Observational cohort study of changing trends in non-invasive respiratory ventilation in very preterm infants and associations with clinical outcomes

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Supplementary information Table 1 online only: List of variables extracted from the National Neonatal Research Database (NNRD) and the ICD-10 codes used to identify congenital anomaly exclusions and number of babies excluded and definitions of exposure and clinical outcomes

List of variables extracted from NNRD	
Baseline Characteristics	- Gestational age was determined using the variables "GestationWeeks" and "GestationDays" - Birth weight was determined using the variable "Birthweight" - Female sex was determined using the variable "Gender" - Multiplicity was determined using the variable "Fetus number" - Any antenatal steroid given was determined using the variable "Antenatal steroids given" and "Steroids antenatal courses" - Caesarean delivery was determined using the variable "Mode of delivery", caesarean section being emergency caesarean section- not in labour, emergency caesarean section – in labour, elective section – not in labour, elective section – in labour - Prolonged rupture of membranes (>18 hours) was determined using the variable "Rupture of membranes" Surfactant given was determined using the variable "Surfactant given at resuscitation" and "Day surfactant given"
Outcomes	- CLD was determined using the variables "Respiratory support", "AddedO2", "Ventilation mode", "NonInvasiveRespiratoryS" and "Daydateanon" - Death before discharge was determined using the variables "Dateofdeath" and "Deathagemin" - Composite Outcome was determined by CLD or death at 36 weeks' gestation - Sepsis was determined by use of antibiotics for ≥5 consecutive days using the variables "drugsday" and searching for "penicillin, flucloxacillin, amoxicillin, gentamicin, metronidazole, meropenem, cephalosporin (cefotaxime, ceftazdime, cefradine, ceftriaxone) and vancomycin; determined that antibiotic was used for ≥5 consecutive days by using the variable "dayoflife" - Early sepsis was determined by the use of ≥5 consecutive days antibiotics in the first seven days of life - Late sepsis was determined by the use of ≥5 consecutive days antibiotics after 7 days of life - Medical NEC was determined by the variable "nectreatment" coded medically for ≥5 consecutive days - Surgical NEC was determined by the variable "nectreatment" coded as surgical - Surgical PDA was determined using the variable "treatmentforpda" and searching for 'ligation' or 'ligature' or 'closure of PDA/ patent ductus arteriosus' or 'open correction of PDA' or 'percutaneous transluminal prosthetic occlusion of PDA' on "principleproceduresduringstay", "principlediagnosisatdischarge" and "diagnosisatadmission" - IVH (Grade 3 or 4) was determined using data from cranial ultrasound variable "rightivh" and "leftivh" (looking for grade 3 and 4) and searching for 'ivh grade 3' and 'ivh grade 4' and 'large intraventricular haemorrhage' and 'intraventricular haemorrhage/ parenchymal haemorrhage' in variables "diagnosisatadmission" and "principaldiagnosisatdischarge"

	- PVL was determined using data from cranial ultrasound variable "pvl" and searching for 'cystic periventricular leucomalacia' and 'pvl' and 'periventricular leucomalacia' in variables "diagnosisatadmission" and "principaldiagnosisatdischarge" - ROP was determined using variables "principleproceduresduringstay" and requiring VEGF and/or laser treatment - Pneumothorax was determined by searching 'pneumothorax' in variables "diagnosisatadmission" and "principaldiagnosisatdischarge" - Postnatal steroid was determined by the use of steroids (dexamethasone >3 days, hydrocortisone >7 days, methylprednisolone >3 days and prednisolone >7 days) using variables "drugsday" and "dayoflife" - Invasive ventilation was determined by using variables "ventilationmode" and "respiratorysupport" - Number of days of invasive ventilation was determined using variables "ventilationmode" and "respiratorysupport" and "dayoflife" - Number of non-invasive ventilation days was determined using variables "respiratorysupport" and "noninvasiverespiratorysupport" and "dayoflife" - Time to first oral feed given was determined using variables "dayenteralfeeds" and "formulaname" and "dayoflife" - Number of days on the neonatal unit was determined using variables "dischtimeanon" and "admittimeanon"

Infants excluded due to missing information

Infant were excluded in there was missing information oon gestational age (GA), birthweight or sex. Where contradictory data were recorded, the entry at the first admission was selected. Infants recorded as born at <22 weeks' gestation, of birthweight for GA z-score >4, or <-4, standard deviations (SD), as admitted >12 hours after birth, had missing records of ≥1 days or had congenital anomalies that impact respiratory support listed below.

