Observational cohort study of use of caffeine in preterm infants and association between early caffeine use and neonatal outcomes

Authors

1. Lisa Szatkowski

   Lisa.szatkowski@nottingham.ac.uk

   Centre for Perinatal Research, Academic Unit of Lifespan and Population Health, School of Medicine, University of Nottingham, UK

2. Sheeza Fateh

   Sheeza.fateh@nottingham.ac.uk

   Centre for Perinatal Research, Academic Unit of Lifespan and Population Health, School of Medicine, University of Nottingham, UK

3. Janine Abramson

   Janine.abramson@nottingham.ac.uk

   Centre for Perinatal Research, Academic Unit of Lifespan and Population Health, School of Medicine, University of Nottingham, UK

4. T'ng Chang Kwok

   Tng.kwok@nottingham.ac.uk

   Centre for Perinatal Research, Academic Unit of Lifespan and Population Health, School of Medicine, University of Nottingham, UK

5. Don Sharkey

   Don.sharkey@nottingham.ac.uk

   Centre for Perinatal Research, Academic Unit of Lifespan and Population Health, School of Medicine, University of Nottingham, UK

6. Helen Budge

   Helen.budge@nottingham.ac.uk

Centre for Perinatal Research, Academic Unit of Lifespan and Population Health, School of Medicine, University of Nottingham, UK

7. Shalini Ojha

   shalini.ojha@nottingham.ac.uk

   Centre for Perinatal Research, Academic Unit of Lifespan and Population Health, School of Medicine, University of Nottingham, Nottingham, UK and Neonatal Unit, University Hospitals of Derby and Burton NHS Trust, Derby, UK

Corresponding author: Dr Shalini Ojha, Academic Unit of Lifespan and Population Health, School of Medicine, University of Nottingham. Room 4117, Medical School Building, Royal Derby Hospital, Derby DE22 3NE; email: shalini.ojha@nottingham.ac.uk

Orchid ID: https://orcid.org/0000-0001-5668-4227

Short title: Caffeine use in very preterm infants

Funding: This study did not receive any external funding.

Acknowledgements

Electronic patient data recorded at participating neonatal units that collectively form the United Kingdom Neonatal Collaborative are transmitted to the Neonatal Data Analysis Unit to form the National Neonatal Research Database (NNRD). We are grateful to all the families that agreed to the inclusion of their baby's data in the

NNRD, the health professionals who recorded data and the Neonatal Data Analysis Unit team.

Word count: 2606/2500

Contributors' statement

Lisa Szatkowski: participated in the concept and design, performed the analysis of data, participated in interpretation of data, and drafted and revised the manuscript.

Sheeza Fateh: participated in the analysis and interpretation of data and revised the manuscript.

T'ng Chang Kwok: participated in the analysis of data and revised the manuscript.

Janine Abramson: participated in the concept and design, analysis of data, and revised the manuscript.

Don Sharkey: participated in the concept and design, interpretation of data, and revised the manuscript.

Helen Budge: participated in the concept and design, interpretation of data, and revised the manuscript.

Shalini Ojha: designed and conceptualised the study, participated in analysis and interpretation of data, and drafted and revised the manuscript.

All authors approve the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interest Disclosures and funding sources: The authors have no conflicts of interest relevant to this article to disclose.

Abstract (words count: 233/250)

Objective: To quantify trends in caffeine use in infants born at <32 weeks' gestational age (GA), and to investigate the effects of early vs. late caffeine on neonatal outcomes.

Study design: Retrospective propensity score matched cohort study using routinely recorded data from the National Neonatal Research Database of infants born at <32 weeks' GA admitted to neonatal units in England and Wales (2012-2020).

Results: 89% (58,913/66,081) of infants received caffeine. In 70%, caffeine was started early (on the day of birth or the day after), increasing from 55% in 2012 to 83% in 2020. Caffeine was given for a median (IQR) of 28 (17-43) days starting on day 2 (1-3) and continued up to 34 (33-34) weeks postmenstrual age.

In the propensity score matched cohort of 13,045 pairs of infants, the odds of preterm brain injury (early caffeine, 2,306/13,045 (17.7%) vs. late caffeine, 2,528/13,045 (19.4%), OR=0.89 (95% CI 0.84 to 0.95)) and BPD (early caffeine, 4,020/13,045 (32.8%) vs. late caffeine, 4,694/13,045 (37.7%), OR=0.81 (95% CI 0.76 to 0.85)) were lower in the group that received early caffeine compared to those who received it later.

