
Medway Maritime Hospital	Dr Ghada Ramadan
Milton Keynes General Hospital	Dr I Misra
Musgrove Park Hospital	Dr Chris Knight
New Cross Hospital	Dr Matt Nash
Newham General Hospital	Dr Imdad Ali
Nobles Hospital	Dr Prakash Thiagarajan
Norfolk & Norwich University Hospital	Dr Muthukumar
North Devon District Hospital	Dr Michael Selter
North Manchester General Hospital	Dr Ajit Mahaveer
North Middlesex University Hospital	Dr Neeraj Jain
Northampton General Hospital	Dr Subodh Gupta
Northumbria Specialist Emergency Care Hospital	Jess Reynolds
Northwick Park Hospital	Dr Richard Nicholl
Nottingham City Hospital	Dr Steven Wardle
Nottingham University Hospital (QMC)	Dr Steven Wardle
Ormskirk District General Hospital	Dr Andreea Bontea
Oxford University Hospitals, John Radcliffe Hospital	Dr Eleri Adams
Peterborough City Hospital	Dr Katharine McDevitt
Pilgrim Hospital	Dr Ajay Reddy
Pinderfields General Hospital (Pontefract General Infirmary)	Dr David Gibson

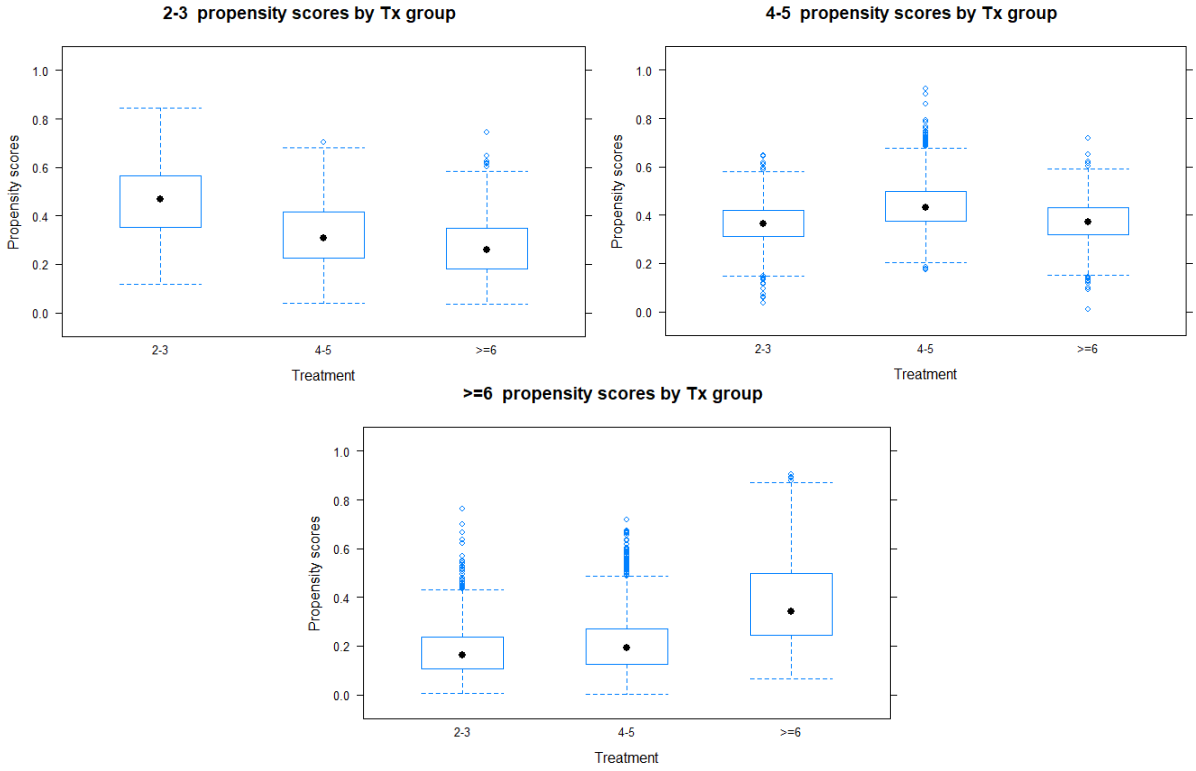
Poole General Hospital	Prof Minesh Khashu
Prince Charles Hospital	Dr Iyad Al-Muzaffar
Princess Alexandra Hospital	Dr Chinnappa Reddy
Princess Anne Hospital	Dr Mark Johnson
Princess of Wales Hospital	Dr Kate Creese
Princess Royal Hospital	Dr P Amess
Princess Royal Hospital (previously Royal Shrewsbury Hospital)	Dr Deshpande
Princess Royal University Hospital	Dr Elizabeth Sleight
Queen Alexandra Hospital	Dr Charlotte Groves
Queen Charlotte's Hospital	Dr Lidia Tyszcuzk
Queen Elizabeth Hospital, Gateshead	Dr Anne Dale
Queen Elizabeth Hospital, King's Lynn	Dr Glynis Rewitzky
Queen Elizabeth Hospital, Woolwich - see notes	Dr Olutoyin Banjoko
Queen Elizabeth the Queen Mother Hospital	Dr Bushra Abdul-Malik
Queen's Hospital, Burton on Trent	Dr Dominic Muogbo
Queen's Hospital, Romford	Dr Khalid Mannan
Queen's Hospital, Romford 2	Dr Khalid Mannan
Rosie Maternity Hospital, Addenbrookes	Dr Angela D'Amore
Rotherham District General Hospital	Dr Soma Sengupta
Royal Albert Edward Infirmary	Dr Christos Zipitis
Royal Berkshire Hospital	Dr Peter De Halpert
Royal Bolton Hospital	Dr Paul Settle
Royal Cornwall Hospital	Dr Paul Munyard
Royal Derby Hospital	Dr John McIntyre
Royal Devon & Exeter Hospital	Dr Chrissie Oliver
Royal Gwent Hospital	Dr Sunil Reddy
Royal Hampshire County Hospital	Dr Lucinda Winckworth
Royal Lancaster Infirmary	Dr Joanne Fedee
Royal Oldham Hospital	Dr Natasha Maddock
Royal Preston Hospital	Dr Richa Gupta
Royal Stoke University Hospital	Dr Jyoti Kapur
Royal Surrey County Hospital	Dr Ben Obi
Royal Sussex County Hospital	Dr P Amess
Royal United Hospital	Dr Stephen Jones
Royal Victoria Infirmary	Dr Naveen Athiraman
Russells Hall Hospital	Dr Chandan Gupta
Salisbury District Hospital	Dr Jim Baird
Scarborough General Hospital	Dr Kirsten Mack
Scunthorpe General Hospital	Dr Pauline Adiotomre
Singleton Hospital	Dr Arun Ramachandran
Southend Hospital	Dr Vineet Gupta
Southmead Hospital	Dr Faith Emery
St George's Hospital	Dr Charlotte Huddy