ICD-10 codes used to identify congenital anomaly exclusions and number of babies excluded

ICD-10 code	Anomaly	Number excluded[a]
Q00	Anencephaly and similar malformations	
Q01	Encephalocele and similar malformations	8
Q05	Spina bifida and similar malformations	27
Q20	Congenital malformations of cardiac chambers and connections	133
Q21.2	Atrioventricular septal defect (AVSD)	70
Q21.3	Tetralogy of Fallot	73
Q21.91	Single atrium	
Q21.92	Single ventricle	
Q22	Congenital malformations of pulmonary and tricuspid valves	236
Q23	Congenital malformations of aortic and mitral valves	80
Q25.1	Coarctation of aorta	109
Q25.2	Atresia of aorta	
Q25.3	Stenosis of aorta (AS)	5
Q25.4	Other congenital malformations of aorta	49
Q25.5	Atresia of pulmonary artery	9
Q25.6	Stenosis of pulmonary artery (PS)	362
Q25.8	Other congenital malformations of great arteries	2
Q26.2	Total anomalous pulmonary venous connection (TAPVD)	12
Q30.0	Choanal atresia	30
Q32	Congenital malformations of trachea and bronchus	102
Q33.0	Congenital cystic lung	45
Q33.2	Sequestration of lung	6
Q33.3	Agenesis of lung	
Q33.4	Congenital bronchiectasis	
Q33.5	Ectopic tissue in lung	

Q33.6	Hypoplasia and dysplasia of lung	16
Q34.0	Anomaly of pleura	
Q34.1	Congenital cyst of mediastinum	
Q34.8	Other specified congenital malformations of respiratory system	
Q35/Q36/Q37	Cleft lip and/or palate	202
Q39	Oesophageal atresia	104
Q41	Congenital absence, atresia and stenosis of small intestine	15
Q42	Congenital absence, atresia and stenosis of large intestine	41
Q60.1	Bilateral renal agenesis	3
Q60.6	Potter's syndrome	4
Q61.1	Polycystic kidney, infantile type	6
Q61.2	Polycystic kidney, adult type	1
Q64.1	Exstrophy of urinary bladder	2
Q64.2	Posterior urethral valves (PUV)	25
Q64.5	Congenital absence of bladder and urethra	1
Q77.1	Thanatophoric short stature	
Q79.0	Congenital diaphragmatic hernia	75
Q79.1	Eventration of diaphragmatic hernia	18
Q79.2	Exomphalos	66
Q79.3	Gastroschisis	50
Q90	Down's syndrome	171
Q91	Edwards' syndrome and Patau's syndrome	42

[a]Sum exceeds total number of exclusions as some infants had more than one anomaly

Defintion of exposure to non-invasive ventilation (NIV)

From variables that record types of respiratory support received (invasive ventilation, NIV, supplemental oxygen, type of NIV), we first identified babies who received any NIV. Those who did not receive any respiratory support, had only mechanical ventilation and/or supplemental oxygen, or where information was not available to discern the type of NIV were excluded.

HFNC group: those who received HFNC for any length of time. Infants in the HFNC group may have received CPAP also.	**CPAP group: t**hose who received CPAP and had no record of receiving HFNC.

Definition of clinical outomces*

Bronchopulmonary dysplasia (BPD)	Infant requiring any supplementary oxygen or respiratory support at 36 weeks' CGA (infants who died before 36 weeks were excluded) [9]
Death before discharge	Infant death prior to discharge from neonatal care
Late onset sepsis (LOS)	recorded diagnosis with either a positive blood culture or antibiotic given for ≥5 consecutive days) after 72 hours of life
Necrotising enterocolitis (NEC)	recorded diagnosis of confirmed NEC); surgical NEC (NEC treatment coded as surgical
Patent ductus arteriosus (PDA)	Recorded diagnosis of PDA requiring surgical closure
Retinopathy of prematurity (ROP)	Recorded diagnosis of ROP requiring vascular endothelial growth factor or laser treatment
Pneumothorax	Recorded diagnosis of pneumothorax
Postnatal steroid administration	Record of infant having received dexamethasone > 3 days, hydrocortisone > 7 days, methylprednisolone > 3 days or prednisolone > 7 days);
Number of days of non-invasive ventilation	Number of days of care where infants was recorded as having received any form of NIV
Number of days of non-respiratory support	Number of days of care where infants was recorded as having received any respiratory support
Number of days spent in neonatal care	Total number of days infant remained in neonatal care including stay in all neonatal units they were cared for in.