Conclusions: Early use of caffeine has increased in England and Wales. This is associated with reduced risks of BPD and preterm brain injury. Randomised trials are needed to find the optimal timing of caffeine use and the groups of infants who will benefit most from early administration of caffeine.

Ethical approval

The dataset was created by the NDAU and the study was approved by Yorkshire & The Humber – Sheffield Research Ethics Committee (IRAS 259802).

Key words: infant, preterm; caffeine, bronchopulmonary dysplasia, neurodevelopment

Abbreviations: BPD, bronchopulmonary dysplasia; CAP trial, Caffeine in Apnoea of Prematurity trial; CI, confidence interval; IQR, inter-quartile range; IVH, intraventricular haemorrhage; MV, mechanical ventilation; NEC, necrotising enterocolitis; NIV, non-invasive ventilation; NMR-2000, neonatal mortality risk score among neonates weighing 2000 g or less; NNRD, National Neonatal Research Database; PHVD, post-haemorrhagic ventricular dilatation; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; ODN, Operational Delivery Networks; OR, odds ratio; SD, standard deviation.

What's known on this subject

- In very low birth weight infants, caffeine reduces exposure to positive airway pressure and the risk of bronchopulmonary dysplasia (BPD).
- Infants who receive caffeine have improved rates of survival without neurodevelopmental impairment.
- Early caffeine use is associated with reduced risk of BPD and adverse neurodevelopment.

What this study adds

- In very preterm infants in England and Wales, use of caffeine increased between 2012 and 2020 with use of caffeine within 2 days of birth increasing from 55% to 83%.
- Infants who received caffeine early had higher odds of death but lower odds of preterm brain injury, BPD, and the composite outcome of death/brain injury/BPD when compared to those who had caffeine later.
-

How this study might affect research, practice, or policy

- This study demonstrates the drift in practice towards using caffeine earlier in preterm infants.
- It supports observational evidence that early use of caffeine may improve respiratory and neurological outcomes in preterm infants.
- It highlights the need for randomised controlled trials to investigate which group of preterm infants would benefit from early caffeine and the optimal time of starting caffeine.

Introduction

Caffeine is the most frequently prescribed medicine in neonates[1]. The Caffeine for Apnea of Prematurity (CAP) trial showed that, in very low birth weight infants, caffeine reduces the risk of bronchopulmonary dysplasia (BPD), and improves the rate of survival without neurodevelopmental impairment at 18-21 months of age[2]. Further follow-up revealed no improvement in survival without disability at 5 years[3] or the combined risk of academic, motor and behavioural impairments at 11 years, although there was reduced risk of motor impairment[4] and improved expiratory flow rate at 11 years[5]. Secondary analyses of data until hospital discharge showed a differential treatment effect of caffeine depending on the age at which the infants were randomised. Those who received caffeine at <3 days had lower risk of BPD compared to those who received caffeine at ≥3 days[6]. These were post-hoc analyses and the allocation of infants to early vs. late caffeine was not random.

Observational studies show increase in use of caffeine and association of early use with reduced risk of BPD[7] and better neurodevelopment at 18-24 months[8] although on there are contrasting results on the duration of mechanical ventilation and death[9] . Following this, there has been an increase in the use of early caffeine therapy[7]. The 2019 European guidelines on management of respiratory distress syndrome recommended that early caffeine should be considered for babies at high risk of needing mechanical ventilation (MV), including those on non-invasive ventilation (NIV)[10].

In the UK, the percentage of infants born at <32 weeks' gestational age (GA) who received caffeine increased from 77% in 2010 to 92% in 2017[1], but no studies have

evaluated early use of caffeine and its impact on clinical outcomes. We aimed to quantify the change in caffeine use in the UK in infants born at <32 weeks' GA, between 2012 and 2020, and to investigate the effects of early vs. late caffeine on neonatal outcomes. We hypothesised that caffeine use has increased, more infants are started on caffeine early, and that early use is associated with reduced risk of preterm brain injury and BPD.

Methods

We carried out a retrospective cohort study using routinely recorded electronic patient record data. We used data from the UK National Neonatal Research Database (NNRD), as previously described[11], for infants born at 22-31 weeks' GA admitted to neonatal units in England and Wales from 01 January 2012 to 31 December 2020.

Exclusions

Infants were excluded if they had missing data on sex, birthweight, final discharge destination or had missing records for one or more episodes of care. We also excluded infants with implausible birthweight for GA z-scores >4 standard deviations (SD) or <-4 SD or who were admitted >24 hours after birth. Finally, infants with major congenital anomalies, oro-facial or respiratory system anomalies or anomalies requiring urgent surgical intervention were excluded (Supplementary Table 1).

