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

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ABSTRACT

Objective To determine the change in non-invasive ventilation (NIV) use over time in infants born at <32 weeks' gestation and the associated clinical outcomes.

Study design Retrospective cohort study using routinely recorded data from the National Neonatal Research Database of infants born at <32 weeks admitted to neonatal units in England and Wales from 2010 to 2017.

Results In 56 537 infants, NIV use increased significantly between 2010 and 2017 (continuous positive airway pressure (CPAP) from 68.5% to 80.2% in 2017 and high flow nasal cannula (HFNC) from 14% to 68%, respectively) (p<0.001)). Use of NIV as the initial mode of respiratory support also increased (CPAP, 21.5%–28.0%; HFNC, 1%–7% (p<0.001)). HFNC was used earlier, and for longer, in those who received CPAP or mechanical ventilation. HFNC use was associated with decreased odds of death before discharge (adjusted OR (aOR) 0.19, 95% CI 0.17 to 0.22). Infants receiving CPAP but no HFNC died at an earlier median chronological age: CPAP group, 22 (IQR 10–39) days; HFNC group 40 (20–76) days (p<0.001). Among survivors, HFNC use was associated with increased odds of bronchopulmonary dysplasia (BPD) (aOR 2.98, 95% CI 2.81 to 3.15) and other adverse outcomes.

Conclusions NIV use is increasing, particularly as initial respiratory support. HFNC use has increased significantly with a sevenfold increase soon after birth which was associated with higher rates of BPD. As more infants survive with BPD, we need robust clinical evidence, to improve outcomes with the use of NIV as initial and ongoing respiratory support.

What is already known on this topic?

- Non-invasive ventilation (NIV) is being used increasingly to provide respiratory support to very preterm infants.
- While continuous positive airway pressure (CPAP) remains the mainstay of NIV, high flow nasal cannula oxygen (HFNC) is a popular mode of NIV and clinicians have reported increasing preference of using HFNC.

What this study adds?

- NIV support, particularly HFNC, in very preterm infants increased significantly between 2010 and 2017 in England and Wales.
- HFNC is increasingly used as initial respiratory support in extremely preterm infants, although there is a high rate of such infants requiring CPAP or mechanical ventilation within 7 days.

INTRODUCTION

In very preterm infants, increased use of antenatal steroids, early surfactant and attempts to minimise lung injury have encouraged increased use of non-invasive ventilation (NIV).[1] Modalities such as nasal continuous positive airway pressure (CPAP) that provide a set distending pressure prevent some adverse effects associated with mechanical ventilation.[2] Similarly, high flow nasal cannula oxygen (HFNC), which delivers a set gas flow, rather than a set distending pressure, has become increasingly popular.[3]

Continuous distending pressure directly, or generated via a continuous flow of oxygen-air mixture, stabilises the upper airway, maintains lung volumes and stimulates upper airways to maintain a respiratory drive.[1] These mechanisms can reduce the need for prolonged invasive ventilation and may reduce the risk of bronchopulmonary dysplasia (BPD) and other ventilator-induced lung injuries.[4] Meta-analyses suggest that, when used for initial respiratory support or as respiratory support after extubation, HFNC and CPAP are not different when comparing the risks of BPD and death in preterm infants.[5] Both are now frequently used. Although UK clinicians report increased use of HFNC,[6] there are no data quantifying the change in use of NIV in actual practice.

We aimed to quantify the change in use of NIV in infants born at <32 weeks' gestation across England and Wales from 2010 to 2017 and analysed the association between these changes and clinical outcomes.

METHODS

We performed a retrospective cohort study of infants born at <32 weeks' gestation in England and Wales from 1 January 2010 to 31 December 2017 inclusive, whose data are held within the UK National Neonatal Research Database.[7 8]

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Infants were excluded if there were missing data as described in online supplemental figure 1 and online supplemental table 1.[7]

Exposures

From variables that record types of respiratory support received (invasive ventilation, NIV, supplemental oxygen, type of NIV), we identified infants who received any NIV (online supplemental table 1). Infants who received NIV were divided into two groups— those who received HFNC for any length of time (HFNC group) and those who received CPAP and had no record of receiving HFNC (CPAP-only group). Infants in the HFNC group may have received CPAP also.