*Code lists are available from the authors on request.

Supplementary information Table 2. Characteristics of infants who received NIV with HFNC or with CPAP only from 2010 to 2017 in England and Wales, by gestational age group.

	All infants	HFNC	CPAP only	P
Gestational age <28 weeks	**n = 13,841**	**n = 10,734**	**n = 3,107**	
Gestational age (weeks, median (IQR))	26 (25-27)	26 (25-27)	26 (25-27)	<0.001
Birth weight (grams, median (IQR))	850 (710-989)	842 (705-980)	860 (720-1000)	<0.001
Birth weight z-score (mean (± SD))[a]	-0.11 (0.86)	-0.12 (0.86)	-0.07 (0.85)	0.002
Female sex, n (%)	6,543 (47.3)	5,068 (47.2)	1,475 (47.5)	0.799
Multiple birth, n (%)	3,339 (24.1)	2,542 (23.7)	797 (25.7)	0.024
Any antenatal steroid given, n (%)[a]	12,497 (90.3)	9,731 (90.7)	2,766 (89.0)	0.002
Caesarean delivery, n (%)[a]	5,605 (40.5)	4,404 (41.0)	1,201 (38.7)	0.008
Rupture of membranes (>18 hours), n (%)	3,813 (27.5)	2,940 (27.4)	873 (28.1)	0.436
Surfactant given, n (%)[a]	12,203 (88.2)	9,311 (86.7)	2,892 (93.1)	<0.001
Mechanical ventilation prior to non-invasive ventilation, n (%)	10,781 (77.9)	8,362 (77.9)	2,419 (77.9)	0.957
NMR-2000 score, categorised as risk of in-hospital mortality, n (%)[a]				
Low risk	0 (0)	0 (0)	0 (0)	
Medium risk	9,713 (70.2)	7,555 (70.4)	2,158 (69.5)	0.010
High risk	2,686 (19.4)	2,105 (19.6)	581 (18.7)	
Gestational age 28-31 weeks	**n = 32,021**	**n = 16,202**	**n = 15,819**	
Gestational age (weeks, median (IQR))	30 (29-31)	29 (28-30)	30 (29-31)	<0.001
Birth weight (grams, median (IQR))	1,355 (1150-1570)	1,300 (1090-1518)	1,410 (1210-1615)	<0.001
Birth weight z-score (mean (± SD))	-0.04 (1.00)	-0.12 (1.05)	0.05 (0.94)	<0.001
Female sex, n (%)	14,340 (44.8)	7,103 (43.8)	7,237 (45.7)	0.001
Multiple birth, n (%)	9,041 (28.2)	4,511 (27.8)	4,530 (28.6)	0.114
Any antenatal steroid given, n (%)[b]	28,612 (89.4)	14,585 (90.0)	14,027 (88.7)	<0.001
Caesarean delivery, n (%)[b]	20,424 (63.8)	10,623 (65.6)	9,801 (62.0)	<0.001
Rupture of membranes (>18 hours), n (%)	7,083 (22.1)	3,374 (20.8)	3,709 (23.4)	<0.001
Surfactant given, n (%)[b]	12,557 (39.2)	6,832 (42.2)	5,725 (36.2)	<0.001
Mechanical ventilation prior to non-invasive ventilation, n (%)	9,330 (29.1)	5,537 (34.2)	3,793 (24.0)	<0.001
NMR-2000 score, categorised as risk of in-hospital mortality n (%)[b]				
Low risk	4,047 (12.6)	1,677 (10.4)	2,370 (15.0)	
Medium risk	24,094 (75.2)	12,656 (78.1)	11,438 (72.3)	<0.001
High risk	533 (1.7)	378 (2.3)	155 (1.0)	

[a]Missing data amongst babies <28 weeks: birth weight for age z-score, 18 (0.1%); exposure to antenatal steroids, 107 (0.8%); born by Caesarean delivery, 683 (4.9%); surfactant given, 513 (3.7%); NMR-2000 score, 1,442 (10.4%)

[b]Missing data amongst babies 28-31 weeks: exposure to antenatal steroids, 405 (1.3%); born by Caesarean delivery, 1,739 (5.4%); surfactant given, 2,034 (6.4%); NMR-2000 score, 3,347 (10.5%)

Supplementary information Table 3. Outcomes in infants born at <28 weeks' gestation who received NIV from 2010 to 2017 in England and Wales: comparison between those who received HFNC vs. those who received CPAP only.