Exposures

From daily records, we identified infants who were prescribed caffeine at least once. We identified the first calendar day on which caffeine was prescribed (taking the day of birth as day 1) and divided infants into those who first received caffeine early (on day 1 or 2) and those who first received caffeine later (on or after day 3) (Supplementary Table 2).

Outcomes

We pre-specified two co-primary outcomes, based on the National Neonatal Audit Programme definitions[12]: preterm brain injury, defined as intraventricular

haemorrhage (IVH) of any grade identified by imaging on or before day 28, cystic periventricular leukomalacia (PVL) or post haemorrhagic ventricular dilatation (PHVD) identified by any imaging during neonatal stay; and BPD, defined as receiving any mode of respiratory support at 36 weeks postmenstrual age (PMA). For BPD analyses, we excluded infants who died before 36 weeks PMA. We also pre-specified several secondary outcomes, including composite outcomes of preterm brain injury or death, BPD or death, and preterm brain injury or BPD or death (Supplementary Table 3).

Statistical analysis

All data management and analyses were performed using Stata, version 17 (StataCorp, College Station, Tx). After exclusions, we calculated the percentage of infants who received caffeine, overall and by year of admission and gestational age group (<28 weeks' GA and 28-31 weeks' GA). In infants who received caffeine, we described its use, compared the characteristics of infants who received caffeine early and late (demographic characteristics, characteristics of pregnancy and delivery and the NMR-2000 score to describe infants' risk of in-hospital mortality[12]) and described changes over time by year of admission and individual GA week in the use of early and late caffeine.

We identified pairs of infants by propensity score matching (one who received caffeine early and one who received caffeine later) with similar demographic and clinical characteristics using the methods outlined by Imbens and Rubin[13]. We used nearest neighbour matching, with a calliper width of 0.2 times SD of the logit of the propensity scores[14]. Detailed description is given in the supplementary material

(Supplementary Figure 1 and Supplementary tables 4 and 5). In the resulting matched cohort, we used logistic regression for binary variables and quantile regression for continuous variables to explore the association between receiving caffeine early versus late and the outcomes. We used a Bonferroni adjustment to account for multiple hypothesis testing. We conducted two sensitivity analyses in the full, non-matched, cohort to explore the impact of the matching process: 1) we used traditional multivariable logistic regression to calculate adjusted odds ratios (aOR) and median differences for adverse outcomes and 2) we used inverse probability weighting to weight the calculation of the measures of effect, such that all infants contributed to the analysis, with their contribution inversely proportional to their propensity score.

Results

Of 68,934 22-31 weeks' GA infants admitted from 2012 to 2020, 66,081 were included (Supplementary Figure 2). 58,913 (89.2%) received caffeine. This increased from 6,101/7,425 (82.2%) in 2012 to 6,070/6,439 (94.3%) in 2020 (<28 weeks' GA, 84.3% to 94.3%; 28-31 weeks' GA, 81.1% to 94.2%). Characteristics and differences between infants who received caffeine and those who did not are given in Supplementary Table 6. Infants who did not receive caffeine were born at a later gestation and higher birthweight than infants who did receive caffeine. However, 30% (n=2,139/7,168) of infants who did not receive caffeine died, on median (IQR) day 2 (1-4) of life.

Caffeine was given for a median of 28 (17-43) days starting on day 2 (1-3) and continued up to 34 (33-34) weeks PMA. Infants born at <28 weeks' GA received caffeine for longer compared to those who were born at 28-31 weeks' GA (Table 1). The overall duration of caffeine treatment increased slightly amongst both the <28 weeks' GA infants (48 (36-60) days in 2012 to 52 (41-64) days in 2020) and the 28-31 weeks' GA infants (21 (13-31) days in 2012 to 24 (17-33) days in 2020).

Table 1. Caffeine use in infants born at <32 weeks' gestational age in England and Wales (2012-2020)

	All infants	**<28 weeks' gestational age**	**28-31 weeks' gestational age**	**p-value**
Number of infants	**58,913**	**18,780**	**40,133**	
Total days of caffeine, median (IQR)	28 (17-43)	50 (39-63)	22 (15-32)	<0.001
Day of life when caffeine was started, median (IQR)	2 (1-3)	2 (1-3)	1 (1-3)	<0.001