Outcomes

BPD was defined as requiring any supplementary oxygen or respiratory support at 36 weeks' corrected gestational age (CGA) (infants who died before 36 weeks were excluded).[9] Other preplanned outcomes and their definitions are given in online supplemental table 1.

Statistical analysis

All data management and analyses were performed using STATA, V.15.1 (StataCorp, College Station, Texas, USA). After exclusions, we quantified the percentage of all admissions each year where HFNC was used, both for all infants and for two prespecified subgroups: those born at <28 weeks', and those born at 28–31 weeks' gestation. We compared the study groups, including demographic, pregnancy and delivery details, and the NMR-2000 score to describe infants' risk of in-hospital mortality.[10]

We quantified and described changes in the highest mode of respiratory support received on the first day after birth. We described the percentage who subsequently 'failed' on the initial mode as those who had escalation of respiratory support within 7 days that is, for those on HFNC initially, if they received CPAP and/or mechanical ventilation and for those on CPAP initially, if they received mechanical ventilation. Where HFNC was not the initial mode of respiratory support, we quantified subsequent exposure to HFNC. Change in use over the study period (2010–2017) was analysed using the χ^2 test for trends.

We used logistic regression for binary variables and quantile regression for continuous variables to explore the association between study groups and the prespecified outcomes. ORs and median differences were adjusted for: gestational age (GA) group (<28 weeks' gestation or 28–31 weeks' gestation); sex; birth weight for age z-score (<−2 SD or ≥−2 SD or between <2 SD and ≥−2 SD); exposure to antenatal steroids; NMR-2000 category (low risk, medium risk or high risk)[10]; need for mechanical ventilation on day 1 and year of admission. Any missing data for confounding variables were treated as separate categories and infants retained in the models. We used a robust variance estimator to account for clustering of infants within units. All p values were two-sided, significance was set at $p<0.05$ and we used a Bonferroni correction to account for multiple testing. A predefined subgroup analysis was performed for all outcomes for infants born at <28 weeks' gestation and those born at 28–31 weeks' gestation.

RESULTS

From the population of 63 210 infants born at <32 weeks' gestation, 56 537 infants were retained after exclusions (online supplemental figure 1). Of these, 45 898 infants received NIV.

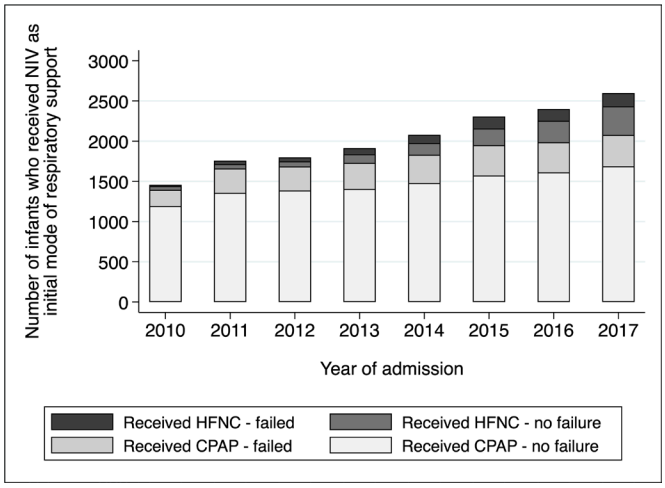

Figure 1 Use of HFNC as the initial mode of respiratory support in infants born at <32 weeks' gestational age in England and Wales (2010–2017). Failure refers to escalation of respiratory support within 7 days, that is, HFNC failed refers to those infants who received HFNC as the initial mode of respiratory support but needed CPAP and/or mechanical ventilation within 7 days and CPAP failed refers to those who received CPAP as the initial mode of respiratory support but needed mechanical ventilation within 7 days. Image created by authors using STATA, V.15.1 (StataCorp, College Station, Texas, USA). CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula; NIV, non-invasive ventilation.