	All infants n (%)	HFNC n (%)	CPAP only n (%)	aOR (95% CI)
Dichotomous outcomes, n (%)				
BPD n=12,694[a,b]	9,086 (71.6)	7,651 (74.7)	1,435 (58.5)	2.10 (1.88 to 2.35)[c]
Death before discharge n=13,841	1,153 (8.3)	498 (4.6)	655 (21.1)	0.12 (0.10 to 0.14)[c]
BPD or death before discharge n = 13,841	10,233 (73.9)	8,144 (75.9)	2,089 (67.2)	1.51 (1.37 to 1.67)[c]
Late onset sepsis	10,060 (72.7)	7,889 (73.5)	2,171 (69.9)	1.35 (1.22 to 1.49)[c]
NEC (confirmed)	4,336 (31.3)	3,310 (30.8)	1,026 (33.0)	0.91 (0.83 to 1.00)
NEC requiring surgery	1,031 (7.4)	765 (7.1)	266 (8.6)	0.81 (0.69 to 0.96)
PDA requiring surgery	839 (6.1)	674 (6.3)	165 (5.3)	1.80 (1.48 to 2.18)[c]
IVH (Grade 3/4)	1,586 (11.5)	1,194 (11.1)	392 (12.6)	0.77 (0.67 to 0.89)[c]
Periventricular leukomalacia	512 (3.7)	392 (3.7)	120 (3.9)	1.00 (0.80 to 1.26)
ROP requiring treatment	2,025 (14.6)	1,802 (16.8)	223 (7.2)	1.95 (1.66 to 2.29)[c]
Pneumothorax	730 (5.3)	570 (5.3)	160 (5.1)	0.94 (0.76 to 1.15)
Received postnatal steroids	2,481 (17.9)	2,087 (19.4)	394 (12.7)	1.59 (1.40 to 1.82)[c]
Continuous outcomes, median (IQR)				
Number of days of invasive ventilation[a]	10 (3-25)	10 (3-26)	7 (2-19)	2.0 (1.3 to 2.7)[c]
Number of days of NIV ventilation[a]	45 (31-60)	47 (34-63)	35 (22-47)	11.0 (9.9 to 12.1)[c]
Number of days of respiratory support[a]	78 (53-103)	81 (57-105)	64 (41-89)	17.0 (15.1 to 18.9)[c]
Length of stay (days)[a]	92 (76-113)	94 (77-115)	84 (69-103)	11.0 (9.6 to 12.4)[c]

Abbreviations: IQR, interquartile range; BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity

aOR, adjusted odds ratio, adjusted for sex, birth weight z-score <-2, exposure to antenatal steroids, NMR-200 category, mechanical ventilation on day 1, year of admission.

[a] excluded infants who died before 36 weeks corrected gestational age

[b] missing observations: BPD, 0; Death before discharge, 4

[c] P< .05 with Bonferroni correction

Supplementary information Table 4. Outcomes in infants born at 28-31 weeks' gestation who received NIV from 2010 to 2017 in England and Wales: comparison between those who received any HFNC and those who received CPAP only.