PMA (in weeks) when caffeine was started, median (IQR)	29 (27-31)	26 (25-27)	30 (29-31)	<0.001
Received caffeine early, n (%)	41,163 (69.9)	12,961 (69.0)	28,202 (70.3)	0.002
Highest mode of respiratory support on the day caffeine was started, n (%)				
Mechanical ventilation	29,007 (49.2)	14,947 (79.6)	14,060 (35.0)	<0.001
Non-invasive ventilation	23,082 (39.2)	3,637 (19.4)	19,445 (48.5)	
Supplemental oxygen	367 (0.6)	32 (0.2)	335 (0.8)	
Day of life when caffeine was stopped, median (IQR)	32 (20-49)	57 (46-70)	25 (18-35)	<0.001
PMA (in weeks) when caffeine was stopped, median (IQR)	34 (33-34)	34 (33-35)	33 (33-34)	<0.001
Number of days between last caffeine use and discharge home, median (IQR)	22 (14-33)	32 (21-46)	19 (13-28)	<0.001
On caffeine within 7 days of discharge home, n (%)	4,067 (7.7)	517 (3.6)	3,550 (9.3)	<0.001

Caffeine use to support extubation and NIV

Among the 29,007 infants who were mechanically ventilated when caffeine was started, 9,536 (32.9%) were extubated on the same day and 6,916 (23.8%) on the day after. Of those who were mechanically ventilated when caffeine was started, the percentage extubated within 2 days decreased over the study period: <28 weeks' GA, 45.2% in 2012 to 35.1% in 2020; 28-31 weeks' GA, 80.8% in 2012 to 73.8% in 2020. 17,115 infants were receiving NIV when caffeine was started and had not been mechanically ventilated before. Of these, 4,163 (24.3%) went on to be mechanically ventilated, 2,823 (16.5%) within 7 days.

Early vs. late caffeine use

Of the 58,913 infants who received caffeine, the drug was started early in 41,163 (69.9%), increasing from 3,333/6,101 (54.6%) in 2012 to 5,012/6,070 (82.6%) in 2020 (<28 weeks' GA infants: from 973/2,004 (48.6%) in 2012 to 1,642/1,929

(85.1%) in 2020; 28-31 weeks' GA infants: from 2,360/4,097 (57.6%) in 2012 to 3,370/4,141 (81.4%) in 2020). The trend, as a percentage of the population, is demonstrated in Figure 1A while use by GA at birth is shown in Figure 1B.

Compared to infants who received caffeine late, those who received caffeine early were more premature and smaller, more likely to be female, one of a multiple birth, have received antenatal steroids, been born by Caesarean section, been at medium risk of in-hospital mortality, and admitted first to a Neonatal Intensive Care Unit but were less likely to have been mechanically ventilated on day 1 and to have had early onset sepsis (Supplementary Table 7).

Adverse outcomes

Preterm brain injury was identified in 11,727/66,081 (17.8%) infants, including 10,711 (18.2%) infants who received caffeine. BPD was present in 21,104/60,980 (34.6%) infants alive at 36 weeks postmenstrual age, including 20,395 (36.5%) of those who received caffeine.

In the propensity score matched cohort of 13,045 pairs of infants, the odds of preterm brain injury and BPD were lower in those who received early caffeine compared to those who received it later (preterm brain injury: early caffeine, 2,306/13,045 (17.7%) vs. late caffeine, 2,528/13,045 (19.4%), OR=0.89 (95% CI 0.84 to 0.95) and BPD: early caffeine, 4,020/13,045 (32.8%) vs. late caffeine, 4,694/13,045 (37.7%), OR=0.81 (95% CI 0.76 to 0.85)) (Table 2 and Figure 2). In the matched cohort, the point estimates for all pre-specified secondary outcomes, except

death before discharge, were lower in those who received early caffeine compared to those who received it later (Table 2 and Figure 2).

Table 2. Odds ratios and median differences outcomes in 13,405 propensity score matched pairs of infants born at <32 weeks' gestational age in England and Wales (2012-2020) who received early caffeine and those who received it later.