Non-invasive ventilation (CPAP or HFNC) on day of birth

On the day of birth, 16 308/56 537 (28.8%) infants received NIV, which included 1065/17 061 (6.2%) infants of <28 weeks' and 15 243/39 476 (38.6%) infants of 28–31 weeks' GA. During the study period, those who received NIV on the first day increased from 1457/6479 (22.5%) to 2598/7401 (35.1%). This increase was larger among the 28–31 weeks' GA group ((from 1357/4570 (29.7%) to 2471/5194 (46.5%)) as compared with that among infants <28 weeks' GA (from 100/1909 (5.2%) to 181/2216 (8.2%)).

Figure 1 shows the respiratory support received by the infants on the first day (initial respiratory support) from 2010 to 2017. The percentage receiving CPAP increased 1.3-fold from 21.5% to 28.0% while HFNC use increased by 7-fold from 1.0% to 7.0%. This increase was seen both in infants born at <28 weeks' and those born at 28–31 weeks' GA, though the magnitude of increase was greater among the latter (table 1).

CPAP was used as initial support in 14 312/56 537 infants (25.3% of all admissions), of whom 18.3% (n=2623/14 312) went on to receive mechanical ventilation within 7 days (table 1). The failure rate was higher among infants born at <28 weeks, of whom 263/836 (31.5%) were ventilated within 7 days compared with 2360/13 476 (17.5%) infants born at 28–31 weeks.

HFNC was used as the initial respiratory support in 1996/56 537 infants (3.5% of all admissions); 748/1996 (37.5%) went onto receive CPAP (n=571/1996 (28.6%)) or mechanical ventilation (n=347/1996 (17.4%)) within 7 days, including 170/1996 (8.5%) who received both CPAP and mechanical ventilation. The failure rate was higher among the more immature infants (<28 weeks' GA: 135/229 (59.0%), including 84/229 (36.7%) who were mechanically ventilated; 28–31 weeks' GA: 613/1767 (34.7%), including 263/1767 (14.9%) who were mechanically ventilated). Among the infants who received HFNC on the first day, those who 'failed' included more infants who were extremely

Table 1 NIV support use on day of birth and rates of requiring escalation in respiratory support within 7 days in infants born at <32 weeks' gestation from 2010 to 2017 in England and Wales

		Received HFNC as initial support* n (%)			Received CPAP as initial support* n (%)	
Year	Total admissions, n	Total, n (%)	Received CPAP and/or mechanical ventilation within 7 days, n (%)	Received mechanical ventilation within 7 days, n (%)	Total, n (%)	Received mechanical ventilation within 7 days, n (%)
Infants born at <32 weeks' gestational age						
2010	6479	63 (1.0)	16 (25.4)	11 (17.5)	1394 (21.5)	203 (14.6)
2011	6929	97 (1.4)	42 (43.3)	17 (17.5)	1660 (24.0)	302 (18.2)
2012	6981	113 (1.6)	49 (43.4)	22 (19.5)	1685 (24.1)	298 (17.7)
2013	7081	183 (2.6)	78 (42.6)	36 (19.7)	1730 (24.4)	325 (18.8)
2014	6963	248 (3.6)	102 (41.1)	47 (19.0)	1831 (26.3)	354 (19.3)
2015	7317	356 (4.9)	149 (41.9)	67 (18.8)	1950 (26.7)	377 (19.3)
2016	7377	415 (5.6)	146 (35.2)	64 (15.4)	1985 (26.9)	374 (18.8)
2017	7410	521 (7.0)	166 (31.9)	83 (15.9)	2077 (28.0)	390 (18.8)
All	56537	1996 (3.5)	748 (37.5)	347 (17.4)	14312 (25.3)	2623 (18.3)
Subgroup of infants born at <28 weeks' gestational age						
2010	1909	12 (0.6)	4 (33.3)	3 (25.0)	88 (4.6)	26 (29.5)
2011	2150	21 (1.0)	9 (42.9)	6 (28.6)	97 (4.5)	28 (28.9)
2012	2171	19 (0.9)	13 (68.4)	7 (36.8)	103 (4.7)	34 (33.0)
2013	2092	16 (0.8)	11 (68.8)	7 (43.8)	82 (3.9)	27 (32.9)
2014	2092	22 (1.1)	19 (86.4)	14 (63.6)	106 (5.1)	45 (42.5)
2015	2199	39 (1.8)	26 (66.7)	14 (35.9)	110 (5.0)	36 (32.7)
2016	2232	44 (2.0)	22 (50.0)	11 (25.0)	125 (5.6)	36 (28.8)
2017	2216	56 (2.5)	31 (55.4)	22 (39.3)	125 (5.6)	31 (24.8)
All	17061	229 (1.3)	135 (59.0)	84 (36.7)	836 (4.9)	263 (31.5)
Subgroup of infants born at 28–31 weeks' gestational age						
2010	4570	51 (1.1)	12 (23.5)	8 (15.7)	1306 (28.6)	177 (13.6)
2011	4779	76 (1.6)	33 (43.4)	11 (14.5)	1563 (32.7)	274 (17.5)
2012	4810	94 (2.0)	36 (38.3)	15 (16.0)	1582 (32.9)	264 (16.7)
2013	4989	167 (3.3)	67 (40.1)	29 (17.4)	1648 (33.0)	298 (18.1)
2014	4871	226 (4.6)	83 (36.7)	33 (14.6)	1725 (35.4)	309 (17.9)
2015	5118	317 (6.2)	123 (38.8)	53 (16.7)	1840 (36.0)	341 (18.5)
2016	5145	371 (7.2)	124 (33.4)	53 (14.3)	1860 (36.2)	338 (18.2)
2017	5194	465 (9.0)	135 (29.0)	61 (13.1)	1952 (37.6)	359 (18.4)
All	39476	1767 (4.5)	613 (34.7)	263 (14.9)	13476 (34.1)	2360 (17.5)