St Helier Hospital	Dr Ralf Hartung
St Mary's Hospital, IOW	Dr Akinsola Ogundiya
St Mary's Hospital, London	Dr Lidia Tyszcuzk
St Mary's Hospital, Manchester	Dr Ngozi Edi-Osagie
St Michael's Hospital	Dr Pamela Cairns
St Peter's Hospital	Dr Peter Martin
St Richard's Hospital	Dr Victoria Sharp
Stepping Hill Hospital	Dr Carrie Heal
Stoke Mandeville Hospital	Dr Sanjay Salgia
Sunderland Royal Hospital	Dr Majd Abu-Harb
Tameside General Hospital	Dr Jacqeline Birch
The Grange University Hospital	Dr Sunil Reddy
The Jessop Wing, Sheffield	Dr Porus Bastani
The Royal Free Hospital	Dr Marice Theron
The Royal London Hospital - Constance Green	Dr Vadivelam Murthy
Torbay Hospital	Dr Siba Paul
Tunbridge Wells Hospital	Dr Hamudi Kisat
University College Hospital	Dr Giles Kendall
University Hospital Coventry	Dr Puneet Nath
University Hospital Lewisham	Dr Ozioma Obi
University Hospital of North Durham	Dr Mehdi Garbash
University Hospital of North Tees	Dr Hari Kumar
University Hospital of Wales	Dr Nitin Goel
Victoria Hospital, Blackpool	Dr Chris Rawlingson
Warrington Hospital	Dr Delyth Webb
Warwick Hospital	Dr Bird
Watford General Hospital	Dr Sankara Narayanan
West Cumberland Hospital	Dr Yee Aung
West Middlesex University Hospital	Dr Eleanor Hulse
West Suffolk Hospital	Dr Ian Evans
Wexham Park Hospital	Dr Sanjay Jaisal
Whipps Cross University Hospital	Dr Caroline Sullivan
Whiston Hospital	Dr Ros Garr
Whittington Hospital	Dr Wynne Leith
William Harvey Hospital	Dr Vimal Vasu
Withybush Hospital	Dr Vishwa Narayan
Worcestershire Royal Hospital	Dr Liza Harry
Worthing Hospital	Dr Katia Vamvakiti
Wrexham Maelor Hospital	Dr Brendan Harrington
Wythenshawe Hospital	Dr Ngozi Edi-Osagie
Yeovil District Hospital	Dr Megan Eaton
York District Hospital	Dr Sundeep Sandhu
Ysbyty Gwynedd	Dr Mike Cronin