Outcome	Early caffeine (n=13,045)	Late caffeine (n=13,045)	Odds ratio or median difference (95% CI)
Pre-specified primary outcomes			
Preterm brain injury, n (%)	2,306 (17.7)	2,528 (19.4)	0.89 (0.84 to 0.95)[b]
BPD, n (%)	4,020 (32.8)	4,694 (37.7)	0.81 (0.76 to 0.85)[b]
Secondary outcomes			
Death before discharge, n (%)	864 (6.6)	719 (5.5)	1.22 (1.10 to 1.35)[b]
Preterm brain injury or death, n (%)	2,717 (20.8)	2,904 (22.3)	0.92 (0.87 to 0.97)
BPD or death, n (%)	4,806 (36.8)	5,297 (40.6)	0.85 (0.81 to 0.90)[b]
Preterm brain injury, BPD or death, n (%)	5,645 (43.3)	6,172 (47.3)	0.85 (0.81 to 0.89)[b]
IVH grade 3/4 and/or PVL, n (%)	837 (6.4)	959 (7.4)	0.86 (0.78 to 0.95)[b]
Received postnatal steroids, n (%)	955 (7.3)	1,155 (8.9)	0.81 (0.74 to 0.89)[b]
Pneumothorax, n (%)	575 (4.4)	730 (5.6)	0.78 (0.70 to 0.87)[b]
ROP requiring treatment, n (%)	836 (6.4)	992 (7.6)	0.83 (0.76 to 0.92)[b]
PDA treated surgically, n (%)	220 (1.7)	301 (2.3)	0.73 (0.61 to 0.87)[b]
Severe NEC, n (%)	334 (2.6)	416 (3.2)	0.80 (0.69 to 0.92)[b]
Late onset sepsis, n (%)	4,117 (31.6)	4,552 (34.9)	0.86 (0.82 to 0.91)[b]
Total number of days of respiratory support, median (IQR)	13 (4-57)	19 (5-67)	-6 (-7 to -5)[b]

Number of days of invasive ventilation, median (IQR)	1 (0-6)	2 (0-10)	-1 (-1 to -1)[b]
Number of days of non-invasive ventilation, median (IQR)	8 (2-34)	9 (3-37)	-1 (-1 to -1)[b]

[b]p<0.05 after Bonferroni adjustment

BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity

The sensitivity analyses using the full cohort showed similar results to the propensity score matched analysis (Supplementary Table 8).

Discussion

Caffeine use, in <32 weeks' GA infants in England and Wales, has increased between 2012 and 2020 with a substantial increase in the use of caffeine within 2 days of birth. We found that the odds of BPD and evidence of preterm brain injury were lower among infants who received caffeine early when compared to those who received it after day 2.

Dobson et al.[7] found lower incidence of BPD, but greater incidence of death, among those who received caffeine in the first 3 days. We also found that the odds of death were higher in the early caffeine group but that this difference did not persist if we excluded infants who died within the first 3 days i.e., before the time they could have been started on caffeine "late".

Post-hoc analyses of the CAP trial data that first suggested benefits of early caffeine explored the potential mechanisms of action and found that 49% of the benefit was accounted for by early discontinuation of positive pressure ventilation[6]. Borszewska-Kornacka et al. used 143 propensity score-matched pairs of ≤32 weeks' GA infants and found that those who received caffeine within 24 hours required shorter duration of MV when compared to those who had caffeine later, but there was no difference in rates of BPD[15]. Although we found lower odds of BPD in those who received caffeine early, they only had one fewer day of MV and two fewer days of NIV compared to those who received caffeine later.

Caffeine may have neuroprotective effects[16]. We found reduced odds of preterm brain injury among those who received caffeine early. For the primary analysis, we

used a broad definition of preterm brain injury but the magnitude of reduction in odds was similar for the most severe brain injury (IVH 3/4 and/or PVL). Lodha et al.,[8] investigated <29 weeks' GA infants who received caffeine within two days and found that the odds of neurological injury at discharge and significant neurodevelopmental impairment at 2 years were reduced compared to those in the late caffeine group, although the odds of any neurodevelopmental impairment were similar. Association between lower rates of BPD and preterm brain injury and early caffeine use has been reported in other studies[17,18] [19][20,21].

The NNRD does not record the indication, dose, or dosing intervals. We were unable to differentiate between early use for prophylaxis of apnoea of prematurity and/or neuroprotection and that for treatment of apnoea of prematurity or for facilitating extubation. With increasing use of NIV[11], it is possible caffeine is given early to support spontaneous breathing and prevent MV. Patel et al.,[22] investigated the effect of caffeine started on the day of birth vs. started after day 1 on rates of CPAP failure among very low birthweight infants who were not mechanically ventilated. There was no difference in CPAP failure between the two groups. We were also not able to explore the answers to other important clinical questions such as the optimal dose and dosing interval for caffeine.

Our results and previous reports [7] show an increase in early administration of caffeine. Other reports have shown that centres in the UK initiate caffeine earlier than in Germany [23]. This practice, supported by results from several cohort studies, is not based on robust evidence which needs to come from RCTs. Amaro et al.[24] conducted a double-blind, placebo-controlled RCT comparing the effect of

early caffeine vs. caffeine immediately before extubation. The study was stopped after interim analyses due to an increasing trend for higher mortality in the early caffeine group. There was no reduction in age at first successful extubation, duration of MV, or incidence of BPD. Katheria et al.[25] investigated caffeine administration in the first 2 hours vs. at 12 hours for reducing the risk of intubation within the first 12 hours. They found that fewer infants who had early caffeine were intubated but MV for longer when compared to those who had caffeine later.