	All infants n (%)	HFNC n (%)	CPAP n (%)	aOR (95% CI)
Dichotomous outcomes, n (%)				
BPD n=31,577[a,b]	6,386 (20.2)	4,685 (29.2)	1,701 (10.9)	3.42 (3.19 to 3.67)[c]
Death before discharge n=32,021	445 (1.4)	180 (1.1)	265 (1.7)	0.51 (0.41 to 0.64)[c]
BPD or death before discharge n=32,021	6,830 (21.3)	4,864 (30.0)	1,701 (10.9)	3.03 (2.83 to 3.24)[c]
Late onset sepsis	8,724 (27.2)	5,345 (33.0)	3,379 (21.4)	1.99 (1.88 to 2.11)[c]
NEC (confirmed)	3,775 (11.8)	2,360 (14.6)	1,415 (8.9)	1.70 (1.57 to 1.84)[c]
NEC requiring surgery	448 (1.4)	300 (1.9)	148 (0.9)	2.16 (1.73 to 2.69)[c]
PDA requiring surgery	97 (0.3)	77 (0.5)	20 (0.1)	4.67 (2.79 to 7.81)[c]
IVH (Grade 3/4)	594 (1.9)	364 (2.2)	230 (1.5)	1.32 (1.09 to 1.59)
Periventricular leukomalacia	534 (1.7)	323 (2.0)	211 (1.3)	1.41 (1.16 to 1.72)[c]
ROP requiring treatment	347 (1.1)	230 (1.4)	117 (0.7)	1.30 (1.03 to 1.64)
Pneumothorax	1,185 (3.7)	767 (4.7)	418 (2.6)	1.97 (1.72 to 2.25)[c]
Received postnatal steroids	388 (1.2)	313 (1.9)	75 (0.5)	3.84 (2.90 to 5.10)[c]
Continuous outcomes, median (IQR)				
Number of days of invasive ventilation[a]	1 (0-2)	1 (0-3)	1 (0-2)	0.0 (-8.2 to 8.2)
Number of days of NIV[a]	7 (3-15)	10 (5-24)	4 (2-8)	6.0 (5.8 to 6.2)[c]
Number of days of respiratory support[a]	10 (4-29)	17 (7-42)	6 (3-15)	8.8 (8.3 to 9.2)[c]
Length of stay (days)[a]	46 (36-60)	51 (39-66)	42 (33-52)	8.0 (7.5 to 8.5)[c]

Abbreviations: IQR, interquartile range; BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity

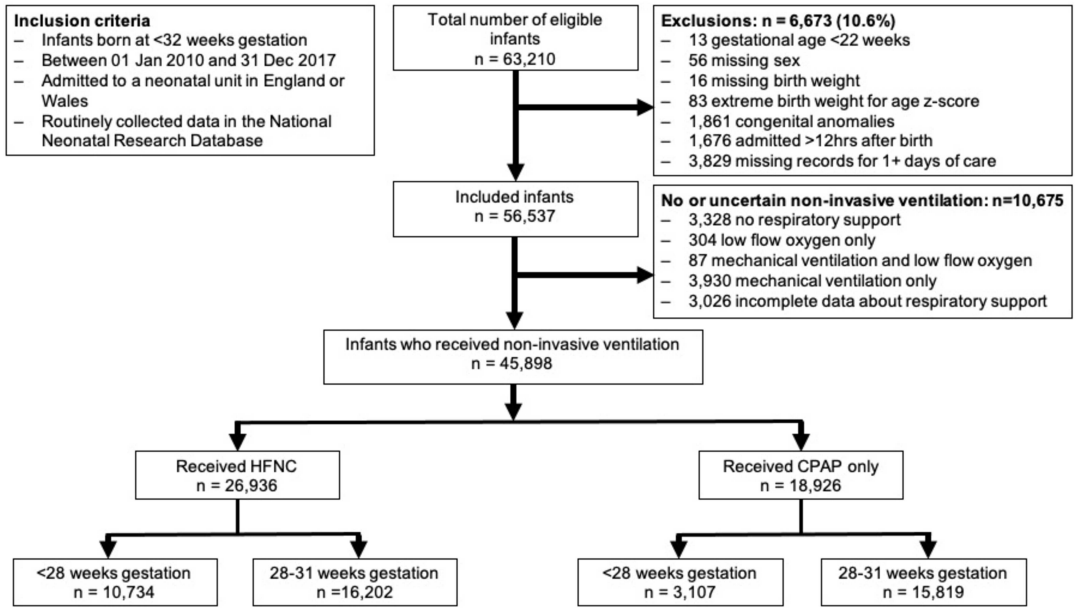
aOR, adjusted odds ratio, adjusted for sex, birth weight z-score <-2, exposure to antenatal steroids, NMR-200 category, mechanical ventilation on day 1, year of admission.

[a] excluded infants who died before 36 weeks corrected gestational age

[b] missing observations: BPD, 8; Death before discharge, 13

[c] P< .05 with Bonferroni correction

Supplementary information Figure 1. Very preterm infants who received NIV in neonatal units in England and Wales (2010-2017)



Supplementary information Figure 2. Survival curve for infants born at <32 weeks' who received any NIV during their neonatal care in England and Wales in 2010 to 2017: comparison between those who received HFNC and those who received CPAP