Supplementary Figure 1: Balance plot demonstrating good balance for all the a-priori variables used in propensity score analysis amongst the three groups after weighting using the inverse probability of treatment weighted estimation with standardised mean differences and variance ratios ranging between 0.0007–0.05 and 1.01–1.17 respectively. BWZ = Birthweight Z scores, Miss = missing, ANS = Antenatal corticosteroids. PROM = Prolonged rupture of membrane. Mat = Maternal. Gest = Gestational. CPR = Cardiopulmonary resuscitation. Admit = Admission. Vent = ventilated. EBM = Expressed breast milk.



Supplementary Figure 2: Box plots of the estimated propensity scores for each of the three postnatal dexamethasone treatment (Tx) groups (2–3 weeks; 4–5 weeks; and ≥6 weeks) for every infant in the propensity score analysis cohort by the treatment groups.



Supplementary Text 1: Propensity score matching analysis methodology

Propensity score weighting analysis was performed using the "mnps" function in the "Twang" package [1] in RStudio. Full details of the codes used could be found in the following tutorials [2, 3]. In summary, five steps were taken in performing the analysis.

1. Selection of a-priori variables or confounders

Based on the literature review [4, 5] and clinical knowledge of the delivery of neonatal care in the UK, a set of variables or confounders that are known to be associated with bronchopulmonary dysplasia or death in premature infants, which occurred before the allocation of the three postnatal dexamethasone (PND) treatment groups were determined a-priori. These a-priori variables are described in **Supplementary Table 2**.

2. Estimation of propensity score

The generalised boosted model approach in the "mnps" function was used to estimate the propensity of the infants being assigned to each of the three PND treatment groups based on the a-priori variables (**Supplementary Table 2**). Generalised boosted model is a machine learning approach whereby multiple tree-based regression models are built in stages in an iterative manner [2]. This iterative approach allows it to capture complex and non-linear relationships between the treatment group assignment and a-priori variables without overfitting. It was found to be superior to standard logistic regression in estimating propensity scores for treatment allocation [2, 3]. Missing values (**Supplementary Table 3**) were controlled for by including missing value indicators and balancing rates of missingness in the three groups (step 4).

Four stopping rules for the iterative process of the gradient boosted model approach were explored: mean absolute standardised mean difference (ASMD), max ASMD, mean Kolmogorov-Smirnov (KS)

and max KS. The mean ASMD stopping rule was used as it provided the best balance among the three groups with the second largest effective sample size.

3. Inverse probability treatment weighted (IPTW)

The propensity scores estimated by the gradient boosted model approach were then used as inverse weights in estimating the treatment effect, whereby the weight of the infant is determined by the inverse of the probability of the infant being allocated to the treatment group. The average treatment effect estimand [6] was used for the IPTW approach as the study aimed at assessing the change in the outcome if all infants in the study had been assigned to a particular PND treatment group relative to another group [3, 6]. The use of IPTW prevents infants to be excluded from the analysis and was found to reduce bias more than other propensity score analysis approaches such as stratification and co-variate adjustment [7].

4. Balance assessment of the a-priori variables

Balance of the a-priori variables (**Supplementary Table 2**) across the three PND treatment groups after weighing was assessed by examining the overlap of the propensity score distribution across the three groups as well as using standardised mean differences (SMD) and variance ratios (VR). SMD <0.1 and VR 0.5–2.0 were used to indicate good balance [8]. The balance diagnostics were visualised using balance plots developed using the "cobalt" package [9]. Boxplots by treatment group were used to assess the overlap of propensity scores.

All the a-priori variables were found to be balanced across the three groups after weighting in our study with a median (range) SMD of 0.009 (0.0007–0.05) and VR of 1.04 (1.01–1.17) (**Supplementary Table 4** and **Supplementary Figure 1**). There was an overlap in the propensity score distribution across the three groups (**Supplementary Figure 2**).

5. Estimation of treatment effect

The difference in weighted means was used to estimate the association between the treatment group and the outcomes of interest as the a-priori variables were balanced across the three groups after IPTW.

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