Increasing use of early caffeine is driven by observational data. However, all observational studies, including ours, have inherent limitations [26]. Nylander et al. conducted a systematic review of studies comparing early vs. late caffeine but were unable to draw conclusions from 12 cohort studies due to methodological problems [26]. We attempted to minimise these. There was baseline imbalance between the comparison groups which we minimised by using propensity score matching and sensitivity analyses using traditional adjustment methods and inverse probability weighting. We found that the results were similar. We followed established methods for propensity score matching [27] and the model was well-balanced across those variables that were included but these only account for measured confounders. Use of routinely collected data reduces risk of ascertainment bias, and despite missing data for some covariates, the study size, and size of the propensity score matched cohort, are larger than previous studies.

We included infants who died at ≤3 days which could have introduced a survivorship bias that may underlie the higher odds of death in the early caffeine group. We categorised risk of mortality using the NMR-2000 score and found that a smaller percentage of infants in both high and low risk categories had caffeine early while

more of those in the moderate risk category had early caffeine. It may be that those who are very sick soon after birth are not given caffeine as they are unlikely to survive while those who are very well are perceived as not needing it.

Preterm infants are not a homogeneous group. With increasing use of NIV[11], a large number are not mechanically ventilated. Early use of caffeine among these infants is aimed at reducing the need for ventilation and trials should compare the effect of starting caffeine early, sometimes as early as in the delivery suite[28], on respiratory and neurodevelopmental outcomes. There are, however, thousands of infants who require MV from birth. It is unclear if giving caffeine early while the infants are on MV will improve neurodevelopment compared to giving it immediately prior to extubation. There is also a third group who do not require any respiratory support. To consider giving early caffeine in this group we need to ask: does early caffeine have neurodevelopmental benefits independent of its respiratory benefits?

Our results suggest an association between early use of caffeine and improved outcomes at discharge. Randomised trials are required, however, to confirm the efficacy of caffeine in improving respiratory or neurodevelopmental outcomes, particularly in the longer term.

References

1 Al-Turkait A, Szatkowski L, Choonara I, *et al.* Drug utilisation in neonatal units in England and Wales: a national cohort study. *Eur J Clin Pharmacol* Published Online First: 13 January 2022. doi:10.1007/s00228-021-03267-x

2 Schmidt B, Roberts RS, Davis P, *et al.* Long-Term Effects of Caffeine Therapy for Apnea of Prematurity. *N Engl J Med* 2007;**357**:1893–902. doi:10.1056/NEJMoa073679

3 Schmidt B, Anderson PJ, Doyle LW, *et al.* Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA* 2012;**307**:275–82. doi:10.1001/jama.2011.2024

4 Schmidt B, Roberts RS, Anderson PJ, *et al.* Academic Performance, Motor Function, and Behavior 11 Years After Neonatal Caffeine Citrate Therapy for Apnea of Prematurity: An 11-Year Follow-up of the CAP Randomized Clinical Trial. *JAMA Pediatr* 2017;**171**:564. doi:10.1001/jamapediatrics.2017.0238

5 Doyle LW, Ranganathan S, Cheong JLY. Neonatal Caffeine Treatment and Respiratory Function at 11 Years in Children under 1,251 g at Birth. *Am J Respir Crit Care Med* 2017;**196**:1318–24. doi:10.1164/rccm.201704-0767OC

6 Davis PG, Schmidt B, Roberts RS, *et al.* Caffeine for Apnea of Prematurity Trial: Benefits May Vary in Subgroups. *The Journal of Pediatrics* 2010;**156**:382-387.e3. doi:10.1016/j.jpeds.2009.09.069

7 Dobson NR, Patel RM, Smith PB, *et al.* Trends in Caffeine Use and Association between Clinical Outcomes and Timing of Therapy in Very Low Birth Weight Infants. *The Journal of Pediatrics* 2014;**164**:992-998.e3. doi:10.1016/j.jpeds.2013.12.025

8 Lodha A, Entz R, Synnes A, *et al.* Early Caffeine Administration and Neurodevelopmental Outcomes in Preterm Infants. *Pediatrics* 2019;**143**:e20181348. doi:10.1542/peds.2018-1348