*Mode of respiratory support on day of birth.
CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula oxygen; NIV, non-invasive ventilation.

preterm, that is, <28 weeks' GA (135/784 (18.0%) vs 94/1248 (7.5%); p<0.001); of lower birth weight (1285 (346) g vs 1396 (318) g; p<0.001); multiple births (35.2% vs 28.2%; p=0.001); born by caesarean section (64.7% vs 55.4%; p<0.001); had prolonged rupture of membranes (17.8% vs 28.6%; p<0.001) and who had not had surfactant (15.0% vs 9.5%; p<0.001). There was no difference in the sex of the infants or receipt of antenatal steroids.

CPAP use during neonatal care

The use of CPAP at any point during an infant's stay in neonatal care significantly increased from 68.5% infants in 2010 (n=4439/6479) to 80.2% in 2017 (n=5941/7410) (χ^2 test for trend p<0.001). Further data on the use of CPAP in infants who received mechanical ventilation as initial respiratory support are described in table 2.

HFNC use during neonatal care

The use of HFNC at any point significantly increased from 14.3% of infants in 2010 (n=928/6479) to 68.0% in 2017 (n=5039/7410) (figure 2, p<0.001). The increase in percentage of infants who received mechanical ventilation or CPAP as their initial respiratory support and then went on to receive HFNC, and data demonstrating earlier and more prolonged use of HFNC, are described in table 2.

Clinical outcomes associated with use of CPAP and HFNC

There were 18926 infants who had CPAP only and 26936 infants who received any HFNC (online supplemental figure 1). Infants receiving HFNC were more immature and smaller at birth, more were exposed to antenatal steroids and received surfactant while a smaller proportion were delivered by caesarean section, were multiple births and were less likely to be born to mothers who had prolonged rupture of membranes (online supplemental table 2).