9 Moschino L, Zivanovic S, Hartley C, *et al.* Caffeine in preterm infants: where are we in 2020? *ERJ Open Res* 2020;**6**. doi:10.1183/23120541.00330-2019

10 Sweet DG, Carnielli V, Greisen G, *et al.* European Consensus Guidelines on the Management of Respiratory Distress Syndrome – 2019 Update. *Neonatology* 2019;**115**:432–50. doi:10.1159/000499361

11 Sand L, Szatkowski L, Kwok TC, *et al.* Observational cohort study of changing trends in non-invasive ventilation in very preterm infants and associations with clinical outcomes. *Arch Dis Child Fetal Neonatal Ed* 2021;:fetalneonatal-2021-322390. doi:10.1136/archdischild-2021-322390

12 RCPCH. Royal College of Paediatrics and Child Health. National Neonatal Audit Programme 2021: Measures Guide. 2021.https://www.rcpch.ac.uk/sites/default/files/2021-03/nnap_2021_audit_measures_guide_v1.1_11.03.2021.pdf (accessed 5 Jan 2023).

13 Imbens G, Rubin DB. *Causal Inference for Statistics, Social, and Biomedical Sciences: An Introduction*. New York: : Cambridge University Press 2015.

14 Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharmaceut Statist* 2011;**10**:150–61. doi:10.1002/pst.433

15 Borszewska-Kornacka MK, Hożejowski R, Rutkowska M, *et al.* Shifting the boundaries for early caffeine initiation in neonatal practice: Results of a prospective, multicenter study on very preterm infants with respiratory distress syndrome. *PLoS ONE* 2017;**12**:e0189152. doi:10.1371/journal.pone.0189152

16 Dix LML, van Bel F, Baerts W, *et al.* Effects of caffeine on the preterm brain: An observational study. *Early Hum Dev* 2018;**120**:17–20. doi:10.1016/j.earlhumdev.2018.03.008

17 Shenk EE, Bondi DS, Pellerite MM, *et al.* Evaluation of Timing and Dosing of Caffeine Citrate in Preterm Neonates for the Prevention of Bronchopulmonary Dysplasia. *J Pediatr Pharmacol Ther* 2018;**23**:139–45. doi:10.5863/1551-6776-23.2.139

18 Patel RM, Leong T, Carlton DP, *et al.* Early caffeine therapy and clinical outcomes in extremely preterm infants. *J Perinatol* 2013;**33**:134–40. doi:10.1038/jp.2012.52

19 Yun WZ, Kassab YW, Yao LM, *et al.* Effectiveness and safety of early versus late caffeine therapy in managing apnoea of prematurity among preterm infants: a retrospective cohort study. *Int J Clin Pharm* Published Online First: 1 August 2022. doi:10.1007/s11096-022-01437-0

20 Taha D, Kirkby S, Nawab U, *et al.* Early caffeine therapy for prevention of bronchopulmonary dysplasia in preterm infants. *J Matern Fetal Neonatal Med* 2014;**27**:1698–702. doi:10.3109/14767058.2014.885941

21 Gupte AS, Gupta D, Ravichandran S, *et al.* Effect of early caffeine on neurodevelopmental outcome of very low-birth weight newborns. *J Matern Fetal Neonatal Med* 2016;**29**:1233–7. doi:10.3109/14767058.2015.1041493

22 Patel RM, Zimmerman K, Carlton DP, *et al.* Early Caffeine Prophylaxis and Risk of Failure of Initial Continuous Positive Airway Pressure in Very Low Birth Weight Infants. *The Journal of Pediatrics* 2017;**190**:108-111.e1. doi:10.1016/j.jpeds.2017.07.006

23 Belkhatir K, Zivanovic S, Lumgair H, *et al.* Variations in preterm stabilisation practices and caffeine therapy between two European tertiary level neonatal units. *Acta Paediatr* 2020;**109**:488–93. doi:10.1111/apa.15011

24 Amaro CM, Bello JA, Jain D, *et al.* Early Caffeine and Weaning from Mechanical Ventilation in Preterm Infants: A Randomized, Placebo-Controlled Trial. *J Pediatr* 2018;**196**:52–7. doi:10.1016/j.jpeds.2018.01.010

25 Katheria AC, Sauberan JB, Akotia D, *et al.* A Pilot Randomized Controlled Trial of Early versus Routine Caffeine in Extremely Premature Infants. *Am J Perinatol* 2015;**32**:879–86. doi:10.1055/s-0034-1543981

26 Nylander Vujovic S, Nava C, Johansson M, *et al.* Confounding biases in studies on early- versus late-caffeine in preterm infants: a systematic review. *Pediatr Res* 2020;**88**:357–64. doi:10.1038/s41390-020-0757-1