The outcomes are shown in table 3 and by subgroup in online supplemental tables 3 and 4. The odds of death before discharge were significantly higher in infants who had CPAP only compared with those who had any HFNC (adjusted OR (aOR) 0.19 (95% CI 0.17 to 0.22)). Infants who had CPAP only died at an earlier chronological age than those who received HFNC (median (IQR) age of death: CPAP group, 22 (95% CI 10 to

Table 2 Use of HFNC and CPAP for respiratory support following support with mechanical ventilation and/or CPAP in infants born at <32 weeks' gestation in England and Wales (2010–2017)

Year	Received invasive ventilation or CPAP as initial mode, n	Subsequently received HFNC, n (%)	Number of days of HFNC received, median (IQR)	Day of care HFNC first received, median (IQR)	Number of days of both HFNC and CPAP, median (IQR)
HFNC use following initial mechanical ventilation or CPAP					
2010	5030	792 (15.7)	6 (2–14)	17 (6–45)	1 (1–2)
2011	5556	1794 (32.3)	8 (2–20)	18 (5–40)	2 (1–4)
2012	5741	2269 (39.5)	9 (3–23)	14 (5–34)	2 (1–4)
2013	5905	2994 (50.7)	11 (4–25)	9 (3–27)	2 (1–5)
2014	5870	3494 (59.5)	12 (4–28)	7 (3–22)	3 (1–6)
2015	6136	3950 (64.4)	14 (5–29)	6 (3–19)	3 (1–7)
2016	6222	4255 (68.4)	13 (5–28)	5 (2–15)	3 (1–7)
2017	6239	4357 (69.8)	13 (5–29)	5 (2–14)	3 (1–7)
All	46 699	23 905 (51.2)	11 (4–27)	7 (3–23)	3 (1–6)

Year	Received invasive ventilation as initial mode, n	Subsequently received CPAP, n (%)	Number of days of CPAP received, median (IQR)	Day of care CPAP first received, median (IQR)
CPAP use following initial mechanical ventilation				
2010	3636	2708 (74.5)	13 (4–29)	3 (2–7)
2011	3896	2989 (76.7)	14 (4–31)	3 (2–6)
2012	4056	3202 (78.9)	14 (5–30)	3 (2–6)
2013	4175	3407 (81.6)	11 (4–26)	3 (2–6)
2014	4039	3331 (82.5)	12 (4–27)	3 (2–7)
2015	4186	3463 (82.7)	11 (4–26)	3 (2–7)
2016	4237	3542 (83.6)	11 (4–25)	3 (2–7)
2017	4162	3465 (83.3)	11 (3–25)	3 (1–7)
All	32 387	26 107 (80.6)	12 (4–27)	3 (2–7)

CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula oxygen.

39) days; HFNC group, 40 (95% CI 20 to 76) days; p<0.001) (online supplemental figure 2). Excluding deaths before 36 weeks' CGA, 3136/18 003 (17.4%) infants who had CPAP only developed BPD compared with 12 336/26 260 (47.0%) who received any HFNC. The odds of developing BPD were significantly higher in the HFNC group (adjusted aOR 2.98 (95% CI 2.81 to 3.15)). Infants who had HFNC spent significantly longer on respiratory support, had longer hospital stay, higher odds of NEC and other complications as compared with those who had CPAP only (table 3).

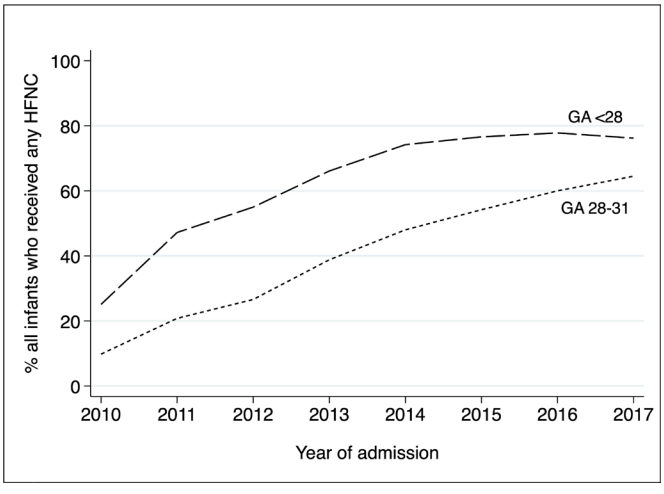

Figure 2 Percentage of all infants born at <28 weeks' gestational age (GA) and those born at 28–32 weeks' GA in England and Wales (2010–2017) who received any high flow nasal cannula oxygen (HFNC) during their neonatal care. Image created by authors using STATA, V.15.1 (StataCorp, College Station, Texas, USA).

DISCUSSION

We found that, in England and Wales, there have been significant changes in the use of NIV in very preterm infants with substantial increase in use of HFNC from <15% of all infants born at <32 weeks' gestation in 2010 to 68% in 2017, both as initial respiratory support (from 1% to 7%) and as support received later (from 15.7% to 69.8%). This is similar to the trend seen in Australia and New Zealand.[11]

Use of NIV on the day of birth has increased from 22% to 35% over the study period although, overall, only 8% of those born <28 weeks' gestation received NIV on this day. In an Australia-New Zealand cohort (2007–2013), 29% of infants <29 weeks' gestation received CPAP for initial respiratory support, 43% of whom required mechanical ventilation within 72 hours.[12] The overall CPAP failure rate was lower in our cohort (31%) even though we measured failure over a longer 7-day period. Systematic reviews of randomised controlled trials (RCTs) comparing early prophylactic CPAP with mechanical ventilation show a nearly 50% reduction in need for mechanical ventilation.[13] Our data demonstrate a more conservative use of CPAP as the initial respiratory support in England and Wales.

The Cochrane systematic review did not find any study that investigated the use of HFNC as the initial mode of respiratory support in infants <28 weeks' gestation while other reviews reported that HFNC has higher failure rates than CPAP when used as first-line support in <28 weeks' gestation infants.[14 15] We found that 60% of <28 weeks' gestation infants who received HFNC as initial support subsequently required escalation of

Table 3 Clinical outcomes in infants who received NIV from 2010 to 2017 in England and Wales: comparison between those who received any HFNC versus those who had CPAP only

	All infants (n=45 862)	HFNC (n=26 936)	CPAP only (n=18 926)	aOR or median difference (95% CI)
Dichotomous outcomes, n (%)				
BPD n=44 271*†	15 472 (34.9)	12 336 (47.0)	3136 (17.4)	2.98 (2.81 to 3.15)‡
Death before discharge n=45 862†	1598 (3.5)	678 (2.5)	920 (4.9)	0.19 (0.17 to 0.22)‡
BPD or death before discharge n=45 862†	17 063 (37.2)	13 008 (48.3)	4055 (21.4)	2.46 (2.33 to 2.60)‡
Late-onset sepsis	18 784 (41.0)	13 234 (49.1)	5550 (29.3)	1.81 (1.72 to 1.90)‡
NEC (confirmed)	8111 (17.7)	5670 (21.0)	2441 (12.9)	1.34 (1.26 to 1.43)‡
NEC requiring surgery	1479 (3.2)	1065 (4.0)	414 (2.2)	1.19 (1.03 to 1.36)
PDA requiring surgery	936 (2.0)	751 (2.8)	185 (1.0)	2.08 (1.73 to 2.50)‡
IVH (grade 3/4)	2180 (4.7)	1558 (5.8)	622 (3.3)	0.94 (0.84 to 1.06)
Periventricular leukomalacia	1046 (2.3)	715 (2.7)	331 (1.7)	1.24 (1.06 to 1.44)
ROP requiring treatment	2372 (5.2)	2032 (7.5)	340 (1.8)	1.73 (1.52 to 1.96)‡
Pneumothorax	1915 (4.2)	1337 (5.0)	578 (3.1)	1.59 (1.41 to 1.78)‡
Received postnatal steroids	2869 (6.3)	2400 (8.9)	469 (2.5)	1.93 (1.71 to 2.18)‡
Continuous outcomes, median (IQR)				
Number of days of invasive ventilation*	2 (0–6)	3 (1–9)	1 (0–3)	0.0 (–2.1 to 2.1)‡
Number of days of NIV*	12 (4–36)	24 (8–46)	5 (2–13)	6.3 (5.7 to 6.9)‡
Number of days of respiratory support*	22 (6–61)	41 (11–77)	7 (3–25)	9.5 (9.1 to 9.9)‡
Length of stay (days)*	55 (40–80)	66 (47–91)	44 (34–59)	8.7 (8.3 to 9.1)‡

Adjusted for gestational age <28 weeks, sex, birth weight z-score <–2, exposure to antenatal steroids, NMR-200 category, mechanical ventilation on day 1, year of admission.
*Excluded infants who died before 36 weeks' corrected gestational age.
†Missing observations: BPD, 8; death before discharge, 17.
‡P<0.05 with Bonferroni correction.
aOR, adjusted OR; BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula oxygen; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NIV, non-invasive ventilation; ROP, retinopathy of prematurity.

support within 7 days, compared with 31.5% of the CPAP group. In the subgroup of infants born at 28–31 weeks' gestation, 34.7% who received HFNC as initial mode required escalation within 7 days. This is similar to the 32.9% failure rate for HFNC among 28–31 weeks' gestation infants reported by Roberts *et al*[16] in an RCT that was stopped early due to the high rate of HFNC treatment failure. When CPAP was used as initial mode of respiratory support, we found that 17.5% were ventilated within 7 days, similar to the rate reported by Roberts *et al* (16.1%), although they measured rates of intubation up to 72 hours only. HFNC use as the initial respiratory mode is increasing in popularity particularly in more mature infants. In a two-centre study in the UK, Zivanovic *et al*, found that use of HFNC without the need for CPAP as 'rescue' was successful in preventing intubation in infants between 28 and 36 weeks' gestation.[17]

Similarly, we found an increase in the use of HFNC later in neonatal care with significant increases in the number of infants who received any HFNC and the number of days on HFNC per infant. In addition, we also found that HFNC was given increasingly earlier with 12 days difference in initiation between 2010 and 2017.

We analysed the associations of these changes in practice with clinical outcomes and found higher mortality among infants who never received HFNC. Among those who survived to 36 weeks' CGA, we found that the adjusted odds of BPD were significantly higher among those who received HFNC compared with those who had CPAP only. Infants in the CPAP only group died significantly earlier than those in the HFNC group. It is possible that attending clinicians did not choose HFNC for infants with more disease in the first few weeks of life. Such infants remained on mechanical ventilation or CPAP and may have died before they were considered well enough to receive HFNC. The survivors, particularly those who required prolonged respiratory support, were then more likely to receive HFNC, resulting in a higher rate of both survival and BPD among them. This suggests an element of confounding by indication, that is, the differences in outcome are related to the way a particular intervention is used rather than the intervention itself, which may explain some of the relationship between HFNC and death and HFNC and BPD. However, the use of HFNC may also be a step in the causal pathway[18] of BPD. The variable and unregulated distending pressure generated by HFNC may cause uncontrollable overexpansion and/or atelectasis that aggravate lung injury leading to higher risks of BPD. Meta-analysis of RCTs showed no difference in BPD between HFNC and CPAP use, although the studies did not include many infants born at <28 weeks' gestation.[5] Our findings are similar to previous smaller observational studies.[19]

Other important clinical outcomes such as late onset sepsis, necrotising enterocolitis, patent ductus arteriosus, pneumothorax and retinopathy of prematurity were also more frequent in babies who received HFNC. Infants who received HFNC required respiratory support for longer and received in-hospital neonatal care for longer. Prolonged need for respiratory support with HFNC has been demonstrated in meta-analyses of RCTs[5] and observational studies.[19 20] Our study, due to its retrospective, observational design, cannot show a direct link between choice of NIV and any of the clinical outcomes we report. It has been suggested that the increased perceived patient tolerance, and ease of application and maintenance, may result in less urgency to wean leading to longer lengths of respiratory support and hospital stay.[21]

Our study of 56 537 infants, limited by observational design, cannot imply a causative link between HFNC and either reduced mortality or increased BPD as highlighted by Roberts *et al*.[22] RCTs remain the gold-standard for demonstrating causation and clinical trials suggest that HFNC does not increase the risk of death or BPD compared with CPAP at least in the more mature population.[5] However, outcomes in research trials can be superior to the same practice in clinical situations, possibly due to the greater level of control over patient selection and better adherence to treatment protocols in trial settings.[23] The worse outcomes, such as increased odds of BPD, in observational studies may be a consequence of indication creep[24] and

outcomes may also vary with experience and training of practitioners. Careful patient selection and individualised application of HFNC may improve outcomes.

With a database that covers almost the entire population of England and Wales, we achieved a large sample size that enabled us to quantify the changes comprehensively and account for several confounding variables. In addition, we have accounted for multiple testing and used a robust variance estimator to account for clustering of infants within units. These make a robust observational study but do not remove the inherent limitation that associations do not imply causation.

CONCLUSION

NIV use is increasing. CPAP use increased 1.3-fold while HFNC use increased by 7-fold as respiratory support soon after birth. As more infants survive with BPD, we need clinical evidence and ongoing monitoring to ensure practice evolves in keeping with the best evidence to support the use of NIV as initial and ongoing respiratory support.

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Contributors LSa: participated in the concept and design, performed the analysis of data, participated in interpretation of data and drafted the manuscript. LSz: participated in the concept and design, performed the analysis of data, participated in interpretation of data and drafted and revised the manuscript. TCK: participated in the concept and design, analysis of data and interpretation of data and revised the manuscript. DS: participated in the concept and design, analysis of data and interpretation of data and revised the manuscript. DAT: participated in the concept and design, interpretation of data and revised the manuscript. HB: participated in the concept and design, analysis of data and interpretation of data and revised the manuscript. SO: designed and conceptualised the study, participated in analysis and interpretation of data and drafted and revised the manuscript.

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Data availability statement Data are available on reasonable request. Data may be obtained from a third party through the National Neonatal Research Database with relevant approvals. The National Neonatal Research Database is a National Data Asset, a registry containing the Neonatal Data Set (a National Data Standard). Details of data items are searchable at the following webpage: https://digital.nhs.uk/data-and-information/information-standards/information-standards-and-data-collections-including-extractions/publications-and-notifications/standards-and-collections/isb-1595-neonatal-data-set.

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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

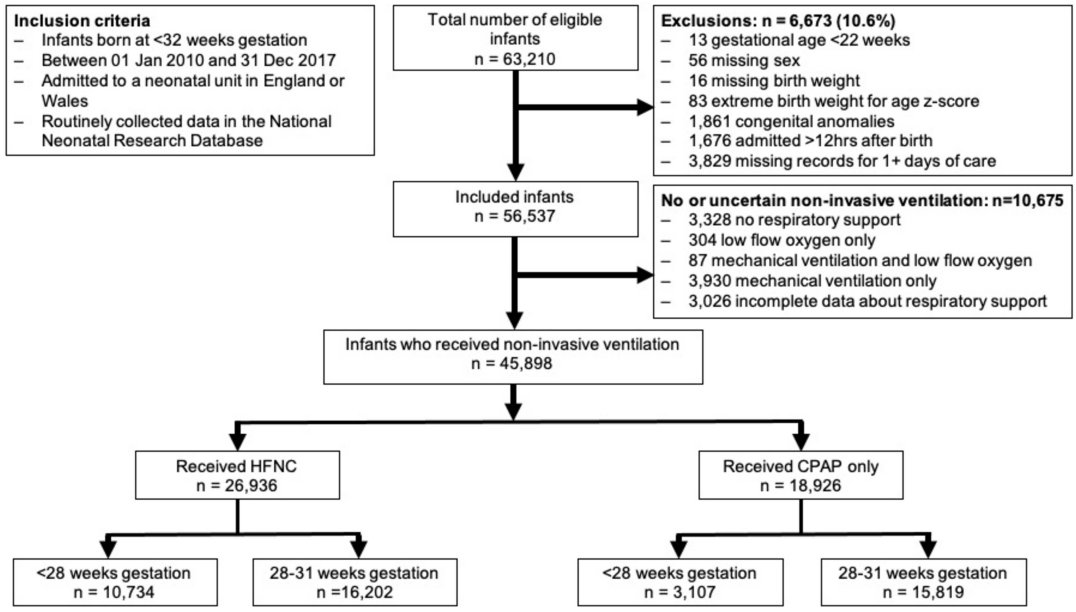
aOR, adjusted odds ratio, adjusted for sex, birth weight z-score <-2, exposure to antenatal steroids, NMR-200 category, mechanical ventilation on day 1, year of admission.

[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