27 Gale C, Longford NT, Jeyakumaran D, *et al.* Feeding during neonatal therapeutic hypothermia, assessed using routinely collected National Neonatal Research Database data: a retrospective, UK population-based cohort study. *Lancet Child Adolesc Health* Published Online First: 20 April 2021. doi:10.1016/S2352-4642(21)00026-2

28 Dekker J, Hooper SB, van Vonderen JJ, *et al.* Caffeine to improve breathing effort of preterm infants at birth: a randomized controlled trial. *Pediatr Res* 2017;**82**:290–6. doi:10.1038/pr.2017.45

Figure legends

Figure 1. Trends in use of any, early (on day of birth or day after), and late (at or after day 3) in infants born at ≤32 weeks' gestational age in England and Wales. A:

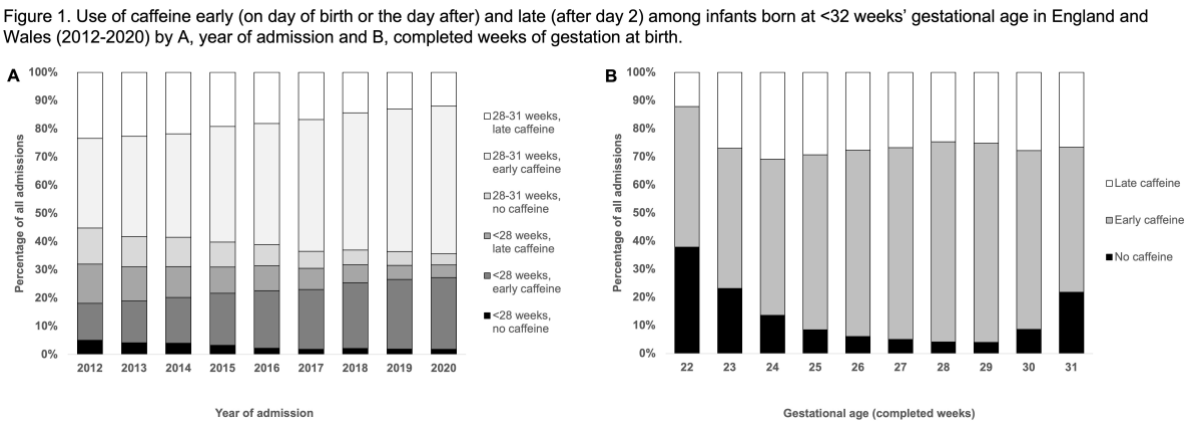
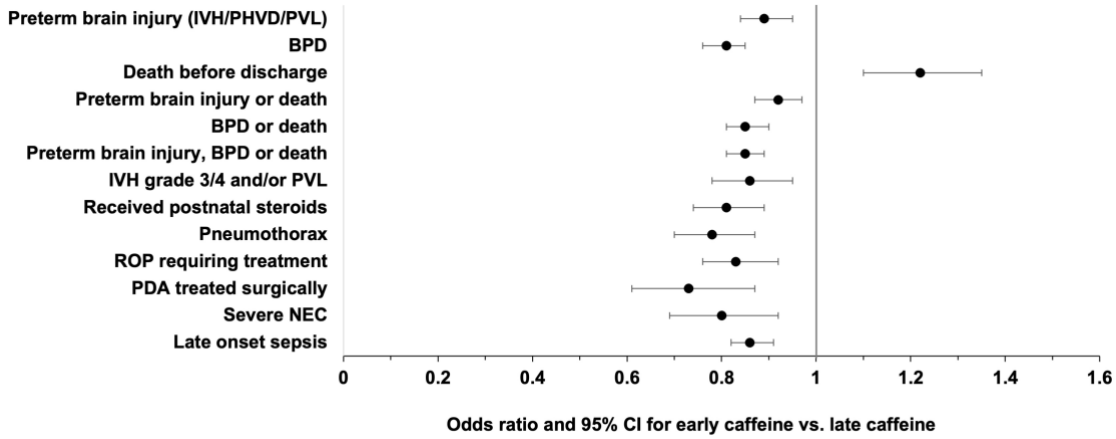


Figure 2: Odds and 95% confidence intervals of outcomes until discharge among propensity matched cohort of ≤32 weeks' gestational age infants in England and Wales (2012-2020) who received caffeine early (on day of birth or day after) vs. late (at or after day 3).



(CI, confidence interval; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PHVD, post-haemorrhagic ventricular dilatation; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity)